Synthesis and Biological Activity of O-Methyl Derivatives of Thyroid Hormones*

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In 1951, MacLagan and Wilkinson (2) discovered that a phenolic compound iodinated in both ortho positions, n-butyl-4-hydroxy-3,5-diiodobenzoate, was methylated by human subjects and excreted in urine as 3,5-diiodo-4- methoxy benzoic acid. The degree of methylation was somewhat higher in hyperthyroid patients than in others. This was the first demonstration of O-methylation in animals, a process which has since been found to occur with other types of compounds such as 3,5-diarylhydroxyphenyl derivatives (3-11). The work by MacLagan and Wilkinson suggested the possibility that thyroid hormones might be methylated in animals and stimulated interest in the biological activity of such compounds.

Synthetic O-methyl-DL-thyroxine which had earlier (12) been reported very effective in stimulating basal metabolic rate when given orally, was found to be about one-third as effective as thyroid hormone (13). The possibility that O-methyl derivatives of physiologically active thyronines, other members of this series were synthesized and their biological activities were determined (1). The possibility that O-methylation is involved in the normal metabolism of thyroid hormones is being investigated.

EXPERIMENTAL PROCEDURE

Most of the chromatographic techniques employed have been described (17); O-methyl thyronines were located on the paper with 0.25% ninhydrin in acetic acid. Tadpole (Rana clamitans) metamorphosis and goiter prevention (Sprague-Dawley rats) assays were conducted as described earlier (18). Initially, the basal metabolic rates were measured by the method of Holtkamp et al. (19) in the Smith, Kline and French Laboratories; later they were measured in this laboratory by a modification of the method of Robbie (20). The ability of various thyronine derivatives to induce ATPase activity in fresh rat liver mitochondria was measured (21) at 30°.

Compounds used were from the following sources: dl-thyroxine, dl-3,5-diiodothyronine, and dl-thyroxine, Hoffmann-LaRoche; l-triiodothyronine and l-thyroxine, Smith, Kline and French Laboratories; 3,5,3'-triiodothyroacetic acid and Diazald for the preparation of diazomethane, Aldrich Chemical. Triiodothyroethanol was synthesized as described previously (22).

The preparation of O-methyl derivatives is described in detail under “Syntheses.” The authentic samples of O-methyl-DL-thyroxine and O-methyl-3,5-diiodo-L-thyronine were generous gifts from Dr. B. A. Hems (Glaxo Laboratories, Ltd., Greenford, Middlesex, England).

RESULTS

Characterization and Identification of O-Methyl Thyronines

In 1938, Loeser, Ruland, and Trikojus (12) reported that the direct methylation of thyroxine with diazomethane produced the O-methyl derivative. In the case of 3,5-diiodothyronine and diiodothyrosine, however, both the phenolic and amino groups were methylated (and also some formation of the allyl side-chain derivative was observed). In our experience, all thyronine methyl esters were smoothly methylated with diazomethane in an ethanol-ether mixture to produce a satisfactory yield of O-methyl derivatives regardless of the number of iodine atoms on the molecule. A proof of the structures of the compounds isolated is summarized in Fig. 1.

O-Methyl thyronine prepared with diazomethane was identical in the following respects with the product obtained by reaction of N-benzoyl thyronine with dimethyl sulfate followed by hydrolysis: (a) the melting points and infrared spectra of their hydrochlorides; (b) the infrared spectra of the free ethers and Dr. Hems' authentic sample, and (c) their paper chromatographic behavior in tert-amyl alcohol saturated with 6 N NH₄OH. The product obtained by refluxing O-methyl thyronine with HBr (48%) acetic acid (1:2, volume for volume) was also compared with authentic thyroxine; they had the same melting point and paper chromatographic behavior. In a similar way, the identity of O-methyl-3,5-diiodothyronine prepared by these two routes was established.

The iodinated thyronines (thyroxine, 3,5,3'-triiodothyronine, and 3,5-diiodothyrosine) were allowed to react with diazomethane and then deiodinated with hydrogen in the presence of

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† Postdoctoral Fellow, National Institutes of Arthritis and Metabolic Diseases, Public Health Service.
‡ Meltzer et al. (14) have reported an unsuccessful attempt to synthesize O-methyl triiodothyroacetic acid, but have since succeeded, for they have used this compound in biological experiments (15, 16).
§ We are indebted to Drs. C. M. Greenberg, A. E. Hemsing, and H. L. Saunders for these determinations.

