Kirk-Othmer Encyclopedia of Chemical Technology.

THYROID AND ANTITHYROID PREPARATIONS

The main role of the human thyroid gland is production of thyroid hormones (iodinated amino acids), essential for adequate growth, development, and energy metabolism (1–6). Thyroid underfunction is an occurrence that can be treated successfully with thyroid preparations. In addition, the thyroid secretes calcitonin (also known as thyrocalcitonin), a polypeptide that lowers excessively high calcium blood levels. Thyroid hyperfunction, another important clinical entity, can be corrected by treatment with a variety of substances known as antithyroid drugs.

Related substances include thyroid-stimulating hormone [9002-71-5] (TSH) or thyrotropin, secreted by the pituitary gland; thyrotropin-releasing hormone [24305-27-9] or thyroliberin (TRH), a hypothalamic tripeptide; D-thyroxine [51-49-0] (dextrothyroxine), the synthetic unnatural enantiomer of one of the thyroid hormones which has blood-cholesterol lowering activity; various radioactive iodine-containing preparations used to destroy excessive thyroid tissue or to measure thyroid function; and long-acting thyroid stimulator [9034-48-4] (LATS), an immunoglobulin.

1. Thyroid Function and Malfunction

Human life without thyroid hormones is possible but of minimal quality. In the fetus, thyroid hormones affect growth and differentiation; in the mature human, they regulate metabolism. The two principal thyroid hormones, L-thyroxine [51-48-9] (L-thyroxine, 3,5,3′,5′-tetraiodo-L-thyronine, T_4) **(1)** and L-triiodothyronine [6893-02-3] (3,5,3′-triiodo-L-thyronine, T_3) **(2)** are produced by the thyroid gland and secreted into the blood stream. The minute amounts secreted are regulated by a complex system (Fig. 1) that originates in the central nervous system (CNS) and is amplified by both the hypothalamus and the anterior pituitary. These amounts can, however, be diminished by feedback loops in which circulating levels of free T_3 and T_4 repress production of the pituitary TSH, and perhaps of this hormone itself by inhibiting release in the hypothalamus of its liberating hormone, TRH. In addition, amounts of hormones reaching the cells to preserve an optimal (euthyroid) condition are regulated by two plasma proteins, ie, thyroid hormone-binding globulin [9010-34-8] (TBG) and thyroid hormone-binding prealbumin [632-79-1] (TBPA). Only a small fraction ($<0.3\%$) of the total hormones in circulation is free. Finally, tissue deiodinases convert T_4 (possibly a prohormone) into the fivefold more active T_3.

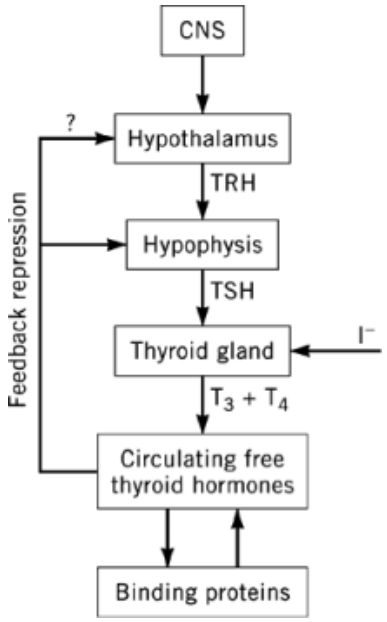
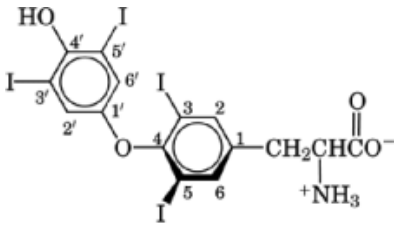
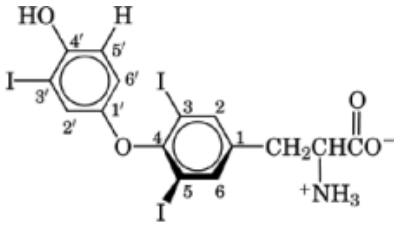


Fig. 1. Mechanisms controlling free thyroid-hormone levels.



(1)



(2)

Thyroid hormones affect growth and development by stimulating protein synthesis. It is thought that a specific receptor protein that strongly binds the hormones is present in cell nuclei (7) (Fig. 2). This protein is closely associated with nuclear deoxyribonucleic acid (DNA), a complex involved in DNA transcription. The binding of the hormones is a specific signal to a DNA template that, when activated, stimulates the synthesis

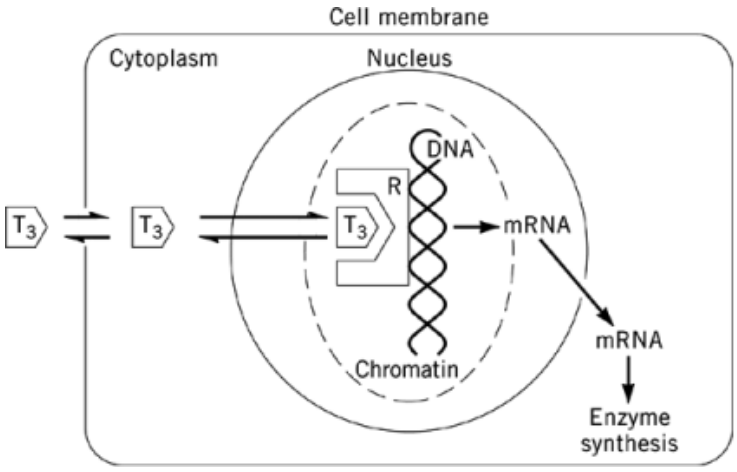


Fig. 2. Early events in thyroid-hormone action. Interaction of T_3 with cell nuclear receptors (6).

