

UNITED STATES PATENT OFFICE

2,679,531

ORTHO (3,5-DIODO BENZYL)- AND ORTHO
(3,5-DIODO BENZOYL)-BENZOIC ACIDSWilliam H. Strain, Rochester, N. Y., assignor to
Eli Lilly and Company, Indianapolis, Ind., a
corporation of IndianaNo Drawing. Application November 27, 1948,
Serial No. 62,407

8 Claims. (Cl. 260—517)

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My invention relates to cholecystographic agents and more particularly to a group of substituted benzoic acids and salts having utility as X-ray contrast agents.

In the practice of cholecystography, compounds possessing opacity to X-rays are administered either orally or intravenously prior to the time at which the radiographic study is to be made. During the interval before radiographic study, the compounds localize in the gall bladder so that the bladder becomes opaque to X-rays and hence may be selectively delineated by means of X-rays.

One compound which has been widely used for radiographic purposes is tetraiodophenolphthalein. The use of this compound, however, is attended by several drawbacks. When tetraiodophenolphthalein is administered orally the compound usually produces nausea and diarrhea, and frequently is adsorbed so poorly that confusing shadows persist in the bowel to such a degree that the gall bladder shadow is masked. Intravenous administration of tetraiodophenolphthalein avoids some of the disadvantages accompanying oral administration but is disadvantageous in that hospitalization of the patient and highly trained personnel are required for production of satisfactory results.

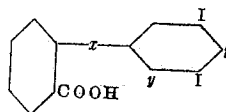
Of recent years β -(4-hydroxy-3,5-diodophenyl)- α -phenylpropionic acid has been employed as a cholecystographic agent. This agent avoids some of the disadvantages accompanying the use of tetraiodophenolphthalein but, on the other hand, markedly inhibits the motor function of the gall bladder and furthermore, the results obtained are diagnostically unreliable when poor filling of the gall bladder occurs so that only a light shadow is obtained. Additionally, unpleasant side effects such as nausea and the like are encountered in a significant percentage of the patients to whom the compound is administered.

An object of my invention is to provide cholecystographic agents which are free from the disadvantageous properties of the compounds of the prior art. Other objects of my invention will be apparent from the following disclosure.

In accordance with the above and other objects I have provided cholecystographic agents comprising a group of substituted benzoic acids and their water-soluble salts. The compounds

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of my invention may be represented by the following formula



wherein x represents a methylene ($-\text{CH}_2-$) or carbonyl



radical, and one y is hydroxyl ($-\text{OH}$), the other being hydrogen ($-\text{H}$), and R represents hydrogen or a metallic radical such as an alkali, alkaline-earth or ammonium radical which forms a water-soluble salt with the acid. The compounds of my invention, therefore, are iodinated hydroxybenzyl-benzoic acids and iodinated hydroxybenzoyl-benzoic acids, and their salts.

The compounds represented above are colorless solids. The acids have a low water solubility but the salts containing the common metallic radicals such as sodium, potassium, ammonium and the like are readily water-soluble.

The novel acids of this invention are prepared by iodination of the appropriate hydroxybenzyl-benzoic acid or hydroxybenzoyl acid, the iodination being carried out with iodine monochloride or with iodine-potassium iodide mixture. The salts of the iodine-containing benzoic acids are prepared by treating the acids with an equivalent amount of base or a basic salt such as a carbonate or bicarbonate salt.

The administration of my compounds for radiographic work may be oral or intravenous. Oral administration preferably is carried out with the free acids, and desirably the acids before administration are finely comminuted, i. e., "micronized." The comminuted material may be given as a powder, or administered in capsules, or may be mixed with a suitable binder and formed into a tablet prior to administration. Since the acids themselves are either tasteless or possess a sweet taste, there is no need of simultaneous administration of agents such as chocolate and the like which are frequently used to mask unpleasant tastes. For intravenous administration, water-soluble salts in aqueous solution are employed, the sodium salt being the

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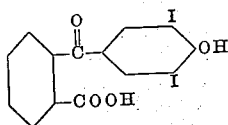
salt of choice. The dosage required for gall bladder visualization varies somewhat with the size of the patient but a dose in the range of 2 to 4 g. will give satisfactory delineation when the usual cholecystographic techniques are employed.