† V. M. Trikojus, personal communication.
Fig. 1. Reaction sequence establishing the identity of O-methyl thyronines. OMe, O-methyl; T, thyroxine; T₃, triiodothyronine; T₄, diiodothyronine.

Raney Ni. The products were identical with O-methyl thyronine with respect to melting points, paper chromatographic behavior and infrared spectra (Table I). It was therefore concluded that our main products prepared with diazomethane were not methylated on the amino group. Smaller amounts of N-methylated derivatives may have been formed during the synthesis and separated from the main product during the repeated crystallizations.

**Biological Activities**

The relative activities of these O-methyl ethers in different bioassays are summarized in Table II. O-Methylolation did not diminish the high activities of thyroxine, triiodothyronine, and triiodothyroacetic acid on tadpole metamorphosis. The activities of diiodothyronine and O-methyl diiodothyronine were assayed only once and are not significantly different. Like its parent compound, O-methyl thyronine was not detectably active. In the rat goiter prevention assay, O-methylolation destroyed virtually all of the activity of thyroxine (13), an appreciable part of triiodothyronine and none of triiodothyroacetic acid. In the basal metabolic rate assay with intact rats, O-methyl thyroxine was about one-third as effective as thyroxine and O-methyl triiodothyronine was about one-half as active as its parent compound. In a determination with thyroidectomized rats O-methyl triiodothyroacetic acid was about two-thirds as active as triiodothyroacetic acid.

The biological activities of O-methyl triiodothyronine and O-methyl triiodothyroacetic acid of industrial origin have been reported in the literature, although the synthesis and physical constants have not been reported previously. Our findings for

<table>
<thead>
<tr>
<th>Compound</th>
<th>Route of preparation</th>
<th>M.d. (decomposition)</th>
<th>Deliodinated product</th>
<th>Demethylated product</th>
</tr>
</thead>
<tbody>
<tr>
<td>O-Methyl-dL-thyronine</td>
<td>CH₃N₂</td>
<td>210-212°</td>
<td>206-208°</td>
<td>0.50</td>
</tr>
<tr>
<td>O-Methyl-nL-thyronine</td>
<td>(CH₃)₂SO₄</td>
<td>210-212°</td>
<td>205-207°</td>
<td>0.50</td>
</tr>
<tr>
<td>O-Methyl 3,5-diiodo-dL-thyronine</td>
<td>CH₃N₂</td>
<td>218-220°</td>
<td>202-205°</td>
<td>0.50</td>
</tr>
<tr>
<td>O-Methyl 3,5-diiodo-nL-thyronine</td>
<td>(CH₃)₂SO₄</td>
<td>217-219°</td>
<td>201-203°</td>
<td>0.48</td>
</tr>
<tr>
<td>O-Methyl 3,3',5-triiodo-L-thyronine</td>
<td>CH₃N₂</td>
<td>212-214°</td>
<td>203-205°</td>
<td>0.49</td>
</tr>
<tr>
<td>O-Methyl-dL-thyroxine</td>
<td>CH₃N₂</td>
<td>224</td>
<td>203-205°</td>
<td>0.49</td>
</tr>
<tr>
<td>Authentic dL-thyroxine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Biological activities of O-methylated compounds

The activities of L-triiodothyronine are taken from (17), assuming the α isomer of thyroxine to be inactive. Values for O-methyl thyroxine are from (13).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Metabolism (in terms of rate constants)</th>
<th>Goiter prevention (rat)</th>
<th>Basic rate (rat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Thyroxine</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>O-Methyl-L-thyroxine</td>
<td>0</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>L-Triiodothyronine</td>
<td>10-40</td>
<td>20</td>
<td>4-6</td>
</tr>
<tr>
<td>O-Methyl-L-triodothyronine</td>
<td>10-40</td>
<td>1.5-3</td>
<td>2-3</td>
</tr>
<tr>
<td>3,5-Diiodo-L-thyronine</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O-Methyl diiodo-L-thyronine</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O-Methylthyroxine</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O-Methyl triiodothyronate</td>
<td>2</td>
<td>0.6</td>
<td>0.2*</td>
</tr>
<tr>
<td>O-Methyl triiodothyroacetic acid</td>
<td>2</td>
<td>0.5-0.7</td>
<td>0.14*</td>
</tr>
</tbody>
</table>

*The basal metabolic rate assays for triiodothyroacetic acid and for O-methyl triiodothyroacetic acid were done on thyroids from rats, with triiodothyronine as the reference standard. The activity is recorded assuming a value of 5 for triiodothyronine.

