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2,820,814

POLYIODINATED 5-AMINOISOPHTHALIC ACIDS, SALTS, AND ESTERS

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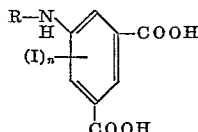
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9 Claims. (Cl. 260—471)

This invention relates to a new group of halogenated compounds which have important X-ray contrast properties. More particularly, this invention relates to new 5-acylaminopolyiodoisophthalic acids, their salts and esters and to methods for preparing same.

It is an object of this invention to provide derivatives of isophthalic acid containing a plurality of iodine atoms and possessing a relatively low toxicity as well as a substantial solubility in water in the form of their salts. It is a further object of this invention to provide for improved contrast media in X-ray diagnosis and to further provide improved X-ray contrast agents which are relatively stable under normal conditions of storage and use in the presence of body fluids.

According to the present invention, it has been found that aliphatic-acylated-5-amino-polyiodoisophthalic acids, specifically, 5-acetylaminio-2,4,6-triiodo-isophthalic acid, possess many valuable properties. These compounds consist of the acids of the general formula:



wherein R is a member of the group consisting of H and lower acyl and n is an integer from 2-3, together with their non-toxic salts and esters.

Some of the compounds of this invention are of value as X-ray contrast agents in urography when visualization of the kidneys is desired. Furthermore, under the proper techniques it is possible to obtain visualization of the calyx and ureters. These particular compounds which are utilized as urographic agents when injected intravenously in the form of a solution of one of their pharmacologically acceptable salts, such as the sodium salt, the diethanolamine salt, glucamine salts and other non-toxic salts, are rapidly concentrated in the kidneys and are excreted in the urine. In addition, under the proper compression techniques whereby the diffusion rate of the injected compound throughout the blood stream is reduced, visualization of the calyx and ureters is made possible within 5 to 20 minutes after injection. These aforementioned urographic properties appear to be peculiar to those compounds of the general formula which contain three iodine atoms, a lower acyl group on the amino-nitrogen atom and a free carboxylic acid group preferably in the form of its salt. For example; the formyl, acetyl and propionyl derivatives of the triiodinated acids of the general formula are excellent urographic agents, with the acetyl compound exhibiting the most desirable properties. As the number of carbon atoms in the acyl group is increased, there is an observable transitional change in the properties of the compounds. Specifically, the urographic

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utility decreases and the compounds become better suited as cholecystographic agents.

Esters of the acids of the general formula, especially those compounds containing three iodine atoms provide for X-ray contrast agents useful in bronchography and hysterosalpingography. For these diagnostic methods the esters are used preferably in oil solution or suspension. It is possible, however, to employ salts of the acids for use in bronchography and hysterosalpingography provided thickening agents such as methyl cellulose, gelatin, dextran, and other acceptable agents are employed whereby proper concentration of the radiopaque material is obtained with concomitant reduction in diffusion rate away from the site under examination.

Thus it is seen that the compounds of this invention may be administered parentally, orally or deposited at the site to be visualized. Depending upon the mode of administration, the compounds therefore are useful in uro-genital, gynecological and gastro-intestinal diagnoses.

The compounds of the invention possess a favorable therapeutic ratio in that the dose: toxicity value is very small. It has been found that the intravenous toxicity of many of the compounds of this invention lie between 5 and 10 grams of substance per kilogram of body weight as compared with a maximum of 400 mg. per kilogram as an effective dose. Thus, these compounds can be utilized effectively at about one-twentieth of the LD/50 dose.

With 5-acetylaminio-2,4,6-triiodo-isophthalic acid, as the preferred compound in the form of a pharmacologically acceptable soluble salt, excellent X-ray visualization is obtainable at a dose which is comparable to other diagnostic agents in use. At the dose employed, there is a marked absence of side effects including venous spasm which is sometimes noted with iodinated acids of this type.

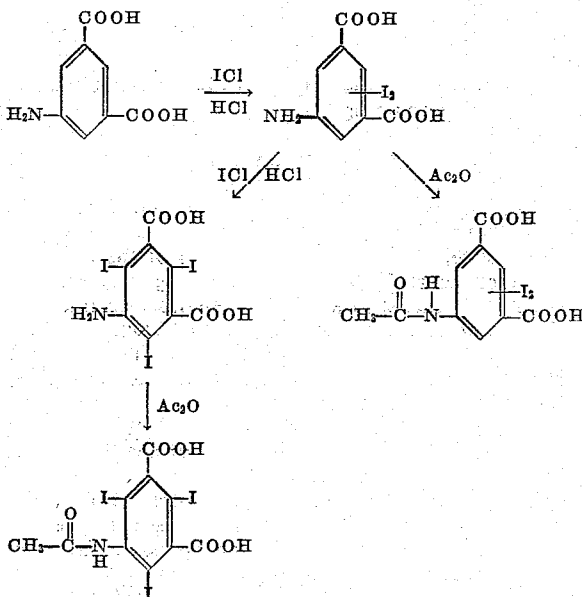
Excretion urography is based upon parenteral administration, usually by intravenous injection, of a contrast agent which is then excreted by the kidneys in such concentration that the kidneys and urinary tract are clearly outlined in a roentgenogram. As stated heretofore, a urogram may generally be taken within about five to twenty minutes after injection. It is generally known, however, that if normal renal function is impaired, sufficient medium may not concentrate in the kidneys until about one to twenty-four hours after injection.

