Enzymic Conversion of Iodinated Thyronines to Iodinated Thyroacetic Acids*  
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(Received for publication, July 11, 1960)  

A previous paper (1) from these laboratories described the enzymic conversion of thyroxine and triiodothyronine to their corresponding acetic acid analogues. The enzyme system responsible for the degradation of the alanine side chain of these compounds was found in the mitochondria of rat kidney homogenate. It has since been shown to be most active in kidney, but to occur also in the mitochondria of liver (2, 3), heart muscle (2), and brain (2, 4).

Further examination of the specificity of this enzyme system has shown that in addition to thyroxine and triiodothyronine, 3,5 diiodothyronine, 3'-iodothyronine, and even thyronine are converted to their corresponding thyroacetic acids. This indicates that the enzyme system is not specific for the substituents on the thyronine rings. The main problem which remained was to determine the pathway by which the thyronines are converted to thyroacetic analogues. Attempts to identify intermediates on this pathway have been unsuccessful, and the synthesis of possible intermediates was therefore undertaken. The biological activity and metabolic conversions of these intermediates are presented in this paper.

EXPERIMENTAL PROCEDURE

Incubation, extraction, and chromatographic techniques were similar to those described before (1). The incubation mixture consisted of 5 ml of 0.1 M phosphate buffer, pH 7.4, 25 mmoles of DPN, and 15 ml of sonically treated rat (Sprague-Dawley, male, 200 to 250 g) kidney mitochondria. From 1 to 2 mg of the substrates were employed. This amount of thyroethanols was dissolved in 0.5 to 1 ml of 50% propyleneglycol; the thyronines were dissolved in 0.5 ml of 0.2 N Na2CO3. The incubation was carried out in 250-ml Erlenmeyer flasks for 2 hours at 37°C. After the reaction mixture was extracted with 10 volumes of n-butanol-concentrated NH4OH (50:1, volume for volume), the concentrated crude material was chromatographed on Whatman No. 3MM paper (descending, about 15 hours at room temperature) with tertiary amyl alcohol saturated with NHOH as solvent. The compounds were located on a strip cut from the dried paper by spraying with 4-aminoantipyrine reagent (5).

For purification of radioactive triiodothyroethanol, after chromatography, the dry paper was cut into 1-cm-wide pieces and the activity was counted with a Geiger counter. The main product was rechromatographed as above.

Commercially available materials were from the following sources: DPN, Pabst Laboratories; 4-aminoantipyrine, Eastman Kodak; p-methoxyphenylacetic acid, Matheson Company; D-thyronine, Nutritional Biochemical Corporation; 3,5-diido-DL-thyronine, Hoffmann-LaRoche; and 3,5,3'-triiodothyroacetic acid (Triac), Smith, Kline and French Laboratories. Other compounds were prepared by established methods: 3'-iodo-DL-thyronine (6, 7), 3,5-diiodothyroacetic acid (Diac) (8).

The synthesis of thyroethanols, by adaptations of the principle of Charmers et al. (9, cf. also 10, 11) is presented later in this paper. The structure of diiodothyroethanol was confirmed by removing iodine from the molecule with hydrogen in the presence of Raney nickel. The product, thyroethanol, was identical with the alcohol obtained by the LiAlH4 reduction of diiodothyroacetic acid. Thyroacetic acid was prepared from triiodo- or diiodothyroacetic acid by the Raney nickel hydrogen reduction. Thyronamine was prepared by decarboxylation of thyronine.