O-methyl triiodothyronine were in the range reported by Money et al. (23). O-Methyl triiodothyroacetic acid was about half as effective as triiodothyroacetic acid in suppression of ß-adrenergic responses (13). O-Methyl triiodothyroacetic acid and its O-methyl ether were highly effective in uncoupling. The activity is recorded assuming a value of 5 for triiodothyronine.

Effects on Mitochondrial Adenosinetriphosphatase

Lardy and Maley (24) found that thyroxine and several of its physiologically active analogues would stimulate the adenosinetriphosphatase activity of rat liver mitochondria. The synthetic O-methyl ethers have been tested in this assay, and the results are summarized in Table III.

With intact mitochondria, thyroxine and triiodothyronine have relatively little ability to enhance ATPase compared with 2,4-dinitrophenol (24, 25). The methyl ethers of these two hormones were ineffective. On the other hand, methylation of triiodothyroacetic acid, which is one-third to one-half as effective as dinitrophenol, further increased the ability to stimulate ATPase. The response of mitochondrial ATPase to increasing concentrations of triiodothyroacetic acid and its O-methyl ether is depicted in Fig. 2. The maximal response to O-methyl triiodothyroacetic acid is greater than with triiodothyroacetic acid and is achieved at a lower concentration. Analogous curves were obtained for O-methyl tetraiodothyroacetic acid and tetraiodothyroacetic acid but the maximal responses were slightly less.

Triiodothyroethanol (22), which is closely related structurally to triiodothyroacetic acid and which is oxidized to that compound by rat kidney mitochondria, enhances ATPase. Methylation abolishes its activity.

Effects on Oxidative Phosphorylation

At $5 \times 10^{-4}$ M or lower concentration, thyroxine and triiodothyronine uncouple oxidative phosphorylation only slightly in conventional experiments (26). With most substrates, triiodothyroacetic acid is somewhat more effective. The effects of the methyl ethers of thyroxine and triiodothyronine were not appreciably different from those of their respective parent compounds but the methyl ether of triiodothyroacetic acid was somewhat more effective than the acid (Table IV). This greater uncoupling activity was not abolished by 0.01 M fluoride.

The presence of sufficient malonate to block the oxidation of succinate produced from glutamate renders kidney mitochondria more susceptible to uncoupling by thyroxine (26). In repeated experiments with kidney mitochondria and malonate present, O-methyl thyroxine was less deleterious to phosphorylation than was thyroxine. Again triiodothyroacetic acid and its O-methyl ether were highly effective in uncoupling.

Metabolic Transformation

Mammalian mitochondria contain an enzyme system capable of degrading the alanine side chain of thyronine and iodinated.
thyronines to the corresponding substituted acetic acids (17, 22). The almost colorless residue was evaporated to dryness in a vacuum. After the mixture had been kept in the cold overnight, it was dissolved in absolute methanol (5 ml) and treated with an excess of ice-cold diazomethane-ether solution. The reaction was almost instantaneous. After the mixture had been kept in the cold overnight, it was evaporated to dryness in a vacuum. The almost colorless residue yielded 410 mg (63% of theoretical) of colorless needles from dilute ethanol. The methyl ester of the O-methyl ether melted at 133-135°C.

\[ C_{14}H_{21}O_4I_5 \] (650.0)

Calculated: C 29.56, H 2.01, I 58.57

Found: C 29.73, H 1.92, I 58.85

The above methyl ester (162 mg, 0.5 mmole) was hydrolyzed in 10 ml of 1 N NaOH in 50% ethanol at room temperature for 1 hour. Acidification with dilute HCl precipitated the free acid, which was dried and recrystallized by dissolving in warm benzene (10 ml) and adding petroleum ether (Skelly C) (30 ml). It was melted at 164-166°C. The question of whether O-methylation plays a significant role in the metabolism of thyroid hormones has not yet been answered. We have been unable to detect any conversion by rat kidney or liver mitochondria of O-methyl thyronine to either O-methyl thyroacetic acid or thyroacetic acid. Rat kidney mitochondria did not convert O-methyl triiodothyronine to O-methyl triiodothyroacetic acid or triiodothyroacetic acid. The limit of detectability in these experiments was approximately 1% of the amount of the substituted acetic acid formed from the corresponding unmethylated compounds.

