fractions with Claisen alkali. Distillation of the neutral fraction gave 0.68 g. (5%) of unchanged ether and 0.47 g. (3.5%) of undistillable material. The acidic fraction on distillation yielded 8.84 g. (65% by weight) and 2.49 g. (18%) of tar. The main fraction was redistilled and the presence of a higher-boiling fraction (about 57%) and a lower-boiling substance (about 10%) was indicated. Rearrangement of 55 g. of the ether and more extensive fractionation of the product allowed the separation of the two components, and their identification as follows:

4-Allyl-2,6-dichlorophenol (the expected rearrangement product) was obtained crystalline from the higher-boiling fractions; b. p. 104–108° (3 mm.); m. p. 33–35°. *Anal.* Calcd. for $C_9H_8OCl_2$: C, 53.2; H, 4.0; Cl, 34.9. Found: C, 53.2; H, 4.0; Cl, 34.8.

2-Allyl-6-chlorophenol was obtained from the lower-boiling fractions, and characterized as the α-naphthylurethan, m. p. 125–126°, which gave no depression when mixed with the derivative prepared below from the rearrangement product of allyl 2-chlorophenyl ether.

Allyl 2-Chlorophenyl Ether.—A mixture of 9.0 g. of sodium hydroxide, 50 cc. of water, 100 cc. of acetone, 25.7 g. of 2-chlorophenol and 30.3 g. of allyl bromide was refluxed one hour and worked up in the usual way. The yield was 90%; b. p. 108–110° (15 mm.); $n^{25}D$ 1.5388; d^{25}_{25} 1.132; MD calcd., 46.2; found, 46.6.

Anal. Calcd. for C_9H_9OCl: C, 64.1; H, 5.4. Found: C, 64.0; H, 5.3.

2-Allyl-6-chlorophenol.—A sample of 2.59 g. of the ether was refluxed gently over a free flame for ten minutes, during which the boiling temperature rose from 220 to 223.5° and the liquid turned light red. It was then distilled, and 2.31 g. (89%) collected at 215–220° (750 mm.); $n^{25}D$ 1.5447. There was no undistillable residue, the remainder being held back in the column of the distilling flask. The distillate was pure, as shown by redistillation under diminished pressure, collecting two fractions at 61–63° (1 mm.) having $n^{25}D$ 1.5447 and 1.5445.

Anal. Calcd. for C_9H_9OCl: C, 64.1; H, 5.4. Found: C, 64.1; H, 5.4.

The **α-naphthylurethan** was prepared, m. p. 125–126°, and gave no depression with the derivative prepared from the rearrangement product of allyl 2,6-dichlorophenyl ether.

Anal. Calcd. for $C_{20}H_{16}O_2NCl$: C, 71.1; H, 4.8. Found: C, 71.3; H, 4.9.

Summary

1. 4-Crotyloxy-3,5-dichlorobenzoic acid rearranges without inversion to give 4-crotyl-2,6-dichlorophenol; the rearrangement does not take place in the presence of dimethylaniline.

2. 4-*s*-Butyl-2,6-dichlorophenol and 4-*n*-butyl-2,6-dichlorophenol have been synthesized and characterized. An abnormal Fries reaction was observed during the synthetic work.

3. Allyl 2,6 dichlorophenyl ether rearranges more slowly than 4-crotyloxy-3,5-dichlorobenzoic acid and gives 2-allyl-6-chlorophenol in addition to the normal product.

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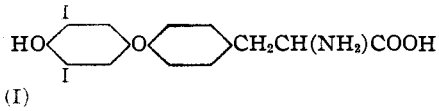
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

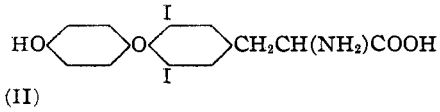
The Synthesis of 3′,5′-Diiodothyronine

BY PAUL BLOCK, JR., AND GARFIELD POWELL

Although several isomers and analogs of thyroxine have been prepared since the original synthesis of this important hormone-like compound by Harington,[1] the absence from the list of the closely related substance, 3′,5′-diiodothyronine (I), has heretofore constituted a gap in the series.