RESULTS

Substrate Specificity of the Thyroxine Degrading System

It has already been shown (1) that the enzymes of kidney mitochondria convert both thyroxine and triiodothyronine to their corresponding acetic acid analogues. The alanine side chains of 3,5-diiodothyronine, 3'-iodothyronine and thyronine itself are also degraded enzymically to form acetic acid analogues as is shown in Table I. The enzyme reaction extracts chromatographed on paper contain two major components detected with 4-aminonitroantipyrrine. The slower moving materials (Spot I) are the added substrates. In each case, Spot II corresponds in RF to the expected thyroacetic acid. Since no 3'-iodothyroacetic acid was available for comparison, the metabolic product from 3'-iodothyronine was deiodinated by hydrogenation. The resulting deiodinated compound migrated at the same rate as thyroacetic acid. More rigorous proof of structure of these metabolic products was considered unnecessary in view of the detailed characterization of the acetic acid derivatives produced from thyroxine and triiodothyronine (1).

Pathway of Side-Chain Degradation

Two possible routes for the degradation of thyronines to thyroacetic acids are depicted in Fig. 1. Decarboxylation via Reaction 1-a could produce thyronamines which have thyroid hormone...
TABLE I
Enzymic conversion of thyronines and of thyronamine to thyroacetic acids

The values recorded are for two separately conducted experiments.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>RF</th>
<th>Authentic thyroacetic acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spot I</td>
<td>Spot II</td>
<td></td>
</tr>
<tr>
<td>3,5-Diiodothyronine</td>
<td>0.40</td>
<td>3,5-Diiodothyroacetic acid</td>
</tr>
<tr>
<td></td>
<td>0.48</td>
<td>0.60</td>
</tr>
<tr>
<td>3'-Iodo-DL-thyronine</td>
<td>0.20</td>
<td>Thyroacetic acid</td>
</tr>
<tr>
<td></td>
<td>0.22</td>
<td>0.48 (after hydrolysis)</td>
</tr>
<tr>
<td>DL-Thyronine</td>
<td>0.29</td>
<td>Thyroacetic acid</td>
</tr>
<tr>
<td></td>
<td>0.26</td>
<td>0.48</td>
</tr>
<tr>
<td>Thyronamine</td>
<td>0.65</td>
<td>0.65</td>
</tr>
</tbody>
</table>

FIG. 1. Pathways of side chain degradation

activity (7, 12). Alternatively, transamination or oxidative deamination could yield thyropyruvic acids which, on oxidative decarboxylation, would form thyroacetic acids.

Synthetic tri- (7) and tetraiodothyronamines (13) were found not to be converted to thyroacetic acids, indicating that Reaction 1-a is not the route between iodinated thyronines and thyroacetic acids. The failure to show the conversion with use of phenolic color tests on paper chromatograms was confirmed in a single experiment with triiodothyronamine labeled with I^31.

The next transformation in the scheme (Reaction 2) should yield iodinated thyroacetaldehydes. The evidence cited immediately above indicates that these carbonyl compounds are also not readily detected. Attempts to synthesize them proved unfruitful. Possible precursors—variously iodinated thyroethanols—were then synthesized as described below and were found to be converted to the corresponding thyroacetic acids (Table II). The parent thyroethanols all moved close to the front in the tertiary amyl alcohol-6 N NH_2OH solvent system. The relative mobilities of the rechromatographed products correspond to those of the authentic acetic acid analogues. The spots formed by mixtures of the product and the authentic acetic acids were not elongated as compared to either alone, attesting to their identity. I^131-labeled triiodothyroethanol was converted to a radioactive product which migrated on paper at the same rate as triiodothyroacetic acid. No such product was produced when the experiment was conducted with a boiled enzyme solution. The product was eluted from the paper and recrystallized with authentic triiodothyroacetic acid. The specific activity (c.p.m. per 100 μg) on successive recrystallizations from methanol by addition of water were: original mixture, 253; 1st recrystallization, 280; 2nd, 285; 3rd, 275; 4th, 276.

