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3,814,769

## CATALYZED RADIOIODINE EXCHANGE

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11 Claims

## ABSTRACT OF THE DISCLOSURE

Isotopic exchange between radioiodine atoms in an iodide salt and stable iodine atoms bound to aromatic carbon atoms is accelerated by the presence of catalytic amounts of copper, for example, by  $2.3 \times 10^{-4}$  mg. of cupric sulfate per mg. of organic compound. The presence of small amounts of water in the reaction medium further enhances the effect of copper. Not only is the conversion of stable iodinated compounds to their radioiodinated isomers substantially increased in many cases, but also lower temperatures and shorter reaction times are feasible with less risk of damage to heat-sensitive organic compounds thereby broadening the range of useful radioiodinated compounds which can be prepared by isotope exchange. Exemplified are quinolines, tryptophans, benzoic and iocetamic acids.

This is a continuation, of application Ser. No. 821,097, filed May 1, 1969, now abandoned.

## BACKGROUND OF THE INVENTION

### (1) Field of the invention

This invention relates to the field of radioactive organic compounds and more particularly to improved methods for preparing same.

### (2) Summary of the prior art

Various organic compounds containing one or more radioactive iodine atoms bound to an unsaturated cyclic carbon atom are used as tracer compounds in medical research and diagnosis. A well known example is the radioiodine analog of sodium o-iodohippurate. More recently it has been shown that the radioiodine analogs of 4 - (3 - dimethylaminopropylamino)-7-iodoquinoline are selectively concentrated in tissues containing melanine and are useful for the location and treatment of melanotic tumors.

These radioiodinated compounds are ordinarily prepared by heating a solution containing the stable iodine analog of the desired compound with a radioactive iodide such as sodium iodide. In the case of compounds where the iodine is tightly bound to carbon, as when the carbon is part of an unsaturated ring system such as a benzene ring, the exchange between stable and radioactive iodine atoms often proceeds very slowly even at elevated temperatures. As a result the yield of the desired radioiodinated compound is poor, there is excessive loss of the valuable radioisotope through natural decay, and if the reaction temperature is raised to increase the rate of exchange, appreciable thermal degradation of the organic compound may occur with further loss of valuable material.

Therefore, methods which would accelerate the exchange between stable iodine atoms and radioactive iodine atoms mentioned above and enable such exchanges to be effected at lower temperatures and/or within shorter times would be of great practical importance. Such methods would not only permit more efficient utilization of valuable radioisotopes, they would also permit the

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economical preparation of a broader range of radioiodinated compounds than has heretofore been feasible.

## SUMMARY OF THE INVENTION

Among the objects of the invention may be mentioned the provision of improved methods for effecting exchange between stable iodine atoms bound to an aromatic carbon atom and radioactive iodine atoms in the form of inorganic iodide salts; and the provision of such methods which may be carried out at lower temperatures and/or which require shorter reaction times than were feasible heretofore. Other objects and features of the invention will be in part apparent and in part pointed out herein-after.

The present invention is broadly directed to methods for preparing radioiodinated organic compounds containing at least one iodine atom bound to an aromatic carbon atom which comprises combining the corresponding organic compound containing stable iodine atoms with an iodide salt containing a radioisotope of iodine and a suitable solvent therefore in the presence of a catalytic amount of copper and a time sufficient to effect substantial exchange between the stable iodine atoms and the radioisotopic iodine atoms, and thereafter recovering the resulting radioiodinated organic compound.

With the aid of the copper catalyst, radioiodine exchange can be effected with many organic compounds within a short time even at room temperature where otherwise prolonged reaction times and/or elevated temperatures would be necessary.

Even in the case of compounds where exchange proceeds reasonably well in the absence of a catalyst, the addition of copper is beneficial in that it permits the use of lower reaction temperatures and shorter reaction times, a particularly important consideration when working with heat-sensitive organic compounds and/or short-lived radioisotopes.

## DESCRIPTION OF THE PREFERRED EMBODIMENTS

The form in which the copper catalyst is added to the reaction mixture appears not to be critical. For example, it can be in the form of a small amount of copper powder or copper oxide, but it is usually more convenient to add a solution of a soluble copper salt, such as cupric sulfate, cupric chloride, cuprous, cupric nitrate, cupric acetate or other soluble copper salts known in the chemical arts.