(I)



(II)

This compound, the synthesis of which we now report, has interest both chemically and physiologically. Harington long ago reported his inability to obtain any pure compound from the iodination of thyronine, the completely uniodinated thyroxine. We have amply confirmed this observation. The use of various methods of iodination invariably led to a decomposing mixture of uncertain iodine content. The present synthesis proves that pure 3′,5′-diiodothyronine is a comparatively stable compound, and furnishes a foundation for an investigation of the question of why 3,5-diiodothyronine (II) can be iodinated smoothly to the tetraiodo compound, thyroxine, while thyronine itself cannot be iodinated at all.

We were enabled to synthesize 3′,5′-diiodothyronine along the lines laid down for the synthesis of thyroxine by Harington after we had found a method for hydrolyzing ethers of ortho iodophenols

(1) Harington, *Biochem. J.*, **21**, 169 (1927).

without also reducing the iodine. This hydrolysis consisted of the carefully controlled use of a dilute solution of constant-boiling hydrobromic acid in acetic acid.

Another modification of the procedure in use for preparation of thyroxine analogs was a return to more drastic conditions for forming the diphenyl ether linkage. This was necessitated by the lesser reactivity of the halogen atom in *p*-chloro or *p*-iodonitrobenzene than of the para iodine atom in 3,4,5-triiodonitrobenzene which has invariably been used in synthesizing this class of compounds.

3′,5′-Diiodothyronine is a white, microcrystalline substance, quite stable at ordinary temperatures, but losing iodine when warmed either in solution or in the dry state. It is purified from traces of its *o*-methyl derivative which remain after the hydrolysis by taking advantage of the insolubility of the latter in 0.1 *N* potassium carbonate solution, and it is separated from thyronine, which is also present after the hydrolysis, by recrystallization of the hydrochlorides from dilute hydrochloric acid. After several such recrystallizations, the product approaches analytical purity if the final liberation of the free amino acid and its subsequent drying take place in the cold.

The desirability of a study of the physiological action of 3′,5′-diiodothyronine has been pointed out by Harington.[2] This compound and its isomer, 3,5-diiodothyronine (II), are structurally half way between thyroxine and inactive thyronine. A comparison of these two diiodinated compounds should help to clarify the relative importance of the 3,5 and the 3′,5′ iodine atoms, as far as biological potency is concerned.

The physiological testing of 3′,5′-diiodothyronine on a human myxedemic patient has been undertaken by Dr. W. T. Salter of the Department of Pharmacology, School of Medicine, Yale University. Preliminary results[3] using this highly specific assay method have shown that the compound is inactive in doses four times larger than thyroxine. On the basis of these incomplete results, it can only be said that the compound is less than one-fourth as active as thyroxine, if, in fact, it has any physiological activity at all.

Experimental

2,6-Diiodo-*p*-nitrophenol (III).—We found the use of iodine monochloride more satisfactory than any of the methods described in the literature for the preparation of this compound.[4]

In a flask fitted with a mechanical stirrer and a reflux condenser a solution of 278 g. of *p*-nitrophenol in 750 cc. of acetic acid was heated to the boiling point. The source of heat was removed and a solution of 660 g. of iodine monochloride in 500 cc. of acetic acid was added rapidly while the reaction was stirred strongly. Fifteen minutes after the addition of the iodine monochloride solution, 1 liter of boiling water was added, and, with continued stirring, the temperature of the reaction was raised to 95°. After thirty minutes, a second liter of boiling water was added, and the temperature readjusted, if necessary to 95°, and stirring continued for another thirty minutes. A third liter of boiling water was then added, and after five minutes the stirring was stopped and the solution containing the precipitated diiodo compound was allowed to cool to room temperature. After addition of sodium bisulfite to remove traces of free iodine, the product was filtered and washed with dilute acetic acid and water; yield, 640 to 675 g. (82 to 87%) melting at 155°. After recrystallization from acetic acid the product melted at 155.5°.

The crude material was purified by converting it into the potassium salt, in which form it was used for the next reaction. The free phenol (130 g.) was dissolved in 1300 cc. of boiling water containing 25 g. of potassium hydroxide. On cooling the solution deposited 130 g. (90%) of the potassium salt (IV). The air-dried salt was anhydrous, as was shown by an iodine analysis.