These data clearly establish that thyroethanols are converted by the enzyme preparation to thyroacetic acids. Thyroacetal-

intermediate in the scheme shown in Fig. 1, attempts were made to detect it as an intermediate and to determine how it was formed. In the enzymic conversion of diiodothyroinc to its acetic acid analogue, no product appeared on paper chromatograms at the spot occupied by synthetic diiodothyropropionic acid, even after very brief incubation periods. The conversion of synthetic diiodothyropropionic to diiodothyroacetic acid was far more rapid than the conversion of thyronine, hence intermediates might not be expected to accumulate. Attempts to trap carbonyl intermediates with NH_2OH, semicarbazide or isoniazide were also unsuccessful.

To determine whether transamination of the thyronines was involved, α-ketoglutarate or pyruvate was added in experiments with well-dialyzed enzyme preparations. Pyruvate enhanced the conversion appreciably, but ketoglutarate did not. Before more critical experiments were done, Yamamoto (17, cf. 18) reported that thyroxine and triiodothyronine are transaminated by enzymes in kidney homogenates and mitochondria.

TABLE II
Enzymic conversion of thyroethanols to thyroacetic acids

<table>
<thead>
<tr>
<th>Substrate</th>
<th>RF</th>
<th>Products</th>
<th>Products of thyroacetic acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroethanol</td>
<td>0.45</td>
<td>Thyroacetic acid</td>
<td>0.47</td>
</tr>
<tr>
<td>3,5-Diiodothyroethanol</td>
<td>0.65</td>
<td>3,5-Diiodothyro-</td>
<td>0.64</td>
</tr>
<tr>
<td>3,5,3'-Triiodothyroethanol</td>
<td>0.57</td>
<td>3,5,3'-Triiodo-</td>
<td>0.56</td>
</tr>
</tbody>
</table>

debix would be compulsory intermediates in such a conversion, and thus evidence is provided that the aldehydes may be intermediates in the conversion of thyronines to thyroacetic acids.

**Biological Activity of Iodinated Thyroethanols**

Assays for thyroid hormone activity were performed as described elsewhere (1). On a molar basis, triiodothyroethanol was 30% as effective as $\text{L-thyroxine}$ in preventing goiter of rats. After washing the solution with 5% NaHCO$_3$ and water, the ether extract was dried over Na$_2$SO$_4$ and evaporated. The crystalline residue was dissolved in hot CHC$_3$H$_2$OAc, treated with charcoal and cooled to yield 53.5 g (77.8% of theory) of almost colorless needles, m.p. 89–91°. The reported m.p. is 93° (20).

Tyrosol Dibenzoate was prepared with benzoyl chloride in pyridine. Colorless fine needles, recrystallized from 95% alcohol, melted at 110–112°.

$$\text{C}_9\text{H}_9\text{O}_3\text{N}_2\ (346.36)$$

Calculated: C 76.28, H 5.33

Found: C 76.32, H 5.35

$p$-Hydroxyphenethyl Acetate (III) — Tyrosol, 69 g (0.5 mole), was dissolved in 150 ml of warm glacial acetic acid and the solution was refluxed for 5 hours in the presence of 1.15 ml of concentrated H$_2$SO$_4$. The reaction mixture was diluted with three volumes of water and extracted with three 200 ml portions of ether. The combined ether extracts were washed with 5% NaHCO$_3$ water, and dried over Na$_2$SO$_4$.

After evaporation of the ether, the red residue was distilled under reduced pressure (b.p. 154–155.5° at 0.7 mm Hg), yielding 74.8 g (83% of theory) of a colorless viscous liquid. This was used for nitration.

A small portion was dissolved in ether, diluted with 2 volumes of petroleum ether (Skelly C) and kept at $-5^\circ$ overnight. The colorless long needles melted at 61–62°. Pistaschimuka (20) prepared the acetate (m.p. 59°) by treating tyrosol with acetyl chloride in ether. We were unsuccessful with this procedure.

$$\text{C}_9\text{H}_9\text{O}_3\ (180.20)$$

Calculated: C 66.64, H 6.71

Found: C 66.63, H 6.93

$\text{p-Hydoxy-3,5-dinitrophenethyl Acetate (IV)}$ — With rapid stirring, tyrosol monoacetate, 36 g (0.2 mole), was added slowly to 720 ml of concentrated H$_2$SO$_4$ in a 2-liter three-necked flask immersed in an alcohol bath at $-25$ to $-30^\circ$. To this cold mixture, 62.5 ml of concentrated HNO$_3$ (sp. gr. 1.4) were added dropwise. The temperature of the contents was kept below $-10^\circ$ during the reaction. After another hour of stirring, the orange-yellow reaction mixture was poured over crushed ice.