My novel compounds when administered in accordance with the customary practices are capable of giving excellent radiographic results, and thus are of great value in the diagnostic armamentarium. Their affinity for the gall bladder is so marked that delineation of the bladder is obtained in a relatively short time. Experiments in dogs have shown that intravenous administration of my compounds, for example sodium o-(4-hydroxy-3,5-diiodobenzyl)-benzoate, produces a good visualization of the gall bladder in 20 minutes, whereas comparable visualization with β -(4-hydroxy-3,5-diiodophenyl)- α -phenylpropionic acid and tetraiodophenolphthalein is obtained only after a much longer period of time. Administration to human patients has produced no nausea as is usually experienced with tetraiodophenolphthalein or commonly observed with β -(4-hydroxy-3,5-diiodophenyl)- α -phenylpropionic acid. Furthermore, no untoward effect on the function of the gall bladder has been observed. More surprisingly, I have found that not only is the gall bladder delineated but also the extrahepatic biliary ducts are made visible. A ready duct visualization cannot be achieved by means of the other cholecystographic agents now employed.

My invention is further illustrated by the following specific examples which describe methods of preparing representative benzoic acids and salts within the scope of my invention.

Example 1

Preparation of o-(4-hydroxy-3,5-diiodobenzoyl)-benzoic acid.
o-(4-hydroxy-3,5-diiodobenzoyl)-benzoic acid represented by the formula



is prepared as follows:

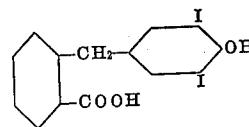
A solution of 43 parts of o-(4-hydroxybenzoyl)-benzoic acid dissolved in 1000 parts of warm glacial acetic acid is treated with a solution of 110 parts of iodine monochloride in acetic acid. After mixing is complete, 1000 parts of warm water are added and the mixture is heated to about 80-90° C. for half an hour. After heating, the reaction mixture is poured into a large volume of cold water and the excess iodine is destroyed by the addition of a small amount of sodium sulfite. The o-(4-hydroxy-3,5-diiodobenzoyl)-benzoic acid which has precipitated is filtered off, washed well with water and dried. o-(4-hydroxy-3,5-diiodobenzoyl)-benzoic acid is obtained in excellent yield as a white powder of high purity. It is further purified by crystallization from dilute alcohol. Pure o-(4-hydroxy-3,5-diiodobenzoyl)-benzoic acid melts at about 223° C.

The sodium salt of o-(4-hydroxy-3,5-diiodobenzoyl)-benzoic acid is obtained by treating an aqueous suspension of the acid with an equivalent amount of sodium hydroxide. The salt is isolated by evaporating the solution to dryness. Alternatively, the salt can be isolated by reducing the volume of the aqueous solution and adding an

excess of acetone to cause precipitation of the salt.

Example 2

Preparation of o-(4-hydroxy-3,5-diiodobenzyl)-benzoic acid.
o-(4-hydroxy-3,5-diiodobenzyl)-benzoic acid represented by the formula



is prepared as follows:

To a solution prepared from 228 parts of o-(4-hydroxybenzyl)-benzoic acid, 400 parts of water and 400 parts of concentrated ammonium hydroxide, are added 2500 parts of crushed ice. To the mixture is added with mechanical stirring and at such a rate that the temperature does not rise above 0° C., a solution comprising a mixture of 508 parts of potassium iodide, 508 parts of iodine and 3000 parts of water. After the iodine solution is added the reaction mixture is stirred for 15 minutes, and 5 parts of sodium sulfite are added to destroy any excess iodine. To the mixture are added 6000 parts of hot (50° C.) water, and the mixture is acidified by the addition of dilute sulfuric acid. The acidified mixture is stirred for 10 minutes. The o-(4-hydroxy-3,5-diiodobenzyl)-benzoic acid which precipitates is filtered off and washed with water until free from mineral acid. The moist o-(4-hydroxy-3,5-diiodobenzyl)-benzoic acid is stirred with about 10 volumes of water, and dissolved by the addition to the mixture of a solution comprising 84 parts of sodium hydroxide dissolved in 400 parts of water and finally 42 parts of dry sodium bicarbonate. After evolution of carbon dioxide has ceased, 5 parts of sodium sulfite and 30 parts of decolorizing carbon are added and the mixture is stirred for 30 minutes and filtered. The filtrate is diluted with an equal volume of hot water and acidified by the addition of dilute sulfuric acid. The o-(4-hydroxy-3,5-diiodobenzyl)-benzoic acid which precipitates upon acidification, is filtered off, washed with water and dried. o-(4-hydroxy-3,5-diiodobenzyl)-benzoic acid thus prepared is obtained in excellent yield. It melts at about 208-209° C.