Anal. Calcd. for $C_6H_2O_3I_2NK$: I, 59.2. Found: I, 59.1.

2,6-Diiodo-*p*-nitroanisole (V).—Although reports of the preparation of this compound have appeared,[5,6] the following modification of a method of methylation due to Ullmann[7] had definite advantages.

Anhydrous potassium carbonate (10 g.) was added to 140 g. of dimethyl sulfate and the mixture shaken until litmus paper was not turned red by it. The potassium salt of the phenol (IV) (429 g.) was added, followed by sufficient nitrobenzene to render the reaction mixture fluid enough for efficient stirring. The flask was heated slowly to 130° and the reaction stirred at that temperature for thirty minutes after the orange color of the potassium salt had completely disappeared. A solution of 20 g. of sodium hydroxide in 600 cc. of water was then added, and the reaction was heated under reflux for one hour. After cooling, the aqueous layer was separated and washed with benzene. The benzene was combined with the nitrobenzene layer and any solid which might have crystallized out, and the whole steam distilled until all of the nitrobenzene had passed over. The solid residue was washed twice with hot sodium hydroxide solution and recrystallized from alcohol containing a small amount of benzene. The product weighed 343 g. (85%) and melted at 133.5–134.5°. After a second recrystallization from alcohol, it melted at 136.5°.

2,6-Diiodo-*p*-aminoanisole Hydrochloride (VI).—The literature reports the preparation of this compound by the

(2) C. R. Harington, "The Thyroid Gland," Oxford Univ. Press, New York, N. Y., 1933, p. 144.

(3) Personal communication from Dr. Salter.

(4) Busch, *Ber.*, **7**, 462 (1874); Weselsky, *Ann.*, **174**, 108 (1874); Körner, *Z. Chem.*, 324 (1868); Datta and Prosad, THIS JOURNAL, **39**, 446 (1917).

(5) Brenans, *Bull. soc. chim.*, [3] **27**, 400 (1902).

(6) Kalb, Schweizer, Zellner and Berthold, *Ber.*, **59**, 1869 (1926).

(7) Ullmann, *Ann.*, **327**, 114 (1903).

reduction of the nitro compound (V) using stannous chloride.[6] The following method employing iron was equally satisfactory and more practical where considerable quantities of the nitro compound were to be reduced. To 2 liters of 50% alcohol containing 20 cc. of acetic acid were added 162 g. of the nitro compound (V) and an equal weight of iron partly as coarse filings and partly as fine powder. The reaction was boiled strongly under reflux for six hours, after which the alcohol was removed by distillation, and the residue allowed to cool overnight. The mixture of amine and iron was filtered off and extracted three times with boiling benzene. The benzene was dried and saturated in the cold with dry hydrogen chloride. The precipitated amine hydrochloride was carefully washed with cold benzene when it was pure enough for use in the next reaction. It melted at 208–209°; yield, 90%. The free amine, prepared by neutralizing a solution of the amine hydrochloride in dilute alcohol, melted at 105°.

The melting point given previously for this compound was 100°.[6]

3,5-Diiodo-*p*-methoxyphenol (VII).—The amine hydrochloride (VI) (72.5 g.) was finely ground and suspended in 710 cc. of acetic acid. After adding 9.5 cc. of sulfuric acid, the suspension was diazotized by the slow addition of 22 g. of butyl nitrite to the well-stirred reaction, the temperature being held at 15–18°. During the reaction the salts of the amine dissolved and some diazonium salt precipitated out. After standing for thirty minutes at room temperature, the suspension was poured into the hot solution formed by adding 385 cc. of sulfuric acid to 710 cc. of water. The resulting clear, orange solution was heated slowly to 110° while being stirred, and held at this temperature for thirty minutes. After cooling somewhat, a little sodium bisulfite was added, followed by 765 cc. of water. The solution containing the precipitated phenol was placed in an ice box overnight. The precipitate was filtered and extracted twice with boiling 0.5 *N* sodium hydroxide, using 400 and 100 cc. The combined solutions were treated with Norite and filtered through paper pulp several times to remove an oily impurity. The phenol resulted on acidification. It was redissolved in sodium hydroxide, treated with a small amount of Norite, and reprecipitated; yield, 50 g. (75%); m. p. 123–123.5°. For analysis the product was recrystallized twice from alcohol, and melted at 125–125.5°.