With 5-acetylaminio-2,4,6-triiodo-isophthalic acid in solution as its sodium, or other therapeutically acceptable salt, generally about twenty milliliters of a 50% solution is sufficient for intravenous urography in adults. For children half the adult dose is generally sufficient. Obviously the restriction of fluid for several hours prior to examination permits greater urinary concentration of the salt allowing for more clearly defined roentgenograms.

It is not intended that the compounds of this invention be limited solely to urographic, cholecystographic and similar media since the properties of these compounds make them useful for many other purposes. As heretofore stated, visualization of the gastro-intestinal tract is made possible by the proper administration of some of the compounds of this invention. In such an indication the compounds may for example be administered orally in the form of solutions, suspensions, tablets, capsules, and the like. It is not even essential that soluble salts be employed. Furthermore, the utility of these compounds is not necessarily restricted to visualization of human organs since they are equally adaptable for X-ray visualization of other structures which can not be visualized directly.

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The compounds of this invention may be prepared from 5-amino-isophthalic acid according to the following scheme:



(The preparation of the requisite starting material 5-amino-isophthalic acid and its precursor 5-nitro-isophthalic acid has been reported in the literature.) In addition to the above scheme, amino-isophthalic acid in glacial acetic acid is iodinated with iodine monochloride in acetic acid giving rise to a mixture of both monoiodo and diiodo-5-amino-isophthalic acid which are easily separable by fractional recrystallization. It is possible to carry out the reaction in such a manner so as to obtain a preponderance of the diiodo acid over monohalogenated substances. By employing an excess of iodine monochloride in hydrochloric acid it is possible to triiodinate the amino-isophthalic acid although one can stepwise iodinate whereby the intermediate mono- or dihalogenated substance is isolated and subjected to further iodination.

The iodinated amino acids are acylated with a suitable agent such as a carboxylic acid, carboxylic acid chloride or anhydride preferably in the presence of a trace of a strong mineral acid such as sulfuric acid. Specific examples of acylating agents which are envisioned as coming within the scope of this invention are formic acid, acetic acid, acetyl chloride, acetic anhydride, propionic anhydride, butyric anhydride and the like. Thus, although acetic anhydride is preferred because of its relative economy and availability, other lower aliphatic acylating agents may be employed.

The salts and esters of these compounds are prepared by the usual methods employed in preparing salts and esters of organic acids.

The following examples further illustrate the invention but in no way limit the said invention except as defined in the appended claims.

EXAMPLE I

Mono-iodo-5-amino-isophthalic acid

To a solution of 26.4 gms. of iodine monochloride and 40 ml. glacial acetic acid is added a stirred suspension of 9 gms. of 5-amino-isophthalic acid in 160 ml. of acetic acid over a one-hour period. After stirring for an additional hour, 200 ml. of water is added dropwise and the mixture is allowed to stand at room temperature for about 30 minutes. The mixture is heated on a steam bath at about 70° for about 40 minutes and then allowed to stand at room temperature overnight. Excess iodine monochloride is destroyed by the addi-

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tion of sodium bisulfite solution and the acetic acid is removed by steam distillation. Upon the addition of concentrated hydrochloric acid to the residue from the steam distillation there is obtained 10 g. of a mixture of iodinated acids melting at 270–285° (dec.). The crude iodinated acid is recrystallized from 500 ml. of water yielding mono-iodo-5-amino-isophthalic acid, M. P. 293° (dec.).

Upon the addition of concentrated hydrochloric acid to the recrystallization liquor, there is obtained about 5 g. of diiodo-5-amino-isophthalic acid as a white microcrystalline solid, M. P. 308–309° (dec.).

EXAMPLE II

Diiodo-5-amino-isophthalic acid

To a suspension of 9 g. of 5-amino-isophthalic acid in 1 liter of water there is added sufficient concentrated hydrochloric acid (about 15 ml.) to effect complete solution. To the solution is then added 26.7 g. of iodine monochloride and the reaction mixture is stirred at room temperature for three days. After removing a small amount of insolubles by filtration, the filtrate is treated with sodium hydrosulfite until the color indicative of excess iodine monochloride disappears. The solution is then saturated with sodium chloride and extracted thoroughly with ether. The ether solution is dried with anhydrous sodium sulfate and evaporated to a residue, yielding 14 g. of crude diiodo-5-amino-isophthalic acid. The crude acid is purified by recrystallization from water using decolorizing charcoal and reprecipitated from the cooled filtrate by the addition of concentrated hydrochloric acid.

