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2,505,634

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2,505,634

4-PYRIDONE-N-CARBOXYLIC ACIDS

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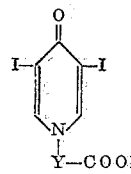
No Drawing. Application October 3, 1947, Serial No. 777,864

9 Claims. (Cl. 260—297)

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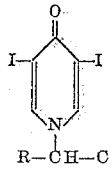
This invention relates to halogenated pyridone derivatives of carboxylic acids capable of forming water soluble salts with inorganic and organic bases.

My new compounds have the formula



where Y is a divalent hydrocarbon radical of from 5 to 9 carbon atoms. They are generally used in the form of a water soluble salt derived from an inorganic or organic base.

These compounds may be prepared by the reaction of 3,5-diiodo-4-pyridone and a halo-carboxylic acid containing from 6 to 10 carbon atoms in alkaline solution. However, in view of the distinctly greater availability of the alpha-halo-carboxylic acids as compared with the beta, gamma, etc., derivatives, I prefer to prepare and use compounds of the formula



where R is an alkyl group of from 4 to 8 carbon atoms.

The lower homologues of my new compounds are already known. Thus 3,5-diiodo-4-pyridone-N-acetic acid and its salts, in particular the diethanolamine salt have been described in Reitmann, U. S. Patent 1,993,039, and Reitmann and Hecht, U. S. Patent 2,064,944, and these compounds have proved of considerable value as X-ray contrast media. These substances are used in intravenous urography and excretion and retrograde pyelography.

It might be assumed from the action of these lower homologues that my new compounds would also be urographic agents. However, it has been found they concentrate in the bile rather than pass through the urinary tract, so that they are cholecystographic rather than urographic agents. It would appear that when Y in the above formula contains less than about 5 carbon atoms, the molecule lacks the characteristics necessary for concentration in the gall bladder.

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The contrast media which have been used up to the present time for oral cholecystography are not entirely satisfactory. Tetraiodophenolphthalein frequently causes violent physiological reactions. 2-(4'-hydroxy-3',5'-diiodophenyl)-quinoline-4-carboxylic acid is much too toxic. 2-(4-hydroxy-3,5-diiodophenyl)-alpha-phenylpropionic acid is better than the others, but occasionally produces pain on urination, interferes with the rate of emptying of the gall bladder following a fatty meal, causes a burning sensation in the throat, or produces nausea, vomiting and diarrhea. This substance is, moreover, too toxic to be used for intravenous cholecystography, and tetraiodophenolphthalein, although used for this purpose, has a toxicity level which is dangerously high in addition to other drawbacks.

The diethanolamine salts of my new compounds have been found to give very good radiograms of the gall bladder at relatively low dosage levels upon intravenous administration, and to be relatively free from physiological side effects. They form colorless solutions in contrast to the sodium salt of tetraiodophenolphthalein which forms a dark blue solution, rendering it difficult to determine whether all of the substance is in solution. The toxicities of the compounds are unusually low for this type of molecule and so offer promise as intravenous cholecystographic agents, an application hitherto limited to the unsatisfactory tetraiodophenolphthalein. Intravenous administration has certain advantages over oral use; smaller quantities of radiopaque are necessary with a greater degree of certainty of concentration in the circulatory system and subsequently the gall bladder, and the administration and radiographic procedure is completed in a much shorter time.

These new compounds can be prepared by treatment of an aqueous solution of 3,5-diiodo-4-pyridone (Dohrn and Diedrich, Ann., 494, 292 (1932), and German Patents 556,142 and 602,943) in a strong base, such as sodium or potassium hydroxide, with a halo-carboxylic acid of the proper carbon content. An alpha-halo-aliphatic carboxylic acid is preferred since it is more readily obtained. The product of the reaction is a 3,5-diiodo-4-pyridone-N-carboxylic acid, the acid being substituted at the position originally occupied by the halogen atom.

The following examples will further illustrate my invention and demonstrate the generality of

the reactions involved, without, however, limiting the scope of the invention thereto.