Anal. Calcd. for $C_7H_6O_2I_2$: C, 22.3; H, 2.0; I, 67.55. Found: C, 22.8; H, 1.8; I, 67.6.

3,5-Diiodo-1,4-dimethoxybenzene (VIII).—In 10 cc. of water containing 1 g. of sodium hydroxide, 0.6 g. of the phenol (VII) was dissolved, and the solution was treated with 0.4 cc. of dimethyl sulfate. After a few minutes the solution was heated to 60° with shaking, then allowed to stand fifteen minutes. The resulting crystals were washed with water twice by decantation and recrystallized from alcohol after which they melted at 55–55.5°.

As a further check on the structure of this compound, it was prepared by the methylation of 3,5-diiodohydroquinone, a compound which had previously been synthesized from 3,5-diiodo-*p*-quinone by Seifert.[8] The quinone itself had been made by this worker by oxidizing diiodo-*p*-aminophenol. It had also been prepared by oxidizing 3,5-diiodo-*p*-phenylenediamine[9] and in negligible yields by the oxidation of other 3,5-diiodobenzenes substituted in the 1,4 positions. A more convenient method than any of these for the preparation of 3,5-dihalogenated paraquinones was indicated by the work of Van Erp in his preparation of the bromine analog.[10] This method was found to be quite satisfactory for the iodine compound, as follows: A solution of 100 g. of 3,5-diiodo-*p*-nitrophenol (III) in 300 cc. of acetic acid was heated to the boiling point and treated with 60 g. of tin while stirring briskly. The end of the reaction was preceded by a fall in the temperature of the reaction and could be further ascertained by adding a drop of the reaction mixture to some sodium hydroxide solution which no longer turned yellow from the alkali salt of unreacted nitrophenol. The cooled reaction mixture was filtered from some unreacted tin into a cold solution of 375 cc. of sulfuric acid in 3750 cc. of water. A solution of 82.5 g. of chromium trioxide in 75 cc. of water was added dropwise with stirring, the temperature being held at 28°. Stirring was continued for two hours. The crude brick red product was filtered off and recrystallized from benzene, yield, 64 g. of glittering yellow plates; m. p. 180.5° (70%, lower than the yield reported for the bromine analog, 87%). Sulfur dioxide was bubbled through a stirred suspension of 41 g. of the quinone in 700 cc. of water until the solution smelled strongly of the gas. The hydroquinone which formed was allowed to stand for several hours; it was then filtered and washed with cold water; yield, 40 g. of white needles, decomposing at 142–143° after recrystallization from water. The diiodohydroquinone was methylated precisely as was the diiodomethoxyphenol above. The melting point of the product, recrystallized once from alcohol, was 56°.

Anal. Calcd. for $C_8H_8O_2I_2$: C, 24.6; H, 2.05; I, 65.1. Found: C, 24.8; H, 2.06; I, 65.5.

A mixture of the two samples of diiododimethoxybenzene melted at 55.5–56°.

4-(3′,5′-Diiodo-4′-methoxyphenoxy)-nitrobenzene (IX).—To 11 g. of potassium hydroxide enough water was added to make a clear solution at 100°. To this hot solution 56.6 g. of the phenol (VII) was added, and the mixture stirred until homogeneous. The cooled, hardened mass was cut into small pieces which were added slowly with stirring to 31.5 g. of *p*-chloronitrobenzene heated in a metal bath to 130°. The addition occupied forty-five minutes. The temperature of the reaction was then raised to 160° and held there for ten minutes after any bubbling had ceased. After cooling, water was added to the flask, a little acetic acid was added to ensure acidity, and the mixture was steam distilled until no more *p*-chloronitrobenzene passed over. The residue was taken up in 300 cc. of benzene, washed twice with dilute sodium hydroxide, once with water, and most of the benzene was distilled off. Alcohol was added to the sirupy residue, and distillation continued to incipient precipitation. After icing overnight, the filtered and dried precipitate weighed 52 g. (70%); m. p. 123.5–124°. For analysis the yellow needles were recrystallized from alcohol with the aid of a little benzene; m. p. 124–124.5°.