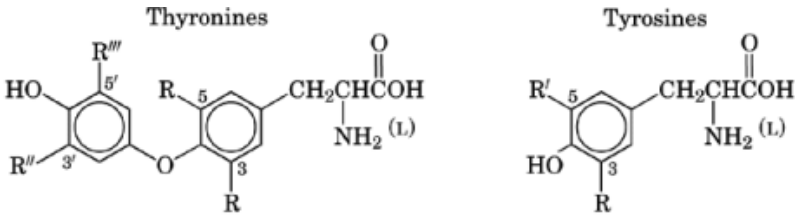
and release of a specific messenger ribonucleic acid (mRNA). The latter stimulates the synthesis of astructural and functional proteins, eg, enzymes and other hormones, which then bring about growth and development.

In mature animals, the main action of the thyroid hormones is their calorigenic effect which is caused by an increase in the basal metabolic rate (BMR). Although many theories have been advanced (8), the mechanism of action of this effect at the molecular level is not understood. Given the importance of the thyroid hormones in bringing about and then maintaining a normal metabolic state, it is not surprising that malfunctions of the thyroid gland have grave consequences (2, 9).

Thyroid underfunction results in a series of hypothyroid states clinically known as cretinism if present in a fetus or an infant, and myxedema in an adult. If the hypothyroidism is owing to insufficient iodine intake, it is known as simple goiter, a state characterized by an enlarged but functionally underactive thyroid gland. Goiter can be avoided by adding iodine to the diet in a convenient form, eg, iodate. In the United States, iodized table salt contains 100 μg of iodate per gram of NaCl (2) (see Sodium compounds, sodium halides–sodium chloride). Even so, endemic goiter is still an important health problem in many areas of the world, especially in those where underdevelopment coincides with remoteness from oceans.

Myxedema and goiter are the main conditions for which thyroid preparations are indicated. The treatment of cretinism is difficult because it is recognized only at or after birth. Even if this disease could be diagnosed *in utero*, thyroid hormones do not readily cross the placental barrier. In addition, the fetus, as does a premature infant, rapidly deactivates the thyroid hormones. The halogen-free analogue DIMIT [26384-44-7] (**3**), which is resistant to fetal deiodinases, may prove useful for fetal hypothyroidism (cretinism).

Thyroid hyperfunction occurs as diffuse toxic goiter, also known as Graves' disease, seen mainly in young adults and premenopausal women. This disease is considered to be caused by an immune disorder. It is characterized by protruding eyeballs (exophthalmos). Another form of thyroid hyperfunction is thyrotoxicosis, ie, a collection of symptoms caused by excessive production of thyroid hormones, including hyperthermia, rapid heart rate, increased appetite and loss of weight, insomnia, anxiety, etc. Toxic nodular goiter (Plummer's disease) is less common. Severe cases are treated by partial surgical removal of the thyroid gland or its partial destruction with radioactive iodine. Milder cases are controlled with antithyroid drugs.



Compound	R	R′	R″	R‴
(**1**) T_4	I	I	I	I
(**2**) T_3	I	I	I	H
(**3**) DIMIT	CH_3	CH_3	i-C_3H_7	H
(**4**) r-T_3	I	H	I	H
(**5**) 3,3′-T_2	I	H	I	I

Compound	R	R′
(**6**) TYR	H	H
(**7**) MIT	I	H
(**8**) DIT	I	I

Fig. 3. Structures of the thyroidal iodinated amino acids and the halogen-free analogue DIMIT (**3**). Compound (**4**) is reverse-T_3.

Table 1. Thyroidal Iodinated Amino Acids[a]

Name	CAS Registry Number	Compound	Mol wt	I, %	pK_a (OH)	$[\alpha]_D$
3-iodo-L-tyrosine	[70-78-0]	(**7**)	307.1	41.3	8.70	−4.4[b]
3,5-diiodo-L-tyrosine	[66-02-4]	(**8**)	433.0	58.6	6.48, 6.36	2.75[b]
3,5-diiodo-L-thyronine	[1041-01-6]	(**9**)	525.1	48.3	9.29	26.0[c]
3,3′-diiodo-L-thyronine	[4604-41-5]	(**5**)	525.1	48.3		18.8[c]
3,5,3′-triiodo-L-thyronine	[6893-02-3][d]	(**2**)	650.9	58.5	8.45	21.5[c]
3,3′,5′-triiodo-L-thyronine	[5817-39-0]	(**4**)	650.9	58.5	6.5[e]	16.7[c]
3,5,3′,5′-tetraiodo-L-thyronine	[51-48-9][f]	(**1**)	776.8	65.3	6.73, 6.45	17.5[c]

[a] Data mainly from Refs. 6 and 10. These compounds decompose; their melting points are indistinct.
[b] In 4.8% HCl.
[c] In 1 *N* HCl–C_2H_5OH.
[d] Anhydrous Na salt [55-06-7].
[e] Value is estimated.
[f] Anhydrous Na salt [55-03-8]; Na salt, 5 H_2O [25416-65-3].