EXAMPLE III

2,4,6-triiodo-5-amino-isophthalic acid

To a solution of 4.5 g. of 5-amino-isophthalic acid in 250 ml. of water and 8.5 ml. of concentrated hydrochloric acid there is added 14 g. of iodine monochloride and the reaction mixture is allowed to stand for two days. After filtration of the insoluble material, the filtrate is treated with sodium hydrosulfite, saturated with sodium chloride and extracted thoroughly with ether. The ether extracts are dried over anhydrous sodium sulfate and evaporated to a residue yielding 7.5 g. of the crude acid of this example, M. P. 270–274°. Purification is effected by treating a hot aqueous solution of the iodinated acid with charcoal and reprecipitating the product from the cold filtrate by the addition of concentrated hydrochloric acid, M. P. 278–280° (dec.).

EXAMPLE IV

Diiodo-5-acetyl-amino-isophthalic acid

A suspension of 4.3 g. of diiodo-5-amino-isophthalic acid in 12 ml. of acetic anhydride is treated with 1–2 drops of concentrated sulfuric acid and the mixture is refluxed for 30 minutes. After cooling, the mixture is poured into 60 ml. of water, neutralized with 5–1 g. of sodium acetate and evaporated to a residue in vacuo. Recrystallization from water and the addition of concentrated hydrochloric acid yields 3 g. of the acetyl amino compound of this example, M. P. over 340°.

EXAMPLE V

2,4,6-triiodo-5-acetyl-amino-isophthalic acid

A suspension of 5 g. of 2,4,6-triiodo-5-amino-isophthalic acid in 15 ml. of acetic anhydride in the presence of 1–2 drops of sulfuric acid is refluxed for 30 minutes. The crude acetylated acid is obtained according to the procedure in the preceding example. Purification is effected by solution in dilute ammonium hydroxide and treatment with decolorizing charcoal followed by filtration, cooling and reprecipitation with concentrated hydrochloric acid. Recrystallization from water as described

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in the preceding example yields the iodinated acid of this example, 3 g., M. P. above 340°.

EXAMPLE VI

2,4,6-triiodo-5-formylamino-isophthalic acid

To a mixture of 50 g. of 2,4,6-triiodo-5-amino-isophthalic acid and 500 ml. of 87-90% formic acid is added about six drops of concentrated sulfuric acid and the resultant reaction mixture is heated and stirred on a steam bath for two hours. After cooling, the sulfuric acid is neutralized by the addition of a small amount of sodium acetate and the mixture is evaporated to a residue in vacuo. Upon recrystallization of the residue from water to which has been added concentrated hydrochloric acid, the formyl derivative of this example is obtained.

EXAMPLE VII

2,4,6-triiodo-5-propionylamino-isophthalic acid

A mixture of 25 g. of 2,4,6-triiodo-5-amino-isophthalic acid, 100 ml. of propionic anhydride and 3-4 drops of concentrated sulfuric acid is stirred and heated at 125 to 130° for approximately two hours. After cooling, 500 ml. of water is added and the resultant mixture is stirred at room temperature until the excess propionic anhydride is completely hydrolyzed. Upon concentration of the aqueous solution in vacuo there is obtained the crude propionylamino acid of this example which is purified by recrystallization from water as analogously described in Example III.

EXAMPLE VIII

2,4,6-triiodo-5-butyrylamino-isophthalic acid

A mixture of 30 g. of 2,4,6-triiodo-5-amino-isophthalic acid, 100 ml. of butyric anhydride and about six drops of concentrated sulfuric acid is stirred and heated at 150 to 160° for about two hours. The excess anhydride is destroyed by the addition of 600 ml. of water as described in the preceding example and the sulfuric acid is neutralized with sodium acetate. Upon evaporation of the resultant mixture in vacuo there is obtained a semi-solid residue which is dissolved in warm, dilute ammonium hydroxide. The alkaline solution is treated with decolorizing charcoal and the butyrylamino acid is reprecipitated by the addition of concentrated sulfuric acid and recrystallized from water as heretofore described.

EXAMPLE IX

2,4,6-triiodo-5-caproylamino-isophthalic acid

A mixture of 55.9 g. of 2,4,6-triiodo-5-amino-isophthalic acid, 500 ml. of anhydrous toluene and 20 grams of caproyl chloride is stirred and refluxed for one hour. After cooling, the crude product is removed by filtration and triturated with ether to remove unacylated material. After decanting the ether layer, the remaining solid is recrystallized from aqueous ethanol affording the caproylamino acid of this example.