(8) Seifert, *J. prakt. Chem.*, [2] **28**, 438 (1883).

(9) Willgerodt and Arnold, *Ber.*, **34**, 3351 (1901).

(10) Van Erp, *Rec. trav. chim.*, **30**, 284 (1911).

Anal. Calcd. for $C_{13}H_9O_4NI_2$: C, 31.4; H, 1.8; I, 51.1. Found: C, 31.5; H, 1.8; I, 51.3.

The nitro compound (0.5 g.) was dissolved in 25 cc. of alcohol containing 1 cc. of 10% sodium hydroxide solution. Palladium hydroxide precipitated on calcium carbonate,[11] (2.5 g.) was added as a catalyst and the solution shaken with hydrogen at atmospheric pressure until no hydrogen was absorbed. The absorption, after deducting a blank value for the catalyst, was equivalent to 5.2 moles; theoretical for reduction of 2 iodine atoms and 1 nitro group, 5 moles. The catalyst was filtered off and the alcoholic solution was evaporated to 2–3 cc. On adding water, a precipitate appeared which after two recrystallizations from alcohol melted at 77°. The literature gives for *p*-(*p*'-methoxyphenoxy)-aniline 79°[12] and 81–82°.[13] With acetic anhydride the compound gave an acetyl derivative melting at 133.5° after recrystallization from dilute alcohol; given, 131°.

4-(3',5'-Diiodo-4'-methoxyphenoxy)-aniline Hydrochloride (X).—The nitro compound (IX) was reduced by the same method as compound (V). Forty grams was suspended in a solution containing 400 cc. of alcohol, 360 cc. of water and 40 cc. of acetic acid, and 20 g. each of coarse iron filings and iron powder were added. The reaction was refluxed on a steam-bath for three hours, after which the flask was set for distillation and heated another hour and a half until boiling ceased. After cooling, the precipitate was filtered and extracted three times with boiling benzene, using successively 300, 200, and 100 cc. The combined benzene solutions were dried by boiling, cooled and saturated with dry hydrogen chloride. The yield of the amine hydrochloride was 36.5 g., or 90%. Heated rapidly from 210°, the compound melted at 232–233° after recrystallization from dilute alcohol containing hydrochloric acid. The free amine was prepared by neutralizing a solution of the hydrochloride in dilute alcohol. It was recrystallized twice from alcohol and melted at 105.5°.

Anal. Calcd. for $C_{13}H_{11}O_2NI_2$: C, 33.4; H, 2.35; I, 54.4. Found: C, 33.8; H, 2.6; I, 54.5.

Treated with acetic anhydride, the amine gave an acetyl derivative melting at 176.5°.

The amine was hydrogenated in the same manner as the nitro compound (IX) to give the same reduction product. The hydrogen absorbed amounted to 2.2 moles, theoretical 2 moles, and the iodine-free amine melted at 78° and its acetyl derivative at 133.5–134.5°.

4-(3',5'-Diiodo-4'-methoxyphenoxy)-benzonitrile (XI).—The amine hydrochloride (X) (40 g.) was suspended in 400 cc. of acetic acid and diazotized by the slow addition of 10 g. of butyl nitrite at 15–18°. The clear solution was stirred for thirty minutes at room temperature and poured into a cold solution made by adding 185 g. of sodium cyanide in 400 cc. of water to 215 g. of copper sulfate in 800 cc. of water. The reaction was stirred for one hour, then heated to 97° and allowed to cool. The supernatant liquid and inorganic crystals were carefully siphoned off the tarry mass which remained on the bottom of the reaction vessel, and this was extracted three times with boiling benzene. The benzene was dried and passed through a column of activated alumina.[14] It was important that all trace of reddish tinge be removed from the solution which should be a light yellow. The benzene was removed, and the oil remaining was crystallized from a mixture of alcohol and ether[15]; yield, 15 g. (40%) of yellow crystals melting at 138.5–139.5°, after softening at 133.5–134.5°. The product from the benzene extraction may also be isolated by removing the benzene and distilling the resulting dark red oil at 0.1 mm. After crystallization from alcohol the crystals obtained were lighter in color, but the melting point, analysis and yield were the same as when the product was isolated without distillation.