2. Thyromimetic Compounds

2.1. Thyroidal Amino Acids

Toward the end of the nineteenth century, it was discovered that the consumption of fresh sheep thyroid glands was beneficial in hypothyroidism. In an attempt to isolate the active principle, an extract was prepared (10) and commercialized (11). In the course of this work, it was discovered that thyroid glands were rich in iodine. In 1914, a biologically active pure compound was isolated from thyroid extracts and was called thyroxin on the mistaken assumption that it had an oxyindole structure. Some years later, the correct structure (**1**) was established by degradation and synthesis. About 25 years later two groups simultaneously identified another biologically active compound that is recognized as the main thyroid hormone. It is the 5′-desiodo analogue of thyroxine, T_3 (**2**). Two more iodinated thyronines have been found in the thyroid (Fig. 3). They are 3,3′,5′-triiodothyronine [5817-39-0] (reverse-T_3) (**4**) and 3,3′-diiodothyronine [4604-41-5] (T_2) (**5**). These compounds

are hormonally inactive and are secreted by the thyroid or arise by partial deiodination of T_3 and T_4. Their physiological significance is not clear. Some properties of these compounds are listed in Table 1.

For many years it was believed that iodine, or some other halogen, had to be present to endow these compounds with thyromimetic activity. This was shown to be incorrect when a halogen-free analogue, DIMIT (3), was found to have 20% of the potency of T_4 in a variety of *in vivo* tests (12).

2.2. Structure–Activity Relationships

In spite of the considerable synthetic and bioassay effort involved in establishing the thyromimetic potency of thyroid-hormone analogues, more than 100 compounds have been studied (Table 2). The main structural requirements for thyromimetic activity can be summarized as follows (6, 12–16).

Table 2. Thyromimetic Compounds: Relative Binding Affinities (BA)[a] and Antigoiter Potencies (AG)[b]

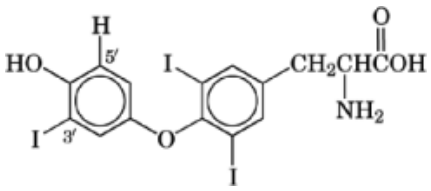
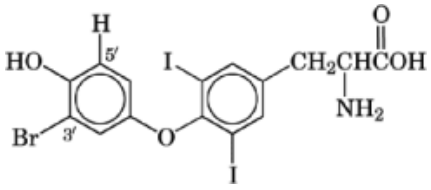
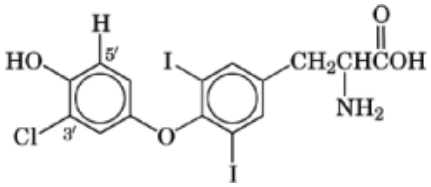
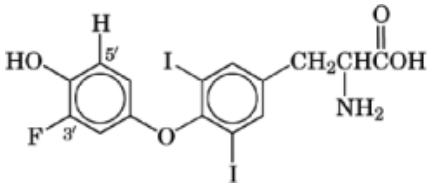
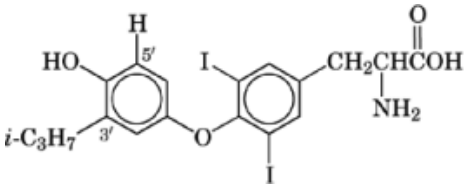
R	R′	CAS Registry Number	BA	AG
I		[6893-02-3]	1	1
Br		[58437-19-7]	0.16	0.24
Cl		[4299-63-2]	0.04	0.05
F		[348-94-7]	0.02	ca 0.01
i-C_3H_7		[51-23-0]	0.89	1.42

Table 2. ***Continued***

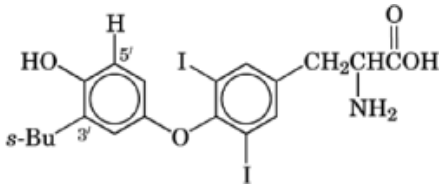
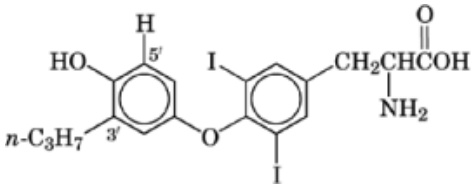
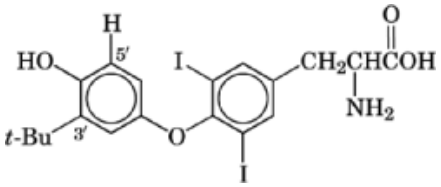
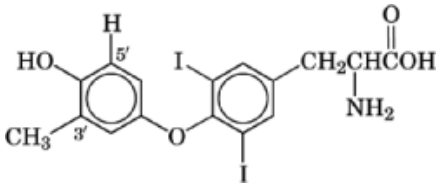
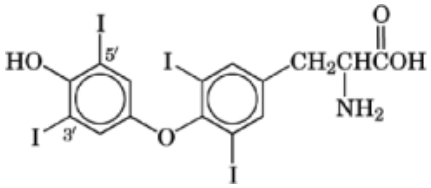
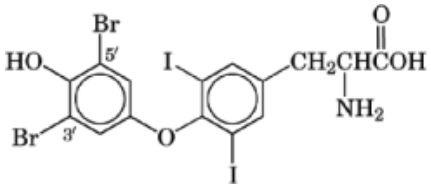
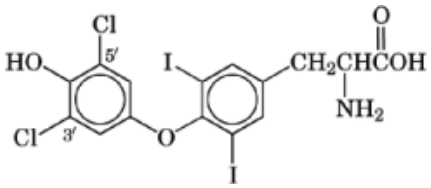
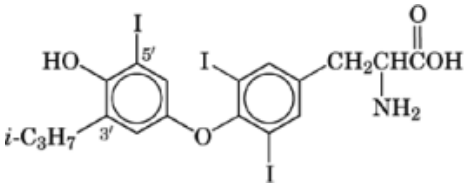
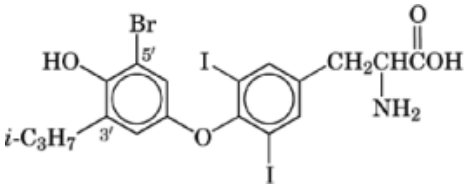
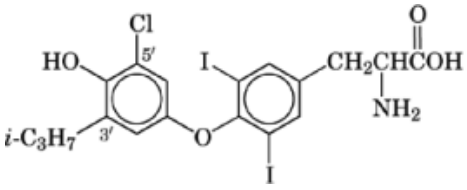
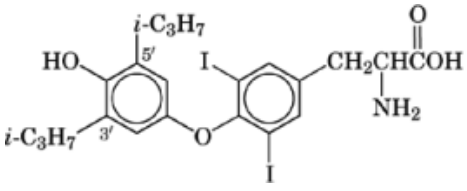
R	R′	CAS Registry Number	BA	AG
s-Bu		[3415-06-3]	0.78	0.80
n-C_3H_7		[72468-99-6]	0.24	0.40
t-Bu		[857-98-7]	0.08	0.22
CH_3		[2378-96-3]	0.03	0.14
I		[51-48-9]	0.14	0.18
Br		[2500-09-6]	0.05	0.02