### DISCUSSION

The question of whether O-methylation plays a significant role in the metabolism of thyroid hormones has not yet been answered. We have been unable to detect any conversion by rat kidney or liver mitochondria of O-methyl thyronine to either O-methyl thyroacetic acid or thyroacetic acid. Rat kidney mitochondria did not convert O-methyl triiodothyronine to O-methyl triiodothyroacetic acid or triiodothyroacetic acid. The limit of detectability in these experiments was approximately 1% of the amount of the substituted acetic acid formed from the corresponding unmethylated compounds.

**Syntheses**

**O-Methyl Triiodothyroacetic Acid. A. By Diazomethane—Triiodothyroacetic acid (622 mg, 1 mmole) was dissolved in absolute methanol (5 ml) and treated with an excess of ice-cold diazomethane-ether solution. The reaction was almost instantaneous. After the mixture had been kept in the cold overnight, it was evaporated to dryness in a vacuum. The almost colorless residue yielded 410 mg (63% of theoretical) of colorless needles from dilute ethanol. The methyl ester of the O-methyl ether melted at 133-135°C.**

**Table IV**

<table>
<thead>
<tr>
<th>Source of mitochondria</th>
<th>Additions</th>
<th>$\beta$-Hydroxybutyrate</th>
<th>Succinate</th>
<th>Glutamate</th>
<th>Glutamate + malonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat kidney</td>
<td>None (control)</td>
<td>230 1.4</td>
<td>560 1.4</td>
<td>520 1.7</td>
<td>225 1.3</td>
</tr>
<tr>
<td></td>
<td>Thyroxine</td>
<td>280 1.1</td>
<td>520 0.9</td>
<td>470 1.5</td>
<td>95 0.8</td>
</tr>
<tr>
<td></td>
<td>O-Methyl thyroxine</td>
<td>290 1.1</td>
<td>535 1.1</td>
<td>500 1.4</td>
<td>190 0.82</td>
</tr>
<tr>
<td></td>
<td>Triiodothyronine</td>
<td>270 1.3</td>
<td>535 1.3</td>
<td>490 1.4</td>
<td>145 0.69</td>
</tr>
<tr>
<td></td>
<td>O-Methyl triiodothyronine</td>
<td>300 1.1</td>
<td>535 1.1</td>
<td>460 1.6</td>
<td>155 0.42</td>
</tr>
<tr>
<td></td>
<td>Triiodothyroacetate</td>
<td>260 0.58</td>
<td>535 0.92</td>
<td>490 1.4</td>
<td>115 0</td>
</tr>
<tr>
<td></td>
<td>O-Methyl triiodothyroacetate</td>
<td>270 0.34</td>
<td>560 0.74</td>
<td>520 1.3</td>
<td>145 0</td>
</tr>
<tr>
<td>Rat liver</td>
<td>None (control)</td>
<td>370 2.3</td>
<td>500 1.7</td>
<td>420 2.7</td>
<td>210 2.5</td>
</tr>
<tr>
<td></td>
<td>Thyroxine</td>
<td>310 2.4</td>
<td>430 1.8</td>
<td>390 2.5</td>
<td>150 2.7</td>
</tr>
<tr>
<td></td>
<td>O-Methyl thyroxine</td>
<td>370 2.1</td>
<td>460 1.7</td>
<td>410 2.3</td>
<td>200 2.3</td>
</tr>
<tr>
<td></td>
<td>Triiodothyronine</td>
<td>310 2.4</td>
<td>410 2.0</td>
<td>410 2.3</td>
<td>190 2.3</td>
</tr>
<tr>
<td></td>
<td>O-Methyl triiodothyronine</td>
<td>350 2.1</td>
<td>420 1.8</td>
<td>350 2.5</td>
<td>140 2.3</td>
</tr>
<tr>
<td></td>
<td>Triiodothyroacetate</td>
<td>280 2.0</td>
<td>390 1.6</td>
<td>400 2.0</td>
<td>140 1.3</td>
</tr>
<tr>
<td></td>
<td>O-Methyl triiodothyroacetate</td>
<td>290 1.4</td>
<td>380 1.3</td>
<td>410 1.8</td>
<td>180 1.3</td>
</tr>
</tbody>
</table>

