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# 3'-SUBSTITUTED-3,5-DIIODOTHYRONINE AND SALTS THEREOF

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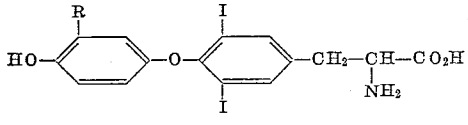
This invention relates to novel thyromimetic agents having a basic 3'-alkylated-3,5-diiodothyronine structure. More specifically the compounds of this invention have very potent pharmacodynamic activity such as in increasing the basal metabolic rate in hypothyroid conditions, inhibiting the thyrotopic hormone, treating goiter and decreasing the cholesterol content of the blood. The calorigenic activity of these compounds is unexpectedly pronounced.

The basic structure of the compounds of this invention is represented by the following formula:



Formula I

in which R is alkyl of from 2 to 7 carbon atoms or phenyl. The term "alkyl" as used here denotes all possible alkyl groups—straight, branched or cyclic such as cyclohexyl or cyclopentyl.

The preferred compounds are represented by Formula I when R is a branched chain acyclic alkyl group of from 3 to 7 carbon atoms. The preferred and advantageous compound of this invention is represented by Formula I when R is isopropyl, particularly in the L-series.

This invention also includes nontoxic, pharmaceutically acceptable salts of the amino acids of Formula I formed either through the acid function with cations such as ammonium, lower alkylated ammonium or alkali metal ions, for example potassium, sodium or calcium ions, or through the amine group with pharmacologically inert strong organic or inorganic acids such as hydrochloric, sulfuric or ethanedisulfonic acid. The salts are formed by methods known to the art such as by dissolving the parent amino acid in a dilute aqueous solution of the acid or base with heat or organic solvent then cooling to separate the salt.

The formulas used herein may be in the form of either DL, D or L isomers. When no designation herein is used any of these isomers can equivalently be present. The DL-mixtures are often preferred because of ease of preparation. If pure biological activity is desired the L-isomers are particularly potent as calorigenic agents while the D-isomers are particularly potent as cholesterol lowering agents. Generally speaking the L-isomers are preferred.

The compounds of this invention have surprising activity being the only thyromimetic compounds known to the applicants to date which have significantly more thyromimetic activity than has the commercial product, liothyronine (L-3'-3,5,-triiodothyronine). For example, L-3'-isopropyl - 3,5 - diiodothyronine of this invention is more than twice as active as liothyronine in the standard calorigenic test.

The fact that the compounds of this invention which have no iodine substituent in the phenolic ring of thyronine but rather are substituted by higher alkyl groups are the most active thyromimetics known to date is even more surprising when the prior art is considered.

The prior art compounds closest to those of the applicants are DL-2'-isopropyl-3,5-diiodothyronine of Zenker et al., J. Am. Chem. Soc., 81, 4643 (1959), and DL-3'-methyl-3,5-diiodothyronine of Pittman et al., Endocrinology, 68 (2), 248 (1961).

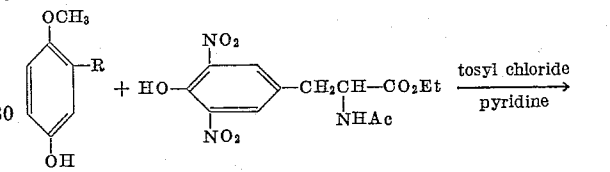


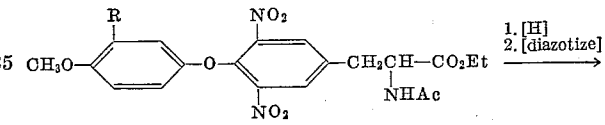
The DL-2'-isopropyl compound of Zenker et al. is only 5% as active as liothyronine in the calorigenic test. [see J. Biol. Chem. 235, 1732 (1960)]. The DL-3'-isopropyl-3,5-diiodothyronine of this invention is at least 17 times more active than the Zenker compound which is for all practical purposes inactive. The L-3'-isopropyl compound is at least 40 times more active.