Table 2. ***Continued***

R	R′	CAS Registry Number	BA	AG
Cl		[4299-64-3]	0.04	0.04
i-C_3H_7		[3458-12-6]	0.12	
i-C_3H_7		[75628-30-7]	0.22	
i-C_3H_7		[75628-29-4]	0.53	
i-C_3H_7		[30804-63-8]	0.01	

[a] To solubilized rat hepatic nuclear protein receptor
[b] Affinities and potencies are relative to L-T_3 taken as 1 (6).

(*1*) Two aromatic rings insulated electronically from each other by connecting oxygen, sulfur, or carbon bridges, forming a central lipophilic core in which the two rings are angled 120°.

(*2*) Substitution at the 3 and 5 positions with alkyl groups or with halogens large enough to force the diphenyl ether nucleus to adopt a minimum energy conformation in which the two rings are approximately in mutually perpendicular planes.

(*3*) At position 1, an acidic side chain two or three carbons long should be present. The natural L-alanyl side chain reduces receptor binding but enhances *in vivo* activity by increasing access to the receptor and by

retarding metabolism and excretion. The enantiomeric D-analogues retain considerable activity in contrast to other bioactive substances (17).

(*4*) The presence of a small substituent capable of forming hydrogen bonds in the 4′-position. Isosteric groups such as NH_2 reduce activity, whereas any other group that cannot be converted metabolically to a 4′-OH group results in inactive compounds.

(*5*) The minimal activity residing in the core structure so far described is greatly enhanced by one lipophilic substituent ortho to the 4′-OH group. High activity imparted by iodine or alkyl groups of similar size, eg, isopropyl. Inspection of structure (**1**) shows that for T_3 two atropisomers (preferred conformers owing to restricted rotation about single bonds) are possible. In the one shown, the 3′-I is distal to the other ring whereas a second one is obtained by rotating the phenolic ring 180° about the C-1′–O bond, in which the lone iodine is proximal to the other ring. Both atropisomers have been detected in a variety of compounds by x-ray crystallography (18). In their interaction with biomacromolecules, however, affinity is increased when the 3′-substituent is distal. A second lipophilic group at the other position ortho to the 4′-OH (ie, at C-5′) always reduces activity because of steric hindrance at the binding site. In a variety of *in vivo* test systems, one synthetic analogue (3,5-diiodo-3′-isopropyl-L-thyronine, see Table 2) has been shown to be more potent than T_3.

Quantitative structure–activity relationships have been established using the Hansch multiparameter approach (14). For rat antigoiter activities (AG), the following (eq. 1) was found, where, as in statistical regression equations, n = number of compounds, r = regression coefficient, and s = standard deviation

$$\log \mathrm{AG} = 1.354\pi 35 + 1.344\pi 3' - 1.324\ \left[(\mathrm{size}{-}3') > \mathrm{I}\right]$$

$$-0.359\pi 5' - 0.658\sigma 3'5' - 0.890\ (\mathrm{OCH_3}{-}4') - 2.836$$

$$n = 36 \qquad r = 0.938 \qquad s = 0.304 \qquad (1)$$

of the dependent variable. In equation 1, AG is the relative antigoiter potency, π and σ are lipophilic and electronic substituent parameters, (OCH_3-4′) is a dummy parameter indicating the presence (1) or absence (0) of this substituent, and (size-3′ > I) is a computed estimate of the size of this substituent beyond that of an iodine atom. This equation does not include a π^2-term (optimal lipophilicity), and therefore the substituent pattern is unimportant in the overall partitioning behavior. Analogous equations have been derived for interactions of thyroid hormone analogues with other systems (TBG, TBPA, or nuclear receptors) (14). Slight but significant differences in the regression constants point to differences in the shape of the recognition site. Nevertheless, good correlations exist between them and *in vivo* activities (see Table 2), and they can be used with confidence to predict intact animal activity (19).