The above methyl ester (162 mg, 0.5 mmole) was hydrolyzed in 10 ml of 1 N NaOH in 50% ethanol at room temperature for 1 hour. Acidification with dilute HCl precipitated the free acid, which was dried and recrystallized by dissolving in warm benzene (10 ml) and adding petroleum ether (Skelly C) (30 ml). It was melted at, 164-166°C. The question of whether O-methylation plays a significant role in the metabolism of thyroid hormones has not yet been answered. We have been unable to detect any conversion by rat kidney or liver mitochondria of O-methyl thyronine to either O-methyl thyroacetic acid or thyroacetic acid. Rat kidney mitochondria did not convert O-methyl triiodothyronine to O-methyl triiodothyroacetic acid or triiodothyroacetic acid. The limit of detectability in these experiments was approximately 1% of the amount of the substituted acetic acid formed from the corresponding unmethylated compounds.

Dr. H. L. Saunders informed us that a preparation of this compound by Dr. J. Kerwin melted at 138-150°C, resolidified, and remelted at 164-166°C.

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4 Dr. H. L. Saunders informed us that a preparation of this compound by Dr. J. Kerwin melted at 138-150°C, resolidified, and remelted at 164-166°C.
O-Methyl tetraiodothyroacetic acid was prepared by Method B described above. The yield was 350 mg from 750 mg of tetraiodothyroacetic acid after several recrystallizations from benzene.

\[
\text{C}_{21}\text{H}_{29}\text{O}_{6}\text{N}_{1}\text{I}_{4} (761.9)
\]

Calculated: C 23.64, H 1.32, I 66.63

Found: C 23.80, H 1.40, I 66.40

**Methyl Esters of Thyronines**

The esters were prepared by the method of Ashley and Harington (27) devised for the preparation of 3,5-diiodothyronine and thyroxine.

**DL-Thyronine methyl ester** formed tiny, colorless needles from benzene or benzene-petroleum ether (Skelly B) that melted at 174-181° (decomposition). Saponification, the products were purified by dissolving in 0.33 N NaOH in 85% ethanol (44 ml) at room temperature overnight. The crude product, which precipitated on addition of 5% NaHCO\(_3\) (5 ml) and cold water, was recrystallized from methanol or ethanol to form tiny, colorless needles. Yield, 80 to 90% of the theoretical.

**3,5,3'-Triiodo-L-thyronine methyl ester** formed tiny, colorless crystals (from dilute ethanol) or cubes (from ethanol) that melted at 174-181° (decomposition).

\[
\text{C}_{16}\text{H}_{17}\text{O}_{26}\text{N}_{1}\text{I}_{4} (665.0)
\]

Calculated: C 28.89, H 2.12, N 2.10

Found: C 28.65, H 2.06, N 1.86

**Preparation of O-Methyl Thyronines with Diazomethane**

The method used was similar to that of Loeser, Ruland, and Trikojus (12), except that anisol was omitted from the reaction mixture. Methyl esters of thyronines (0.5 mmole) suspended in 10 ml of methanol were treated with diazomethane in ether for 3 to 4 days at 0° with occasional shaking. The crystals slowly went into solution. Attempts to purify O-methyl thyronine methyl esters at this stage were unsuccessful. After saponification, the products were purified by dissolving in 0.33 N HCl in 85% ethanol and treatment with charcoal. They were crystallized by addition of 2 N sodium acetate to bring the pH to approximately 6.