The sodium salt of o-(4-hydroxy-3,5-diiodobenzyl)-benzoic acid can be prepared by adding to an alcoholic solution of the acid, an equivalent amount of sodium ethoxide dissolved in alcohol, and filtering off the sodium o-(4-hydroxy-3,5-diiodobenzyl)-benzoate which precipitates.

Example 3

Preparation of o-(4-hydroxy-3,5-diiodobenzyl)-benzoic acid.

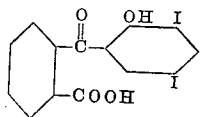
o-(4-hydroxy-3,5-diiodobenzyl)-benzoic acid may also be prepared from 68 parts of o-(4-hydroxybenzyl)-benzoic acid dissolved in 1000 parts of warm glacial acetic acid by the iodination technique described in Example 1. The o-(4-hydroxy-3,5-diiodobenzyl)-benzoic acid is obtained in good yield as a fawn colored product and is purified by crystallization from ethyl alcohol or acetic acid.

Example 4

Preparation of o-(2-hydroxy-3,5-diiodobenzoyl)-benzoic acid.

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o-(2-hydroxy-3,5-diiodobenzoyl)-benzoic acid represented by the following formula



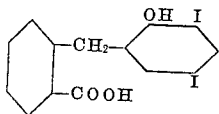
is prepared as follows:

A solution of 73 parts of o-(2-hydroxybenzoyl)-benzoic acid dissolved in 1000 parts of warm glacial acetic acid is iodinated according to the procedure described in Example 1. The o-(2-hydroxybenzoyl)-benzoic acid is obtained in good yield as a white powder. It is purified by crystallization from dilute alcohol, and is obtained in the form of white crystals which melt at about 216-218° C.

Example 5

Preparation of o-(2-hydroxy-3,5-diiodobenzyl)-benzoic acid.

o-(2-hydroxy-3,5-diiodobenzyl)-benzoic acid represented by the formula



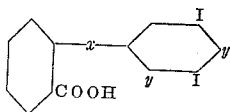
is prepared by iodinating a solution of 68 parts of o-(2-hydroxybenzyl)-benzoic acid in 1000 parts of warm glacial acetic acid according to the procedure described in Example 1. The o-(2-hydroxy-3,5-diiodobenzyl)-benzoic acid is obtained in good yield as a tan colored product. It is purified by crystallization from acetic acid and when so purified is obtained as white crystals melting at 200-201° C.

Example 6

The salts of the acids described in Examples 3, 4 and 5 are obtained by the procedures for preparing salts described in Examples 1 and 2.

I claim:

1. A member of the group consisting of an acid represented by the following formula



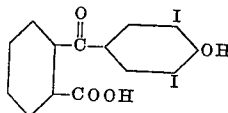
and its alkali metal, alkaline-earth metal and ammonium salts, in which x represents a radical of the group consisting of the methylene and carbonyl radicals, and one y represents $-OH$ and the other represents $-H$.

2. o-(4-hydroxy-3,5-diiodobenzyl)-benzoic acid.

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3. A compound selected from the group consisting of

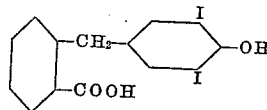
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and its salts with alkali-forming inorganic cations.

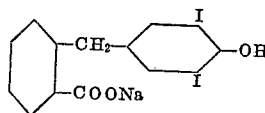
4. An alkali metal salt of an acid represented by the following formula

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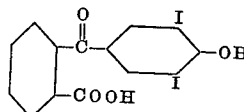
5. The compound represented by the following formula

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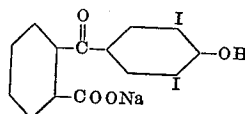
6. An alkali metal salt of an acid represented by the following formula

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7. The compound represented by the following formula

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8. o-(hydroxy-3,5-diiodobenzoyl)-benzoic acid.

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