2.3. Biosynthesis, Distribution, and Metabolism

Although iodine is a trace element in the environment (0.006% in ocean water) and the diet, the thyroid gland avidly extracts it from the blood as iodide ion via an active transport system. In the thyroid cells it is converted by a peroxidase to a form capable of iodinating tyrosyl residues present in a large glycoprotein called thyroglobulin [9010-34-8]. It is believed that the resulting mono- and diiodinated residues react with each other in the protein matrix (possibly by a free-radical coupling mechanism) to form all the possible di-, tri-, and tetraiodothyronines (20–22). Thyroglobulin is a glycoprotein having several subunits. Its molecular weight is 660,000 (19*S*), and it contains ca 10% carbohydrate (corresponding to 300 residues) and ca 5500 amino acid residues of which only two to five are thyroxine. Its amino acid composition and further details of its structure and physical properties are available (23).

The iodinated thyroglobulin is stored as a colloid in thyroidal follicular cells, and T_3 and T_4 are liberated from it by proteolysis as required. It is estimated that ca 90 μg of T_4 and 6 μg of T_3 are secreted daily by the thyroid gland, giving mean plasma concentrations of 80 and 2 μg/L, respectively, of which only 0.03 and 0.3%

are in the free form, ie, not protein bound (21). The half-life of T_4 in the body is long (6–7 d) (2); that of T_3 is somewhat shorter (2 d).

The biosynthesis and release of the hormones can be interfered with in various ways, which is the basis of action of certain antithyroid preparations.

Only the small amounts of T_4 and T_3 that are free in the circulation can be metabolized. The main route is deiodination of T_4 to T_3 and r-T_3, and from these to other inactive thyronines (21). Most of the liberated iodide is reabsorbed in the kidney. Another route is the formation of glucuronide and sulfate conjugates at the 4′-OH in the liver. These are then secreted in the bile and excreted in the feces as free phenols after hydrolysis in the lower gut.

2.4. Synthesis

In the syntheses of T_4 and its congeners, formation of the sterically hindered diaryl ether core is difficult, as is the introduction of the alanyl side chain (or the preservation of its L (*S*) absolute configuration) and iodination to the desired degree (T_3 or T_4).

The most widely employed route is the so-called Glaxo method (24) (Fig. 4). The starting material is tyrosine, which is readily available in the L-form and accessible in the D-form. Nitration and protection of the side chain give the key intermediate, *N*-acetyl-3,5-dinitrotyrosine, ethyl ester [29358-99-4]. The activating effect of the two ortho nitro groups allows the phenolic OH to be displaced readily by pyridine. The resulting quaternary pyridinium adduct, in turn, displays a high reactivity toward nucleophilic displacement by phenoxides, which is the key factor in the successful formation of the ether link in spite of the formidable steric hindrance presented by the nitro groups. In the original procedure the pyridinium tosylate was isolated and purified (24). A modification, in which methanesulfonyl chloride is used, obviates this isolation and results in a faster reaction with higher yields (25). The dinitro ether is then subjected to a Sandmeyer procedure in which the nitro groups are converted to iodines, followed by removal of the blocking groups to give 3,5-diiodothyronine. Finally, one or two additional iodines are introduced to give T_3 and T_4, respectively. In the original procedure, L-T_4 was obtained in an overall yield of 26% based on L-tyrosine (20). By starting with D-tyrosine, D-T_4, which is used clinically to reduce high cholesterol blood levels, can be obtained (26).

This versatile synthetic route has been used extensively with a great variety of phenols and thiophenols to establish structure–activity relationships for thyromimetic activity. Other routes can be summarized as follows (13).

(*1*) In the first synthesis of T_4, the diphenyl ether was formed from *p*-methoxyphenol and 3,4,5-triiodonitrobenzene. The nitro group was replaced by a nitril which was then built up into the alanyl side chain by a series of steps (10).

(*2*) In a biomimetic synthesis, two DIT (**8**) molecules have been coupled to give T_4 (27).

(*3*) In a procedure known as the iodonium condensation, substituted diaryliodonium compounds react with tyrosines. Thyronines with substituents other than NO_2 or I at the 3 and 5 positions are obtained.

(*4*) Many other routes have been used to prepare analogues with structures that differ more from T_4, eg, a methylene, carbonyl, or no bridge in place of the ether linkage (13). The halogen-free analogue DIMIT was synthesized by an ingenious route involving the replacement of the iodines at the 3- and 5-positions with cyano groups and their reduction to methyl groups (28).

2.5. Chemical Assay

In view of the similarity of their chemical and physical properties (see Table 1) (29), the main problem in the chemical analysis of the thyroid hormones is their separation. A USP procedure gives the details of a paper chromatographic separation in which T_3 is examined for contamination by T_4 and 3,5-diiodothyronine (30). Other systems are also employed (29).