Only very small amounts of copper are required to catalyze the exchange between the organically bound stable iodine atoms and the anionic radioactive iodine atoms. For example, as little as  $4.45 \times 10^{-4}$  mole of copper per gram atom of organically bound iodine has been found to be catalytically effective, while a ten-fold increase in the amount of catalyst was not appreciably more effective.

The choice of solvent depends primarily upon the solubility characteristics of the iodinated organic compound. If the latter compound is insoluble in water, a water-miscible solvent such as diglyme (diglycol methyl ether) is preferred, since it has been found that a small amount of water, e.g., 5% by volume of the total solvent, increases the effectiveness of the copper catalyst. However, other common organic solvents and solvent systems, whether or not miscible with water, can also be used.

## EXAMPLE 1

To a Pyrex tube constructed from 9 mm. O.D. tubing was added 100 mg. of 4-(3-dimethylaminopropyl-amino)-7-iodoquinoline followed by 4 ml. of diglyme that had been freshly distilled from sodium hydride. The mixture was warmed slightly to dissolve the iodinated compound, after which 100 microliters of a diglyme solution containing 4.0 millicuries of sodium iodide-131 and 100 microliters of an aqueous solution containing 0.1 mg. cupric

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sulfate were added. The water content of the mixture was approximately 5% by volume based on the diglyme. The tube was sealed and heated in an oil bath at a temperature of 160° C. for 17 hours.

The tube was then cooled and the contents were poured into 25 ml. of water made basic with 0.3 ml. of concentrated ammonium hydroxide. The basic solution was extracted 4 times with a total of 25 ml. of chloroform, and the chloroform extract was then extracted 4 times with a total volume of 23 ml. of 0.1 N hydrochloric

Finally, this acid extract was quantitatively transferred into a 25 ml. volumetric flask and diluted to volume with 0.1 N hydrochloric acid. Radioactivity measurement of the final solution showed that approximately 90% of the iodine-131 was incorporated in the iodine compound, allowance being made for natural decay of the radioisotope during the conversion. When the amount of cupric sulfate was reduced to 0.01 mg. the results were essentially the same, but when cupric sulfate was omitted entirely, all other conditions remaining the same, only 14.2% of the iodine-131 was incorporated in the iodinated compound.

#### EXAMPLE 2

The procedure described in Example 1 was modified as follows. The reaction tube was constructed from 9 mm. O.D. "Vycor" quartz tubing. To avoid adsorption of radioactive iodine by the quartz, the tube was pretreated with a solution of sodium bisulfite and sodium iodide as directed in the U.S. Pharmacopoeia XVII, page 800.

With these modifications the incorporation of radioactive iodine into the iodinated organic compound was essentially quantitative after 2 hours at 160° C. When copper sulfate and the pretreatment of the tube with sodium bisulfite and sodium iodide were omitted, all other conditions remaining the same, the incorporation of radioactive iodine was only 32.1% after 17 hours.

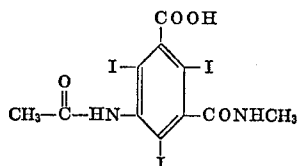
#### EXAMPLE 3

The organic compound of Examples 1 and 2 was also radioiodinated using mesitylene as the solvent with the following modifications in technique.

The mesitylene was shaken in a separatory funnel with an aqueous solution containing 0.1 mg. cupric sulfate per 100 microliters until the mesitylene was saturated with the solution. The sodium iodide-131 was introduced as before as a solution in diglyme. When the mixture was heated in a sealed quartz tube at 160° C. the incorporation of iodine-131 was 72.3% after 17 hours whereas, if the treatment with copper sulfate solution was omitted, the incorporation was only 54.9%.

#### EXAMPLE 4

Copper sulfate was used as follows to catalyze the radioiodination of iothalamic acid (5-acetamido-2,4,6-triiodo-N-methylisophthamic acid) whose structural formula is:



The exchange was carried out in an aqueous reaction mixture consisting of 1 N sodium hydroxide (150 microliters), pH 4.0 sodium acetate-acetic acid buffer (0.55 ml.), 10<sup>-3</sup> M potassium iodate (100 microliters) and water (10 microliters). Cupric sulfate (0.01 mg.) was dissolved in the water. The iothalamic acid (100 mg.) was dissolved in this solvent and to it was added a solution containing sodium iodide-131 (150 microcuries).