The yellow precipitate was collected, washed with cold water and resuspended in 2 liters of water. The acid was neutralized with 5% NaHCO$_3$ and reacidified with acetic acid to pH 3 to
4. The precipitate was collected and recrystallized twice from dilute acetic acid; yield, 38.2 g (70.8% of theory), m.p. 91.5-92.5°.

\[ \text{C}_{11} \text{H}_{17} \text{O}_4 \text{N}_4 \]  (270.20)
Calculated: C 44.44, H 3.73, N 10.36
Found: C 44.58, H 3.57, N 10.43

Dinitrotyrosol Diacetate—A mixture of IV (2.5 g) and 10 ml of acetic anhydride was heated with one drop of concentrated \( \text{H}_2\text{SO}_4 \) for 3 hours at 100 110°. The dark reddish solution was diluted with 50 ml of ice water and left at room temperature overnight. The light brown crystalline precipitate, after being washed with cold water, was recrystallized from glacial acetic acid (about 5 ml) three times, yielding light yellow prisms which melted at 90-92°.

\[ \text{C}_{12} \text{H}_{18} \text{O}_5 \text{N}_2 \]  (312.2)
Calculated: C 46.15, H 3.87, N 8.97
Found: C 46.29, H 3.89, N 9.23

β-[3,5-Dinitro-4-(4'-methoxyphenoxy)phenyl]-ethyl Acetate (V)—A mixture of IV, 10.8 g (40 mmoles), and \( p \)-toluenesulfonyl chloride, 8.4 g (44 mmoles), in dry pyridine, 16 ml, was heated in an oil bath (100-105°) for 30 minutes. \( p \)-Methoxyphenol, 14.9 g (120 mmoles) was added, and the solution was heated in an oil bath (100-105°) for 30 minutes. The reaction mixture was filtered through a sintered glass funnel into ice-cold, magnetically stirred, concentrated \( \text{H}_2\text{SO}_4 \) (50 ml). The color of the filtrate (diamine) was from almost colorless to light blue.

The crystalline residue (10.1 g) was recrystallized from glacial acetic acid, yielding yellow prisms; m.p. 110-111.5°.

\[ \text{C}_{13} \text{H}_{18} \text{O}_5 \text{N}_2 \]  (376.31)
Calculated: C 44.58, H 3.57, N 10.43
Found: C 44.42, N 7.48

\( p \)-Toluenesulfonyl chloride could be replaced with methane sulfonyl chloride, 5.27 g (46 mmoles). The reaction mixture was refluxed for 10 minutes before adding \( p \)-methoxyphenol and for 20 minutes after the addition. The yield was about the same.

β-[3,5-Dinitro-4-(4'-methoxyphenoxy)phenyl]-ethyl Alcohol—Dry HCl gas was passed for 30 minutes through an ice-cold, magnetically stirred, concentrated \( \text{H}_2\text{SO}_4 \) (50 ml). The reaction mixture was filtered through a sintered glass funnel into ice-cold, magnetically stirred, concentrated \( \text{H}_2\text{SO}_4 \) (50 ml). The filtrate (diamine) was from almost colorless to light blue.