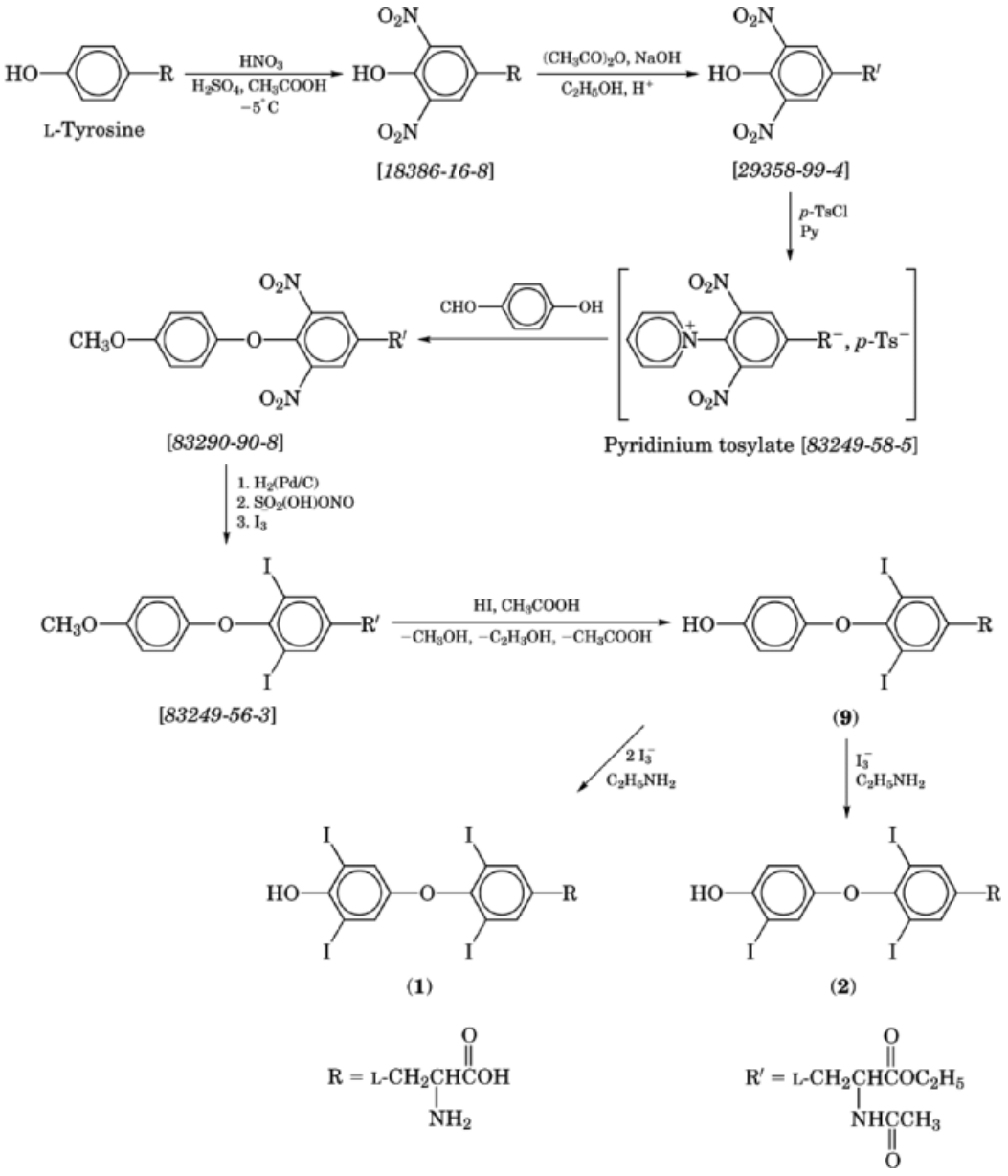


Fig. 4. Glaxo synthesis of T_3 and T_4 where $_{p-TsCl=}$ *p*-toluenesulfonyl chloride and $_{Py=}$ pyridine (24).

When the purity of the preparation has been ascertained, both T_3 and T_4 are assayed on the basis of their iodine content after combustion in an oxygen flask (29, 30).

Body fluids are analyzed for T_3 and T_4 by a variety of radioimmunoassay procedures (31) (see Immunoassays). The important clinical parameter for estimating thyroid function, the protein-bound iodine (PBI), is measured as described in treatises of clinical chemistry. High performance liquid chromatographic (hplc) methods have replaced tlc (32, 33).

2.6. Bioassay

Although the chemical assays described above have replaced bioassays for the determination of T_3 and T_4, several *in vivo* and *in vitro* bioassays are used to determine the potency of thyroglobulin preparations and to establish the thyromimetic or antithyroid potency of new compounds.

2.6.1. In Vivo Tests

The rat antigoiter assay is the most common test for thyromimetic activity. Rats are fed an antithyroid compound, eg, propylthiouracil, for 10 days. At the end of this period, they have developed a goiter of such size that the thyroid weighs ca six times that of control rats. A group of rats is injected daily with standard doses of T_4 (2.5 μg/100 g body wt) or T_3 (0.5 μg/100 g body wt) which are sufficient to prevent goiter formation. Other groups of rats are treated with the appropriate amounts of the thyromimetic compound. Comparison of the equiactive dose with that of T_3 or T_4 establishes its relative potency. Putative antagonists are administered concurrently with T_3 or T_4 and their activity is assessed from the weight of the goiter formed. Strictly speaking, this assay is based on the relative efficacy of the analogues in their interaction with a thyroid-hormone receptor found in anterior pituitary cells which modulates the secretion of TSH (see Fig. 1).

The mouse anoxia or oxygen-consumption test is based on the stimulation of the basal metabolic rate by thyromimetic compounds. Mice or other small animals are placed in airtight containers of known volume and their survival time is determined (34).

The amphibian metamorphosis test is based on the ability of thyroid hormones to induce precocious transformation of a tadpole into a frog or of the axolotl into a salamander. It is rarely used because of solubility problems and the difficulty of applying the results to humans.