EXAMPLE 1

Alpha-n-butyl-3,5-diiodo-4-pyridone-N-acetic acid

3,5-diiodo-4-pyridone (35.5 g.) is added to a solution of 4 g. of sodium hydroxide in 100 cc. of water and heated to give a turbid solution at 90–95° C. A solution of 19.5 g. of alpha-bromocaproic acid in 150 cc. of water containing 6 g. of sodium hydroxide is then added over a period of five minutes. Heating with stirring is continued for one and one-quarter hours longer, after which the mixture is cooled and carbon dioxide passed in until the solution is acid to phenylphthalein and all of the unreacted 3,5-diiodo-4-pyridone has been precipitated. The solid, about 20 g., is filtered, and the filtrate is cooled in ice and acidified with hydrochloric acid. A gum precipitates which is filtered and dissolved in alcohol. The alcohol solution is decolorized with activated charcoal, filtered, and diluted with an equal volume of water. Upon cooling and standing, the product crystallizes and is filtered, dissolved in ether, dried over anhydrous sodium sulfate, and again decolorized. After removal of the ether, the product is crystallized from dilute alcohol, filtered and dried; yield about 17 g., M. P. 205–207° C., of alpha-n-butyl-3,5-diiodo-4-pyridone-N-acetic acid.

EXAMPLE 2

Alpha-n-amyl-3,5-diiodo-4-pyridone-N-acetic acid

3,5-diiodo-4-pyridone (35 g.) and 23 g. of 2-bromoheptanoic acid are caused to react in the same manner as the components in Example 1. The final product, alpha-n-amyl-3,5-diiodo-4-pyridone-N-acetic acid, crystallizes from 50% alcohol and has the M. P. 200–203° C.

EXAMPLE 3

Alpha-n-hexyl-3,5-diiodo-4-pyridone-N-acetic acid

3,5-diiodo-4-pyridone (109 g.) is dissolved in a solution of 14 g. of sodium hydroxide at 90° C. 2-bromooctanoic acid (70 g., B. P. 97–110° C.) in alkaline solution is added with stirring in three portions over a period of one and one-half hours as follows:

(1) Thirty grams of acid and 6.2 g. of sodium hydroxide in 100 cc. of water.

(2) Same as (1).

(3) Ten grams of acid and 5 g. of sodium hydroxide in 50 cc. of water.

Heating is continued for two and one-half hours longer, 300 cc. of water added, and carbon dioxide is passed into the mixture until it is acid to phenolphthalein. The precipitated, unreacted 3,5-diiodo-4-pyridone (about 70 g.) is filtered and washed with water, and the filtrate is acidified with hydrochloric acid, producing a brown oily solid. The product is filtered, dissolved in alcohol, and decolorized by bubbling sulfur dioxide through the solution and also with activated charcoal. Addition of water to the clarified solution brings about crystallization of a yellowish solid, M. P. 180–182° C., when dry. Two more recrystallizations, each with a repetition of the decolorizing procedure gives about 55 g. of alpha-n-hexyl-3,5-diiodo-4-pyridone-N-acetic acid, M. P. 191–194° C.

EXAMPLE 4

Alpha-isoamyl-3,5-diiodo-4-pyridone-N-acetic acid

3,5-diiodo-4-pyridone (95 g.) and 50 g. of 2-bromo-5-methylhexanoic acid are caused to react in the same manner as the components in Example 3. About 57 g. of alpha-isoamyl-3,5-diiodo-4-pyridone-N-acetic acid is obtained having the M. P. 198.5–200.5° C.

EXAMPLE 5

Alpha-n-heptyl-3,5-diiodo-4-pyridone-N-acetic acid

3,5-diiodo-4-pyridone (30 g.) and 21 g. of 2-bromononanoic acid are caused to react in the same manner as the components in Example 1. The crude product is recrystalized from ether-petroleum ether (B. P. 40–60° C.), giving about 18 g. of alpha-n-heptyl-3,5-diiodo-4-pyridone-N-acetic acid, M. P. 130–132° C. A final recrystallization from dilute alcohol gives a product with the M. P. 132–133° C.

EXAMPLE 6

Alpha-n-octyl-3,5-diiodo-4-pyridone-N-acetic acid

3,5-diiodo-4-pyridone (35 g.) and 25.1 g. of 2-bromodecanoic acid are caused to react in the same manner as the components in Example 1. The product, alpha-n-octyl-3,5-diiodo-4-pyridone-N-acetic acid, crystallizes from dilute alcohol and has the M. P. 124.5–126.5° C.