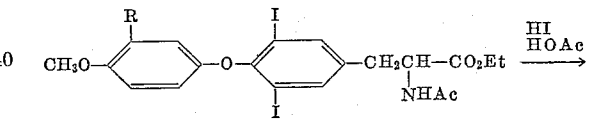
The DL-3'-isopropyl compound of this invention has been found to be 250 times more active as a hypocholester-olemic agent than DL-3'-methyl-3,5-diiodothyronine reported by Pittman et al. The DL-3'-ethyl compound is about 100 times as active as the prior art 3'-methyl. It is apparent that the closest related prior art compounds are, for all practical purposes inactive while the higher alkylated compounds of this invention are extremely potent and useful compounds with no untoward signs of toxicity.

The compounds of this invention are prepared by the following general synthetic methods starting from the known 3-alkyl-4-lower-alkoxyphenols (Method A) or from the known 2-alkyl lower-alkoxybenzenes (Method B.

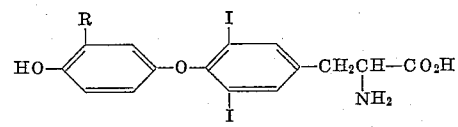
METHOD A





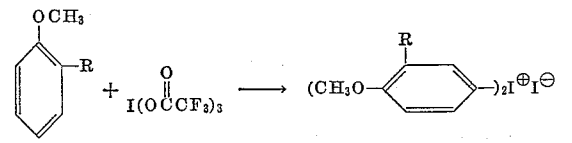


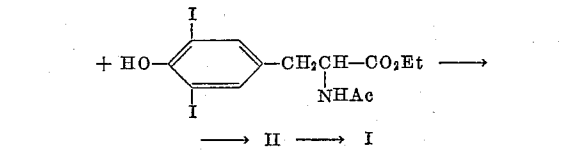
Formula II



Formula I

METHOD B





In the above processes other variations of the reactions and intermediates described will be apparent to those skilled in the art. The term "Ac" represents acetyl. All starting materials are known to the art. The processes to the ether ester intermediates (Formula II) are similar to those known to the art. These compounds are then converted to the desired amino acids of Formula I

by treatment with an excess of constant boiling hydriodic acid diluted with acetic acid. The reaction advantageously is carried out at elevated temperatures of from about 60° C. to the boiling point of the mixture for from about 30 minutes to about 6 hours. Other variations of these reaction conditions have proved to be of little advantage. The reaction mixtures are worked up by quenching in ice water, neutralizing with alkali and filtration of the separated product.

The compounds of this invention are used to treat the abnormal conditions outlined herebefore necessarily combined with a pharmaceutical carrier such as lactose, talc, ethylcellulose, glycerin monostearate, hydrogenated castor oil, etc. in a dosage unit adapted for internal administration in the form of a capsule, tablet, suppository, aqueous suspension, etc. In certain skin disorders a lotion or ointment form is desirable. The dose per dosage unit may vary widely as to the condition being treated and the weight of the patient but a range from about 0.5 to about 100 mcg. is particularly useful. A typical daily dosage regimen would be from 1 to about 200 mcg. Of course, conditions such as a marked increase of BMR or heart rate would warn of overdosing and warrant reducing the intake of drug. For use as a hypocholesterolemic agent compounds having less calorigenic activity for example the D-isomers may be used in somewhat higher doses than those described above.

Variations of this invention will be apparent to one skilled in the art such as other substitutions on the basic nucleus of this invention. The following examples are designed to make the practice of this invention fully apparent.

*Example 1*

(METHOD A)

A solution of 14.2 g. (0.041 mole) of N-acetyl-3,5-dinitro-L-tyrosine, ethyl ester (Clayton J. Chem. Soc., 1951, 2472) in 90 ml. of dry pyridine is stirred while 8.03 g. (0.042 mole) of p-toluenesulfonyl (tosyl) chloride is added. After heating on the steam bath for 10 minutes the mixture is mixed with a solution of 7.0 g. (0.042 mole) of 3-isopropyl-4-methoxyphenol in 10 ml. of pyridine. After heating at reflux for 1.5 hours, the mixture is evaporated under reduced pressure to remove the pyridine. The residue is taken up in chloroform. After washing, the dried organic extracts are evaporated to give an oily residue which crystallizes from ethanol, N-acetyl-3-[4-(4-methoxy-3-isopropylphenoxy) - 3,5 - dinitrophenyl]-L-alanine, ethyl, ester, M.P. 107–109° C.