2.6.2. In Vitro Biological Tests

The inherent complexities, vagaries, and high cost of whole animal assays spurred the development of a series of *in vitro* binding assays to various macromolecules that avidly bind thyroid hormones. In general, and allowing for differences in metabolism, excellent agreement with *in vivo* assays was found, and studies of thyroid-hormone structure–activity relationships (SAR) have been greatly simplified.

Using any of the carrier proteins available in highly purified form, eg, TBG or TBPA, a convenient and accurate quantitative determination of T_3 and T_4 is possible by displacement of radioiodinated T_3 or T_4. This procedure enables their quick determination at low concentrations even in the presence of countless other substances that occur in body fluids (31). In a similar fashion, intact cell nuclei or solubilized proteins from rat liver cell nuclei, which display high affinities for thyroid hormones, especially T_3, have been used to establish relative binding affinities of many thyromimetic compounds (7).

3. Antithyroid Substances

In principle, antithyroid effects (35–39) can be produced by destroying excess thyroid gland tissue surgically or by treatment with radioiodine; blocking synthesis of thyroid hormones with goitrogens such as certain thionamides; inhibition of thyroid-hormone release with lithium; inhibition of the peripheral deiodination of T_4 to the more active T_3 with thiouracils; increasing excretion of thyroid hormone (*n*-butyl-3,5-diiodo-4-hydroxybenzoate [51-38-7] as a result of displacing T_3 and T_4 from serum proteins; and competitive antagonism at the receptor level (r-T_3).

12 THYROID AND ANTITHYROID PREPARATIONS

3.1. Intrathyroidal Inhibitors

3.1.1. Iodide and Other Inorganic Anions

When large doses of iodide ion are administered, a transient inhibition of synthesis and release of the thyroid hormones is brought about by the so-called Wolff-Chaikoff effect.

The selective uptake of iodide ion by the thyroid gland is the basis of radioiodine treatment in hyperthyroidism, mainly with ^{131}I, although various other radioactive isotopes are also used (40, 41). With a half-life of eight days, the decay of this isotope produces high energy β-particles which cause selective destruction within a 2 mm sphere of their origin. The γ-rays also emitted are not absorbed by the thyroid tissue and are employed for external scanning.

Certain inorganic monovalent anions, similar in size to I, are also taken up by the thyroid gland and competitively inhibit active iodide transport with the following decreasing potencies:

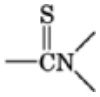
$$TcO_4^- \gg ClO_4^- > ReO_4^- > BF_4^- > I^-$$

Clinical use of perchlorate salts (Na or K) is limited because of side effects.

Thiocyanate ion, SCN^-, inhibits formation of thyroid hormones by inhibiting the iodination of tyrosine residues in thyroglobulin by thyroid peroxidase. This ion is also responsible for the goitrogenic effect of cassava (manioc, tapioca). Cyanide, CN^-, is liberated by hydrolysis from the cyanogenic glucoside linamarin it contains, which in turn is biodetoxified to SCN.

3.1.2. Thionamides

A large group of compounds incorporating thionamide,



or thiourea,

moieties are potent antithyroid agents. These inhibit the peroxidases which catalyze the iodination of tyrosine residues in thyroglobulin and their coupling. Although several hundred such compounds are known (42), only four (Fig. 5, Table 3) are used clinically and only two are accepted by the USP XX.

The imidazoles methimazole [60-56-0] (MMI) (**12**) and Carbimazole [22232-54-8] (**13**) act by inhibiting intrathyroidal hormone synthesis, whereas the thiouracils (**10**) [51-52-5] and (**11**) [56-04-2] also inhibit the peripheral deiodination of T_4 to T_3. Thus, the latter are preferred in the treatment of thyroid storm (thyrotoxic crisis) where a quick drop in circulating T_3 is desired (2, 9). In general, the imidazoles are 10 times as active as the thiouracils.

The synthesis of these compounds is shown in Figure 5. Extensive compilations of the chemical, and chromatographic and spectral properties of compounds (**10**) and (**12**) are given in References 43 and 44, respectively.

Although several metabolites of propylthiouracil have been found (36, 44), it is mainly excreted in urine as the glucuronide. Its relatively short plasma half-life requires that it be administered four times daily.