Anal. Calcd. for $C_{14}H_9O_2NI_2$: C, 35.2; H, 1.9; I, 53.25. Found: C, 35.4; H, 2.0; I, 53.2.

4-(3',5'-Diiodo-4'-methoxyphenoxy)-benzaldehyde (XII).—Dry hydrogen chloride was bubbled through a suspension of 28 g. of anhydrous stannous chloride in 140 cc. of dry ether kept below 20° in a water-bath until the solid had gone into solution and only two liquid layers remained. To this was added a solution of 12 g. of the nitrile (XI) in 20 cc. of anhydrous chloroform, and the reaction shaken three hours. The pressure was released from the flask and the yellow crystals of the aldimine hydrochloride–stannic chloride complex were allowed to remain in the refrigerator overnight. These were separated, boiled five minutes with dilute hydrochloric acid, and the resulting aldehyde, after it had solidified, was filtered off and recrystallized from 70% acetic acid; yield, 6.5 g. (55%); m. p. 116.5–118.5°. For analysis the aldehyde was recrystallized a second time from 70% acetic acid; m. p. 119° after softening several degrees lower.

Anal. Calcd. for $C_{14}H_{10}O_3I_2$: C, 35.0; H, 2.1; I, 52.9. Found: C, 35.1; H, 2.25; I, 53.2.

α-Benzoylamino-4-(3',5'-diiodo-4'-methoxyphenoxy)-cinnamic Acid (XIII).—The azlactone of this compound was prepared by heating on a steam-bath for one hour 4.8 g. of the aldehyde (XII) with 4 cc. of acetic anhydride, 2.4 g. of hippuric acid, and 1 g. of anhydrous sodium acetate. The yellow mass was treated with 200 cc. of boiling water, and after standing to decompose the excess acetic anhydride was washed with a second 200 cc. of boiling water. The crude azlactone was boiled for five minutes in a solution containing 180 cc. of ethanol, 60 cc. of water and 4 g. of sodium hydroxide. Water (240 cc.) was added and the solution heated again to boiling, cooled, filtered, and acidified with dilute hydrochloric acid. After a second precipitation from aqueous sodium hydroxide solution, the product was sufficiently pure for the next reaction; yield, 5.5 g. (85% based on the aldehyde). For analysis it was recrystallized from acetic acid, m. p. 230–231°.

Anal. Calcd. for $C_{23}H_{17}O_5NI_2$: C, 43.1; H, 2.65; I, 39.6. Found: C, 43.5; H, 2.7; I, 39.2.

3',5'-Diiodothyronine (I).—Three grams of the above cinnamic acid derivative was refluxed for one hour and a half in 45 cc. of acetic acid to which had been added 3 g. of red phosphorus and 1.2 cc. of constant-boiling hydriodic

(11) Busch and Stove, *Ber.*, **49**, 1063 (1916).
(12) Stohr, *Z. physiol. Chem.*, **201**, 146 (1931).
(13) Oesterlin, *Monatsh.*, **57**, 42 (1931).
(14) Bovarnick, Bloch and Foster, THIS JOURNAL, **61**, 2473 (1939).
(15) Schuegraf, *Helv. chim. acta*, **12**, 409 (1928).

acid containing 0.5% of hypophosphorous acid. Constant-boiling hydrobromic acid (7.5 cc.) was added and the refluxing continued for three and a quarter hours longer. The solution was filtered through asbestos, and the phosphorus washed with hot acetic acid. The combined filtrates were evaporated almost to dryness at reduced pressure. The residue was taken up in water and extracted with ether; the ether was washed with a little water and the combined aqueous layer washed twice more with ether. The water solution with a final volume of about 60 cc. was heated to boiling to expel ether, removed from the hot-plate and neutralized by the cautious addition of powdered sodium acetate until basic to congo red paper. After refrigerating overnight, the precipitate was filtered, washed with water and dissolved in the minimum quantity of boiling 0.1 *N* potassium carbonate solution. This was placed in the ice box overnight, centrifuged, and the clear solution treated in the cold with acetic acid to precipitate the amino acid. After carefully warming the solution in a water-bath with stirring until the precipitate was no longer gelatinous, it was allowed to remain in the refrigerator. The dissolution in boiling carbonate and subsequent reprecipitation were repeated. The amino acid was then dissolved in boiling dilute hydrochloric acid and separated from a small amount of a dark flocculent precipitate. The solution was cooled and concentrated hydrochloric acid added to precipitate the hydrochloride of the thyronine. After several hours in the refrigerator, the hydrochloride was separated and dissolved in boiling water containing a little hydrochloric acid and the free amino acid precipitated with sodium acetate. The product, a white microcrystalline powder, was substantially pure. For analysis, however, it was necessary to repeat several times the solution in dilute hydrochloric acid and precipitation by concentrated hydrochloric acid before liberating the free amino acid by sodium acetate. The product had to be carefully dried in a vacuum desiccator at room temperature, as heating caused loss of iodine, not only when the compound was in the dry state, but also in neutral solution.