This compound (9.6 g., 0.0195 mole) together with 2.3 g. of 10% palladium-on-charcoal and 200 ml. of acetic acid is hydrogenated at low pressure for about 30 minutes. The filtered reaction is added dropwise to a cooled solution of nitrosyl sulfuric acid (prepared from 100 ml. of acetic acid, 300 ml. of sulfuric acid at 60–70° C.) at 0° C. After stirring an hour at 0° C. the mixture is added to a stirred mixture of 41.5 g. of sodium iodide, 33.2 g. of iodine, 800 ml. of water and 500 ml. of chloroform. The mixture is stirred at room temperature for 2 hours and the organic layer separated. After washing, the dried organic layer is evaporated to give N-acetyl-3-[4-(4-methoxy-3-isopropylphenoxy)-3,5 - diiodophenyl]-L-alanine, ethyl ester, M.P. 128–130° C. from ethanol.

A mixture of 7.5 g. (0.0115 mole) of this compound, 50 ml. of constant boiling hydriodic acid and 65 ml. of acetic acid is heated under reflux for 3 hours. The mixture is poured into several volumes of ice water, then adjusted to pH 5–6 with 10% sodium hydroxide. The cooled mixture is filtered to give a pink precipitate which is recrystallized from ethanol containing a small amount of hydrochloric acid by the addition of an equal volume of water and hot 2 N sodium acetate to give the desired L-3′-isopropyl - 3,5 - diiodothyronine hemihydrate, M.P. 225–226° C.

*Example 2*

(METHOD B)

A mixture of 59.3 g. (0.32 mole) of o-cyclohexylanisole, 125 ml. of acetic anhydride and 20 ml. of trifluoroacetic acid is added dropwise at −10° C. to a solution of 0.16 mole of iodine trifluoroacetate in 50 ml. of acetic anhydride. The reaction mixture is stored in a refrigerator overnight and stirred at room temperature for 3 hours. The solvents are evaporated in vacuo to leave a dark oil which is taken up in 400 ml. of methanol. The solution is diluted with 75 ml. of 10% sodium bisulfite and 500 ml. of water containing 125 g. of potassium iodide. Addition of 125 ml. of ether precipitates a yellow solid, bis(3-cyclohexyl-4-methoxyphenyl)iodonium iodide, M.P. 167–168° C.

A mixture of 12.7 g. (0.02 mole) of this compound, 5.1 g. (0.01 mole) of N-acetyl-3,5-diiodo-DL-tyrosine, ethyl ester (J. Chem. Soc., 1950, 2824), 1.5 ml. of triethylamine, 0.1 g. of activated copper in 175 ml. of methanol is stirred at room temperature for 24 hours. The filtered solution is evaporated. The residue is taken up in benzene then washed with dilute hydrochloric acid. The precipitated amine salt is separated and the filtrate washed with water, 10% sodium hydroxide and then water. The dried benzene solution is concentrated to a yellow oil. Trituration with petroleum ether gives a white solid, N-acetyl-3-[4 - (3-cyclohexyl-4 - methoxyphenoxy) - 3,5-diiodophenyl-]-DL-alanine, ethyl ester, M.P. 143–144° C.

A mixture of 4.1 g. of the ester, 25 ml. of hydriodic acid and 40 ml. of acetic acid is heated at reflux for 5 hours, quenched and worked up as in Example 1 to give DL-3′-cyclohexyl-3,5-diiodothyronine, M.P. 228–230° C.