**O-Methyl Triiodo-L-thyronine**—M.p., 212-214° (decomposition); yield, 180 mg from 400 mg of L-triiodothyronine.

\[
\text{C}_{16}\text{H}_{17}\text{O}_{26}\text{N}_{1}\text{I}_{4} (665.0)
\]

Calculated: C 28.89, H 2.12, N 2.10

Found: C 28.65, H 2.06, N 1.86

**O-Methyl-3,5-diiodo-DL-thyronine** Some difficulties were encountered with the purification of this compound. The solution of the crude product in ethanolic HCl was diluted with boiling water until it became turbid. The impurities aggregated during continued boiling and were separated. On dilution of the hot filtrate with water, tiny crystals of the hydrochloride were obtained, and further purification was carried out as above; m.p. 215-217° (decomposition).

\[
\text{C}_{16}\text{H}_{17}\text{O}_{26}\text{N}_{1}\text{I}_{4} (599.1)
\]

Calculated: C 35.64, H 2.80, N 2.59, I 66.40

Found: C 35.80, H 2.78, N 2.59, I 66.40

**O-Methyl-DL-thyronine**—Whereas the above two O-methyl ethers of iodothyronines did not form good crystals from boiling 2 N HCl, O-methyl-DL-thyronine was readily purified from this solvent. Fine, colorless needles of the hydrochloride melted at 206-208° (decomposition).

\[
\text{C}_{16}\text{H}_{17}\text{O}_{26}\text{N}_{1}\text{I}_{4} \cdot \text{HCl} (723.8)
\]

Calculated: C 59.35, H 5.60, N 4.32, Cl 10.95

Found: C 59.07, H 5.59, N 4.58, Cl 10.89

The free O-methyl thyronine was crystallized in the manner described above; m.p., 210-212° (decomposition) when the temperature increment was 2° per minute. Clayton and Hems (29) reported that this compound, made by a different route, melted at 246-248° (decomposition). 3

**Methyl Esters of O,N-Dibenzyol Thyriones**

The methyl esters of thyronines (1.5 mmoles), dissolved in dry pyridine (10 ml), were treated with benzoyl chloride (0.5 ml) at room temperature overnight. The crude product, which precipitated on addition of 5% NaHCO\(_3\) (5 ml) and cold water, was recrystallized from methanol or ethanol to form tiny, colorless needles. Yield, 80 to 90% of the theoretical.


## Analytical Data

<table>
<thead>
<tr>
<th>Substance</th>
<th>Calculated</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₁₆H₁₇O₆Ni₁I₄</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C₂₀H₁₂O₆Ni₁I₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C₁₆H₁₇O₆Ni₁</td>
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</tr>
<tr>
<td>C₂₀H₁₂O₆Ni₁</td>
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<tr>
<td>C₁₆H₁₇O₆Ni₁I₄</td>
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<tr>
<td>C₂₀H₁₂O₆Ni₁I₂</td>
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<td>C₂₀H₁₂O₆Ni₁I₂</td>
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<tr>
<td>C₁₆H₁₇O₆Ni₁</td>
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<tr>
<td>C₂₀H₁₂O₆Ni₁</td>
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<td></td>
</tr>
</tbody>
</table>

3 Dr. B. A. Hems (personal communication) found this compound to melt at "210-240", depending greatly on the rate at which the sample is heated." Somewhat higher melting points were observed in a capillary tube as compared with a block.
O-Methylated Thyroid Hormones

2986 O-Methylated Thyroid Hormones

thyronines produced were purified as for those prepared with

m.p. 137-139°.

and recrystallized from dilute ethanol as tiny, colorless needles;

compounds prepared by these two routes were similar.

Phosphatase activity of rat liver mitochondria to a greater extent

5-triiodothyroacetic acid is approximately equal to that of

enhancing basal metabolic rate of rats. The activity of O-

active than triiodothyronine in rat goiter prevention and in

phosphorylation.

than any other thyro-active substance tested. Within this

series, it is also the most effective uncoupler of oxidative phos-

converted to their corresponding thyroacetic acids by mito-

phosphorylation.

O-Methyl Triiodothyroethanol

Triiodothyroethanol (22) was methylated with diazomethane

and recrystallized from dilute ethanol as tiny, colorless needles;

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Molar Mass</th>
<th>Calculated</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₁₈H₁₀O₉NI₂</td>
<td>543.2</td>
<td>C 28.94, H 2.28, I 69.99</td>
<td>C 28.96, H 2.10, I 61.21</td>
</tr>
</tbody>
</table>

SUMMARY

1. The synthesis of the O-methyl ethers of 3,5-diiodothyro-

3,3',5-triiodothyroacetic acids from their respective parent thy-

2. O-Methyl triiodothyronine is as effective as triiodo-

3. O-Methyl triiodothyroacetic acid enhances adenosinetri-

4. O-Methyl thyronine and O-methyl triiodothyronine are not

REFERENCES