Anal. Calcd. for $C_{15}H_{13}O_4NI_2$: C, 34.3; H, 2.5; I, 48.4; OCH_3, 0. Found: C, 34.8; H, 2.7; I, 47.9; OCH_3, 0.

The 3′,5′-diiodothyronine gave a positive Kendall test and a positive ninhydrin reaction. It decomposed with evolution of iodine at 206° when heated rapidly from 190°.

One-tenth gram of the diiodothyronine was dissolved in 10 cc. of 1 *N* sodium hydroxide solution and shaken with hydrogen using the Busch–Stove paliadium hydroxide on calcium carbonate catalyst. The solution was evaporated to 1 cc., and acidified with acetic acid. After standing in the ice box overnight the precipitate was centrifuged and crystallized twice from 1–1 hydrochloric acid. The product was separated and dried over potassium hydroxide. It decomposed at 238–239° (uncor.) when heated at 10° per minute from 230°. Some of the product was dissolved in hot water and precipitated with sodium acetate. This decomposed at 252–253° (uncor.), heated at the rate of 10° per minute from 233°. Harington gives for thyronine hydrochloride 238–240°, and for thyronine 253–254°. Both of these compounds exhibited a positive Kendall reaction, turning yellow instead of cherry as in the case of compounds containing the iodophenol group, as noted by Harington.[16] Both of these compounds crystallized in the spherules highly typical of thyronine and its hydrochloride.

***o*-Methyl-3′,5′-diiodothyronine (XIV).**—The cinnamic acid derivative (1 g.) was treated as above with 1 g. of red phosphorus and 0.4 cc. of hydriodic acid in 15 cc. of acetic acid. After one and a half hours, 2.5 cc. of hydrobromic acid was added and refluxing continued for one and a quarter hours. The solution was treated as above, retaining, however, the precipitate which came down on icing the solution of the crude material in 0.1 *N* potassium carbonate. The filtrate was discarded as no pure compound could be isolated from it. The precipitate was dissolved in a little water and the free amino acid precipitated by means of acetic acid. This was recrystallized from dilute alcohol. About 100 mg. of *o*-methyl-diiodothyronine was obtained as white microcrystals decomposing without evolution of iodine at 212° when heated rapidly from 190°. The substance gave no Kendall test. For analysis the compound was again dissolved in the minimum quantity of boiling potassium carbonate solution, and the precipitated potassium salt converted to the free amino acid.

Anal. Calcd. for $C_{16}H_{15}O_4NI_2$: C, 35.6; H, 2.8; I, 47.1; OCH_3, 5.75. Found: C, 36.0; H, 3.0; I, 46.8; OCH_3, 5.7.

Summary

For the purpose of inquiry into the mechanism of the action of thyroxine 3′,5′-di-iodo-thyronine has been prepared. 4-(3′,5′-Di-iodo-4′-methoxyphenoxy)-nitrobenzene was converted to the amine, nitrile, aldehyde successively and then condensed with hippuric acid. The resulting α-benzoylamino-4-(3′,5′-diiodo-4′-methoxyphenoxy)-cinnamic acid was reduced with very dilute hydriodic acid. Demethylation and debenzoylation was effected, without attack on the iodo groups, by the use of a dilute solution of hydrobromic acid in acetic acid.

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(16) Harington, *Biochem. J.*, **20**, 304 (1926).