EXAMPLE 7

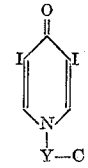
Alpha-isobutyl-3,5-diiodo-4-pyridone-N-acetic acid

3,5-diiodo-4-pyridone (95 g.) and 46.6 g. of alpha-bromoisocaproic acid are caused to react in the same manner as the components in Example 3. Repeated recrystallization of the product from dilute alcohol gives about 36 g. of alpha-isobutyl-3,5-diiodo-4-pyridone-N-acetic acid, M. P. 185–186° C.

In order to obtain water soluble radiopaque media, the acids prepared in the above examples, and others within the scope of the invention, can be dissolved in an aqueous solution of an equivalent amount of a suitable inorganic or organic base. Suitable bases are those which are innocuous and otherwise therapeutically acceptable to the organism; for example, sodium hydroxide, diethylamine and diethanolamine.

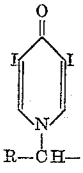
I claim:

1. A compound of the formula



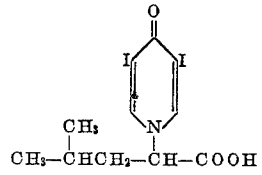
where Y is an alkylene radical containing from 5 to 9 carbon atoms, and salts thereof.

2. A compound of the formula



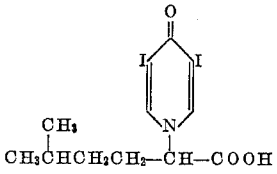
where R is an alkyl group containing from 4 to 8 carbon atoms, and salts thereof.

3. Alpha - isobutyl - 3,5 - diiodo - 4 - pyridone-N-acetic acid having the formula



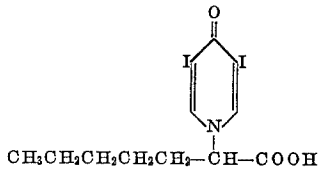
and salts thereof.

4. Alpha - isoamyl - 3,5 - diiodo - 4 - pyridone-N-acetic acid having the formula



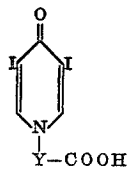
and salts thereof.

5. Alpha-amyl-3,5-diiodo-4-pyridone-N-acetic acid having the formula



and salts thereof.

6. The process of preparing compounds of the formula

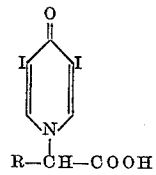


where Y is an alkylene radical containing from 5 to 9 carbon atoms, which comprises reacting an alkali metal salt of 3,5-diiodo-4-pyridone with an alkali metal salt of a halo-carboxylic acid of the formula

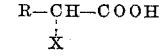
X—Y—COOH

where X is halogen, and recovering the resulting 3,5-diiodo-4-pyridone-N-carboxylic acid.

7. The process of preparing compounds of the formula

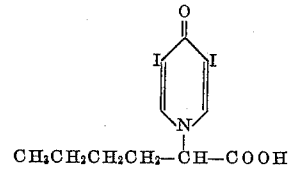


where R is an alkyl group containing from 4 to 8 carbon atoms, which comprises reacting an alkali metal salt of 3,5-diiodo-4-pyridone with an alkali metal salt of a halo-carboxylic acid of the formula



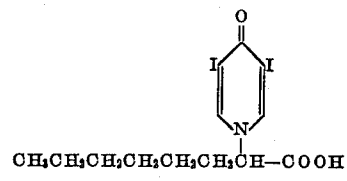
where X is halogen, and recovering the resulting 3,5-diiodo-4-pyridone-N-acetic acid.

8. Alpha-n-butyl-3,5-diiodo - 4 - pyridone - N - acetic acid having the formula



and salts thereof.

9. Alpha - n - hexyl - 3,5 - diiodo - 4 - pyridone-N-acetic acid having the formula



and salts thereof.

SYDNEY ARCHER.

REFERENCES CITED

The following references are of record in the file of this patent:

UNITED STATES PATENTS

Number	Name	Date
2,064,944	Reitmann et al.	Dec. 22, 1936