The residue was recrystallized three times from dilute acetic acid after being treated with charcoal. Yield, 310 mg of colorless needles, m.p. 162-164°.

\[ \text{C}_{13} \text{H}_{18} \text{O}_5 \text{N}_2 \]  (400.4)
Calculated: C 46.04, H 6.09, N 6.99
Found: C 46.23, H 6.07, N 7.21

β-[3,5-Diiodo-4-(4'-methoxyphenoxy)phenyl]-ethyl Acetate (VII)—3,5-Diiodo-4-(4'-methoxyphenoxy)phenyl ethyl acetate, 7.5 g (0.02 mole) suspended in glacial acetic acid (100 ml) was hydrogenated in the presence of 0.4 g of 10% \( \text{Pd} \) on charcoal. The crystals went into solution as hydrogenation proceeded. The theoretical amount of hydrogen was consumed in 3 to 5 hours. The reaction mixture was filtered through a sintered glass funnel into ice-cold, magnetically stirred, concentrated \( \text{H}_2\text{SO}_4 \) (50 ml). The color of the filtrate was from almost colorless to light blue.

Hydrogenation—\( \text{H}_2\text{SO}_4 \) (5 g) was suspended in ice-cold concentrated \( \text{H}_2\text{SO}_4 \) (40 ml) and washed carefully with shaking to make a clear, pale yellow solution which was placed in a 1-liter three-necked flask equipped with a thermometer, a dropping funnel, and a powerful stirrer. The flask was placed in an ice water bath (0 to -5°), and glacial acetic acid (80 ml) was added slowly with rapid stirring to form a thick white suspension. After the bath temperature was lowered to -10°, the filtered hydrogenation mixture was added dropwise over 2 hours. The temperature of the contents was kept below -10°. Staining of the redish brown tetrazo solution was continued for an additional hour.

Iodination—A mixture of 27 g of \( \text{NaI} \), 15.2 g of \( \text{I}_2 \), and 300 ml of water was stirred for several hours and, before the iodination, 3.6 g of urea and 200 ml of \( \text{CHCl}_3 \) were added. The tetrazo solution was poured into the iodination mixture through a cold funnel during 5 minutes and the stirring was continued for 1 to 2 hours at room temperature. The chloroform layer was separated, and the aqueous layer was extracted several times with 150 ml portions of \( \text{CHCl}_3 \). The combined \( \text{CHCl}_3 \) extracts were washed with water, 5% sodium metabisulfite, water again, and dried over \( \text{MgSO}_4 \). After evaporation of the solvent, the dark crystalline residue (10 to 12.5 g) was taken up in benzene (75 ml) and passed through an alumina column (2 x 10 cm). The eluate was collected until it contained a negligible residue on evaporation (total, 350 ml). The crystalline residue (10.1 g) was recrystallized from glacial acetic acid, yielding yellow prisms; m.p. 110-111.5°.

\[ \text{C}_{13} \text{H}_{18} \text{O}_5 \text{N}_2 \]  (334.28)
Calculated: C 53.89, H 4.22, N 8.38
Found: C 53.95, H 4.15, N 8.60

Acetylation of the 3,5-dinitro-4-(4'-methoxyphenoxy)phenyl-ethyl alcohol thus obtained with glacial acetic acid and \( \text{H}_2\text{SO}_4 \) gave a product identical to V, thus establishing the nature of the side chain.

β-[N,N'-Diacetyl-3,5-diamino-4-(4'-methoxyphenoxy)phenyl]-ethyl Acetate (VI)—Dinitro compound (V), 1 g, suspended in 100 ml of glacial acetic acid was hydrogenated in the presence of 0.1 g of 10% \( \text{Pd} \) on charcoal at room temperature (1 to 2 hours). The filtered solution was evaporated to dryness in a vacuum at 40°. The residue was heated with 30 ml of acetic anhydride at 70-80° for 3 hours. After the excess of reagent was decomposed with water, the reaction mixture was evaporated in a vacuum. The residue was recrystallized three times from dilute acetic acid after being treated with charcoal. Yield, 310 mg of colorless needles, m.p. 162-164°.