EXAMPLE X

Diethyl 2,4,6-triiodo-5-acetylaminophthalate

To a mixture of 50 grams of 2,4,6-triiodo-5-acetylaminophthalic acid and 200 ml. of anhydrous ethanol is added 15 ml. of acetyl chloride. The reaction mixture is allowed to stand at room temperature overnight with occasional shaking whereupon it is diluted with one liter of water and the precipitate so formed is removed by filtration or decantation. The crude ester is dissolved in ether and the ether solution is washed, in turn, with sodium bicarbonate solution and water. After drying the ether solution with anhydrous sodium sulfate, the solvent is removed in vacuo. There is obtained the diethyl ester of this example which is purified by recrystallization from aqueous alcohol.

Alternatively the diethyl ester is prepared by treating 75

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a solution of 2,4,6-triiodo-5-acetylaminophthalic acid in absolute ethanol containing a catalytic amount of sodium ethoxide with diethyl sulfate and isolating the ester in a known manner.

In addition to the foregoing procedures the diethyl ester of this example is prepared by distilling an ethanolbenzene solution of the amino acid in the presence of 0.5 g. of p-toluene sulfonic acid (or 0.5 ml. of concentrated sulfuric acid) and azeotropically removing the water so formed.

EXAMPLE XI

Disodium salt of 2,4,6-triiodo-5-acetylaminophthalic acid

A suspension of 5.58 grams of purified 2,4,6-triiodo-5-acetylaminophthalic acid (obtained in Example V) in 15 ml. of distilled water is neutralized with 30% aqueous sodium hydroxide until the pH rises to 7 to 7.5. The alkaline solution is filtered and the filtrate is evaporated in vacuo. Upon recrystallization of the residue from alcohol-ether, using decolorizing charcoal, six grams of the sodium salt of this example is obtained as a white crystalline solid.

It is generally not necessary to isolate the sodium salt per se if the appropriate quantities of amino acid, water, and alkali are used to yield a solution containing the desired concentration of sodium salt.

EXAMPLE XII

Di-N-methylglucamine salt of 2,4,6-triiodo-5-acetylaminophthalic acid

To an intimate mixture of 4.67 grams of 2,4,6-triiodo-5-acetylaminophthalic acid and 3.03 grams of N-methylglucamine is added 4.0 ml. of distilled water and the mixture is stirred until complete solution is effected.

The solution is then diluted to 10 ml. with distilled water affording a 77% w./v. solution which is comparable in iodine content to a 50% w./v. solution of the sodium salt.

Alternatively the di-N-methylglucamine salt is isolated by evaporation of the aqueous solution in vacuo.

EXAMPLE XIII

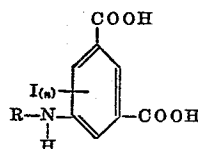
Di-diethanolamine salt of 2,4,6-triiodo-5-acetylaminophthalic acid

One mole of 2,4,6-triiodo-5-acetylaminophthalic acid and two moles of diethanolamine are mixed and dissolved in water according to the procedure described in Example XII, giving rise to a similar w./v. concentration.

Isolation of the salt is accomplished by evaporation of its aqueous solution in vacuo.

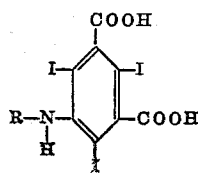
I claim:

1. A compound selected from the group consisting of a 5-amino-polyiodo-isophthalic acid of the general formula:



wherein R is a member of the group consisting of hydrogen and lower aliphatic carboxylic acyl radicals, n is an integer from 2 to 3, and the ethyl ester and non-toxic salts thereof.

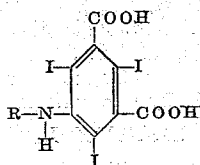
2. 5-amino-2,4,6-triiodo-isophthalic acids of the general formula:



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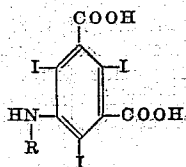
wherein R represents a lower aliphatic carboxylic acyl radical.

3. A non-toxic salt of an aliphatic 5-acylamino-2,4,6-triiodo-isophthalic acid of the general formula:



wherein R represents a lower aliphatic carboxylic acyl radical.

4. The diethyl ester of an aliphatic 5-acylamino-2,4,6-triiodo-isophthalic acid of the general formula:



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wherein R represents a lower aliphatic carboxylic acyl radical.

5. 5-acetylamino-2,4,6-triiodo-isophthalic acid.
6. 5-propionylamino-2,4,6-triiodo-isophthalic acid.
7. Diethyl 5-acetylamino-2,4,6-triiodo-isophthalate.
8. The non-toxic salts of 5-acetyl-amino-2,4,6-triiodo-isophthalic acid.
9. Disodium 5-acetylamino-2,4,6-triiodo-isophthalate.

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