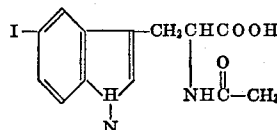
When the mixture was heated at 100° C. in a sealed Pyrex tube, 65.4% of iodine-131 was incorporated in the iothalamic acid after 1 hour and 85-86% was incorpo-

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rated after 18 hours. Without the cupric sulfate, the incorporation was only 58.6% after 1 hour.

#### EXAMPLE 5

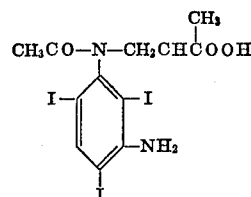
Copper also catalyzes the introduction of iodine-131 into N-acetyl-5-iodotryptophan whose structural formula is:



The reaction mixture contained the organic compound (50 mg.) and sodium iodide-131 dissolved in diglyme (2 ml.) to which was added 100 microliters of an aqueous solution containing 0.01 mg. of cupric sulfate. When this mixture was heated for 18 hours at 160° C. in a sealed Pyrex tube 72% of the iodine-131 was incorporated in the organic compound whereas, without the cupric sulfate and water, only 39% was incorporated after 17 hours.

#### EXAMPLE 6

The following substituted alkanolic acid, iocetamic acid, was also radioiodinated with the aid of a copper catalyst:



The reaction was carried out following the general procedure of Example 2. The reaction mixture contained 25 mg. of the above compound and approximately 100 microcuries of sodium iodide-131 dissolved in 1 ml. of diglyme.

When the reaction mixture also contained 5% water and 4 micrograms Cu as copper sulfate (1.5 × 10<sup>-3</sup> mole Cu per mole of the iodinated compound), the percentage incorporation of iodine-131 was 95.3% after 22 hours at 160° C.

When the copper catalyst was omitted, the percentage incorporation was 87.5% after 22 hours at 160° C.

When both the water and the copper catalyst were omitted, the percentage incorporation was only 77.5% after 22 hours at 160° C.

It will be understood that the method of the invention may be applied to various other organic compounds having an iodine atom bound to an aromatic carbon atom with similar results.

The invention accordingly comprises the methods hereinafter described, the scope of the invention being indicated in the following claims.

As various changes could be made in the above methods without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

What is claimed is:

1. In an isotope exchange process for preparing an iodinated organic compound enriched in radioiodine content containing at least one iodine atom bound to an aromatic carbon atom by combining an organic compound having at least one stable iodine atom bound to an aromatic carbon atom with an iodide salt containing a radioisotope of iodine in a solvent for said organic compound enriched in radioiodine content and thereafter recovering the resulting iodinated organic compound from the reaction mixture, the improvement which comprises incorporating a catalytic amount of copper in the reaction mixture to effect substantial exchange between the stable iodine atoms and the radioisotopic iodine atoms.

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2. A method according to claim 1 wherein the organic compound is an iodinated quinoline derivative.
3. A method according to claim 1 wherein the organic compound is an iodinated benzoic acid derivative.
4. A method according to claim 1 wherein the iodide salt is an alkali metal iodide.
5. A method according to claim 1 wherein the radioisotope of iodine is iodine-131.
6. A method according to claim 1 wherein the radioisotope of iodine is iodine-125.
7. A method according to claim 1 wherein the solvent contains approximately 5% water.
8. A method according to claim 1 wherein the solvent is diglycol methyl ether.
9. A method according to claim 1 wherein the organic compound is an iodinated indole derivative.
10. A method according to claim 1 wherein at least  $4.45 \times 10^{-4}$  mole of copper per gram atom of organically bound iodine is present as the catalytic amount of copper.
11. A method as set forth in claim 7, said copper being present in the form of a water soluble copper salt.

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DONALD G. DAUS, Primary Examiner

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260—326.14 T, 518 A; 424—1

UNITED STATES PATENT OFFICE  
CERTIFICATE OF CORRECTION

Patent No. 3,814,769 Dated June 4, 1974

Inventor(s) George B. Hoey, Donald R. Peckels and Philip E. Wiegert

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 1, second paragraph of the heading, "821,097" should read --821,093--.

Signed and sealed this 8th day of October 1974.

(SEAL)  
Attest:

McCOY M. GIBSON JR.  
Attesting Officer

C. MARSHALL DANN  
Commissioner of Patents

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Column 1, second paragraph of the heading and line  
30, "821,097" should read -- 821,093 --.

This certificate supersedes Certificate of Correction  
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Attest:

RUTH C. MASON  
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Commissioner of Patents  
and Trademarks

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