\[ \text{C}_{13} \text{H}_{18} \text{O}_5 \text{N}_2 \]  (400.4)
Calculated: C 62.98, H 6.04, N 6.99
Found: C 63.33, H 5.07, N 7.21

β-[3,5-Diiodo-4-(4'-hydroxyphenoxy)phenyl]-ethyl toluide (VIII)—β-[3,5-Diiodo-4-(4'-methoxyphenoxy)phenyl]-ethyl toluide (VII), 10 g, was refluxed for 7 hours with 100 ml of glacial acetic acid at 100-108°. For analysis, the compound was recrystallized three times; m.p. 108-110°.

\[ \text{C}_{13} \text{H}_{18} \text{O}_5 \text{N}_2 \]  (538.14)
Calculated: C 37.04, H 2.96, I 47.17
Found: C 38.23, H 2.92, I 47.50

β-[N,N'-Diiodo-3,5-diamino-4-(4'-methoxyphenoxy)phenyl]-ethyl Acetate (VII)—β-[3,5-Diiodo-4-(4'-methoxyphenoxy)phenyl]-ethyl acetate (VII), 10 g, was refluxed for 7 hours with 100 ml of glacial acetic acid at 100-108°. For analysis, the compound was recrystallized three times; m.p. 108-110°.

\[ \text{C}_{13} \text{H}_{18} \text{O}_5 \text{N}_2 \]  (538.14)
Calculated: C 37.04, H 2.96, I 47.17
Found: C 38.23, H 2.92, I 47.50
presence of 1 g of red phosphorus. The clear red solution was decanted, the phosphorus was washed with water three times, and the cloudy washings (about 500 ml) were mixed with the decanted solution. After the mixture was cooled overnight, the yellow precipitate was collected, washed with water, and recrystallized from 30 ml of glacial acetic acid (charcoal) to yield 10 g (91% of theory) of almost colorless needles, m.p. 164-166°. The analytical sample was recrystallized several times from the same solvent or from absolute alcohol; m.p. 166-168°.

The compound gave positive phenol tests with Folin-Dennis and 4-aminoantipyrine reagents. With 2% ethanolic AgNO₃ solution it produced precipitates which were not soluble in 5% HNO₃.

Two grams of VIII were dissolved in warm ethanol (30 ml) and mixed with 30 ml of 2 N NaOH. After 2 hours at room temperature, the reaction mixture was slightly acidified with concentrated HCl, diluted further with water, and cooled overnight. The white precipitate was recrystallized once from dilute ethanol and then twice from Skelly C. Colorless clustered needles, m.p. 123-125°, gave positive phenol tests, but a negative halogen test. The product was probably 3,5-diiodo-4-(4'-hydroxyphenoxy)styrene.

β-[3,5-Diiodo-4-(4'-hydroxyphenoxy)phenyl]ethyl Acetate (IX)—The iodide (VIII), 5.92 g (0.01 mole), was dissolved in glacial acetic acid, 750 ml; dried silver acetate, 3.34 g (0.02 mole), was added and the mixture was stirred for 1 hour at room temperature, and for 3 hours in a boiling water bath. The silver salts were separated by filtration and the filtrate was evaporated to dryness in a vacuum (40°). The dark residue was extracted three times with 150 ml portions of CHCl₃; the combined extracts were washed with water, 10% NaHC0₃, water again, and concentrated NH₄OH, 2 ml. A cyclohexane solution of 150 mg of I₂ containing 100 mc I₃⁻ was added, and the mixture was agitated until the purple color disappeared. The reaction mixture was concentrated and the residue extracted twice with n-butanol. After being washed with water, the butanol extracts were evaporated to dryness in a vacuum. The residue was taken up in a small amount of alcohol and chromatographed on paper to remove the remaining iodide which stayed near the origin. The radioactivity near the solvent front migrated at a rate characteristic of triiodothyroethanol (Rf = 0.88). It was extracted from the paper and used as a substrate without further purification.