*Example 3*

A mixture of 7 g. of N-acetyl-3,5-dinitro-DL-tyrosine ethyl ester, 45 ml. of pyridine, 4 g. of tosyl chloride and 3.5 g. of 3-ethyl-4-methoxyphenol is reacted and worked up as in Example 1 to give N-acetyl-3[4-(4-methoxy-3-ethylphenoxy)-3,5-dinitrophenyl]-DL-alanine, ethyl ester, M.P. 125–127° C. This compound is catalytically reduced and diazotized in equimolar amounts as in Example 1 to give N-acetyl-3-[4-(4-methoxy-3-ethylphenoxy)-3,5-diiodophenyl]-DL-alanine, ethyl ester, M.P. 129–131° C. This intermediate (3 g.) is hydrolyzed with hydriodic acid-glacial acetic acid by a one hour reflux period to give DL-3′-ethyl-3,5-diiodothyronine hemihydrate, M.P. 232–234° C.

*Example 4*

Substituting equimolar quantities of o-tert. butylanisole for o-cyclohexylanisole of Example 2 gives the bis(3-tert. butyl-4-methoxyphenyl)iodonium iodide, M.P. 177–178° C., then N-acetyl-3-[4-(3-tert. butyl-4-methoxyphenoxy)-3,5-diiodophenyl]-DL-alanine, ethyl ester, M.P. 137–139° C. and finally DL-3′-tert. butyl-3,5-diiodothyronine.

*Example 5*

Substituting equimolar quantities of either DL or D N-acetyl-3,5-dinitrotyrosine, ethyl ester for the L compound of Example 1 gives first the dinitro intermediates (DL, M.P. 128–130° C. and D, M.P. 104–105° C.) then the diiodo intermediates (DL, M.P. 116–118° C. and D, M.P. 119–121° C.) and finally DL-3′-isopropyl-3,5-diiodothyronine hemihydrate, M.P. 202–204° C. as well as D-3′-isopropyl-3,5-diiodothyronine hemihydrate, M.P. 224–226° C.

*Example 6*

Substituting equimolar quantities of 3-phenyl-4-methoxyphenol for the 3-isopropyl-4-methoxyphenol of Example 1 and working in the DL series gives the dinitro compound, M.P. 173–175° C., the diiodo intermediate, M.P. 128–130° C. and finally DL-3′-phenyl-3,5-diiodothyronine hydrate, M.P. 219–221° C.

*Example 7*

Substituting o-isopropylanisole for o-cyclohexylanisole in Example 2 gives bis(3-isopropyl-4-methoxyphenyl) iodonium iodide, M.P. 148–150° C. as well as the other compounds with melting points as mentioned in Example 5.

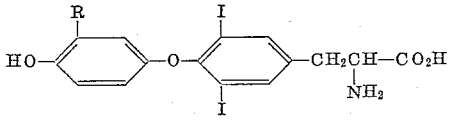
*Example 8*

L-3'-isopropyl-3,5-diiodothyronine (500 mg.) is heated in 50 ml. of 2% sodium carbonate solution until the mixture is clear. Cooling separates the sodium salt. Another sample (250 mg.) is heated with 5% hydrochloric acid. The cooled solution gives the hydrochloride salt.

DL-3'-isopropyl-3,5-diiodothyronine (500 mg.) is dissolved in acetone and reacted with hydrogen chloride to separate the salt. Another portion (250 mg.) is heated with dilute potassium carbonate to give the potassium salt on cooling. Similarly the calcium salt is prepared.

What is claimed is:

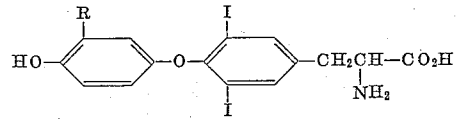
1. A chemical compound of the formula:






in which R is a member selected from the group consisting of phenyl and alkyl having from 2 to 7 carbon atoms.

2. A chemical compound of the formula:




in which R is a branched acyclic alkyl group of from 3 to 7 carbon atoms.

3. L-3'-isopropyl-3,5-diiodothyronine.

4. DL-3'-isopropyl-3,5-diiodothyronine.

5. DL-3'-cyclohexyl-3,5-diiodothyronine.

6. DL-3'-phenyl-3,5-diiodothyronine.

7. The sodium salt of L-3'-isopropyl-3,5-diiodothyronine.

8. The hydrochloride salt of L-3'-isopropyl-3,5-diiodothyronine.

**References Cited** in the file of this patent

UNITED STATES PATENTS

2,970,165 Michel et al. ---------- Jan. 31, 1961