Thyroethanol—Preparation A: From 3,5-diiodothyroacetic acid—3,5-diiodothyroacetic acid, 1.5 g, was dissolved in a mixture of methanol, 2 ml, and concentrated NH₄OH, 2 ml. A cyclohexane solution of 150 µg of I₂ containing 100 mc I₃⁻ was added, and the mixture was agitated until the purple color disappeared. The reaction mixture was concentrated and the residue extracted twice with n-butanol. After being washed with water, the butanol extracts were evaporated to dryness in a vacuum. The residue was taken up in a small amount of alcohol and chromatographed on paper to remove the remaining iodide which stayed near the origin. The radioactivity near the solvent front migrated at a rate characteristic of triiodothyroethanol (Rf = 0.88). It was extracted from the paper and used as a substrate without further purification.

Preparation B: From 3,5-diiodothyroethanol—3,5-diiodothyroethanol, 40 mg, in a mixture of ethanol, 15 ml, and concentrated NH₄OH, 5 ml, was hydrogenated under ordinary pressure in the presence of Raney nickel, W-2 (21), (3 ml, about 1.8 g)
for several hours. The filtrate was evaporated to dryness in a vacuum and the residue recrystallized from dilute ethanol or benzene; the m.p. of 141–142°C was not depressed by mixing the product with preparation A.

\[ \text{C}_3\text{H}_5\text{I}_3\text{O}_3 \] (235.3)
Calculated: C 73.02, H 6.12
Found: C 73.00, H 6.12

The dibenzoate of thyroethanol prepared with benzoyl chloride and pyridine melted at 119–121°C when crystallized from 95% ethanol.

\[ \text{C}_3\text{H}_5\text{I}_3\text{O}_5 \] (498.5)
Calculated: C 76.51, H 5.13
Found: C 76.50, H 5.13

\textbf{DISCUSSION}

The conversion of various iodinated thyronines to corresponding thyroacetic acids is a natural process in extrathyroidal mammalian tissues. Roche and Michel et al. (22–25) have demonstrated the occurrence of triiodothyroacetic-131 acid in several tissues of thyromycochromatized rats after the administration of labeled triiodothyronine. They too have found that the number of iodine atoms or their position on the thyronine rings is not critical (26, 27). In contrast to the report (28) that 3',5,3'-triiodo-L-thyronine is converted to triiodothyroacetic acid in the intact rat, it has been found that the kidney mitochondrial enzyme system does not convert D-thyronine to triiodothyroacetic acid (29). Thus, there may be additional routes for the degradation of the thyronines in the intact animal, but the combined evidence from several laboratories now points to Reactions 1b, 2, and 3 of Fig. 1 as the main pathway.

\textbf{SUMMARY}

An extract of rat kidney mitochondria, fortified with diphenylhydantoin nucleotide, converts 3,5-diiodothyronine, 3'-iodothyronine, and uniodinated thyronine, as well as thyroxine and triiodothyronine, to their corresponding acetic acid analogues. Although thyronamine is converted to thyroacetic acid, iodinated thyronamines are not, indicating that they are not intermedias in the conversion of iodinated thyronines to acetic acid analogues.

Iodinated thyropyruvic acids and thyroacetaldehydes could not be detected as intermediates, but synthetic diiodothyro- pyruvic-2-C14 acid was converted to radioactive diiodothyroacetic acid.

The synthesis and biological activity of 3,5,3'-triiodo-, 3,5diiodo-., and non-iodinated thyroacetic acids are described. These compounds were oxidized to their respective thyroacetic analogues by the kidney enzyme system.

It is concluded that the enzymic conversion of iodinated thyronines to iodinated thyroacetic acids proceeds by way of iodinated thyropyruvic acids and thyroacetaldehydes.

\textbf{REFERENCES}

Enzymic Conversion of Iodinated Thyronines to Iodinated Thyroacetic Acids
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