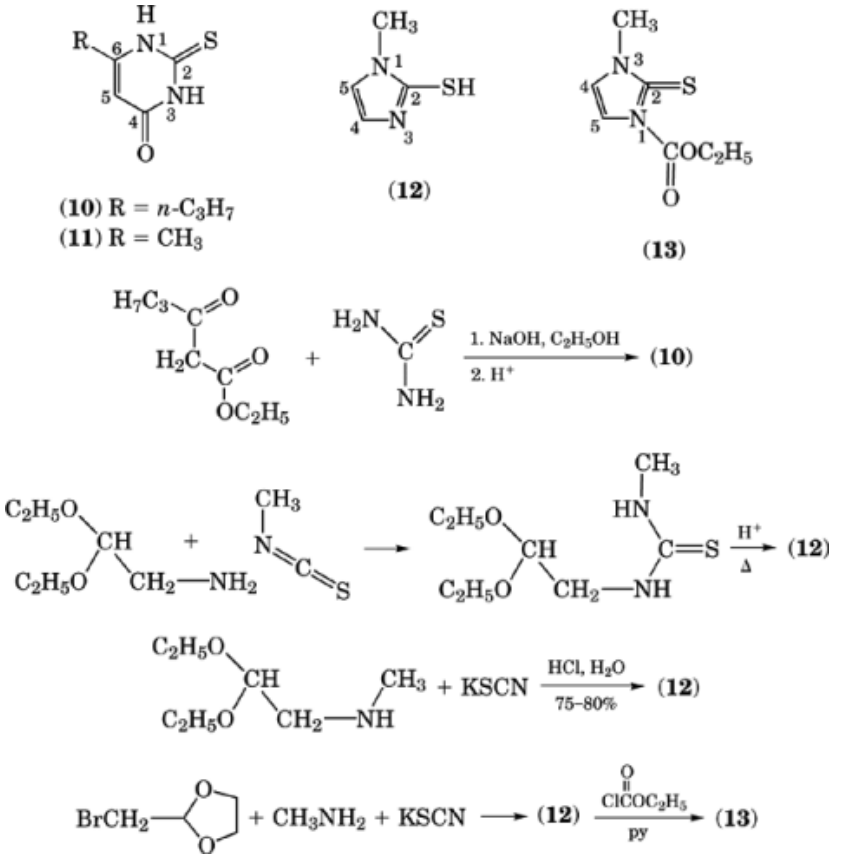


Fig. 5. Structures and syntheses of the clinically employed thionamides, where py=pyridine.

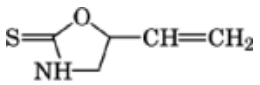
Table 3. Antithyroidal Thionamides

Name	CAS Registry Number	Structure	Composition	Mol wt	S, %	Mp, °C
6-propyl-2-thiouracil (propylthiouracil, PTU)	[51-52-5]	(**10**)	$C_7H_{10}N_2OS$	170.23	18.84	219–221
6-methyl-2-thiouracil	[56-04-2]	(**11**)	$C_5H_6N_2OS$	142.18	22.55	325 dec
1-methyl-2-mercaptoimidazole (methimazole, MMI)	[60-56-0]	(**12**)	$C_4H_6N_2S$	114.16	28.09	146–148
3-methyl-1-carbethoxy-2-thio-imidazoline (carbimazole)	[22232-54-8]	(**13**)	$C_7H_{10}N_2O_2S$	186.23	17.22	122–125

Extensive studies have been carried out on the metabolic fate of compounds (**12**) and (**13**) (36). After initial accumulation in the thyroid gland, the unchanged drugs and various metabolites appear in the urine. The carbethoxy group in carbimazole, which was introduced to mask the bitter taste of methimazole, is metabolically removed, and therefore carbimazole can be considered a prodrug of methimazole.

Recommended daily maintenance doses are 50–200 mg for PTU, and 5–20 mg (three times per day) for the imidazoles. The incidence of side effects is low.

It has been known for a long time that some foodstuffs, eg, turnips and rutabaga, are goitrogenic because of the presence of progoitrin. This substance is hydrolyzed to goitrin, or (*S*)-5-vinyl-2-oxazolidinethione [500-12-9] **(14)**, which is goitrogenic when iodine intake is low.



(14)

3.1.3. Aromatic Amines and Phenols

The discovery that sulfaguanidine [57-67-0] was goitrogenic to rats was serendipitous. Many related compounds were then examined, and the aniline moiety was usually present (2, 6). Such compounds, as well as resorcinol-like phenols, may act as goitrogens by inhibiting thyroid peroxidases. These are not used clinically.

3.1.4. Lithium

In the lithium carbonate treatment of certain psychotic states, a low incidence (3.6%) of hypothyroidism and goiter production have been observed as side effects (6, 36) (see Psychopharmacological agents). It has been proposed that the mechanism of this action is the inhibition of adenyl cyclase. Lithium salts have not found general acceptance in the treatment of hyperthyroidism (see Lithium and lithium compounds).

3.2. Peripheral Antagonists

The relatively long duration of action of the thyroid hormones makes it desirable to have compounds capable of blocking them competitively at their site of action. This is desirable in the treatment of thyroid storm where the reduction of circulating hormone levels brought about by the inhibition of their synthesis is too slow.

A large number of thyroid hormone analogues have been tested for this effect (6). Among others, r-T_3 (**3**) and 3,3′-T_2 (**5**) and their propionic acid side-chain analogues decrease oxygen consumption at molar ratios of 50–200:1 of T_4. Nevertheless, no potent or clinically useful peripheral antagonists have been found.

The level of circulating hormones is lowered indirectly by *n*-butyl 3,5-diiodo-4-hydroxybenzoate which displaces them from their carriers (TBG and TBPA) and thus accelerates their metabolism and excretion (6).

4. Calcitonin

Several years ago, it was discovered that the thyroid gland was also the source of a hypocalcemic hormone having effects in general opposition to those of the parathyroid hormone. This hormone is produced in mammals by the parafollicular C-cells and in other vertebrates by the ultimobrachial bodies (45). Originally called thyrocalcitonin, it is now referred to as calcitonin (CT).

Calcitonins from several species have been characterized and synthesized. They are all single-chain 32-residue polypeptides (ca 3600 mol wt), although a disulfide link between the first and seventh cysteine residues results in a cyclic structure that is indispensable for activity (Fig. 6).

Calcitonin is secreted when abnormally high calcium levels occur in plasma. Although plasma concentrations are normally minute (<100 pg/mL), they increase two- to threefold after calcium infusion. Calcitonin has a short plasma half-life (ca 10 min). Certain thyroid tumors are the result of CT concentrations 50–500 times normal. The mechanism of action is a direct inhibition of bone resorption. Calcitonin is used clinically in various diseases in which hypercalcemia is present, eg, Paget's disease (46).

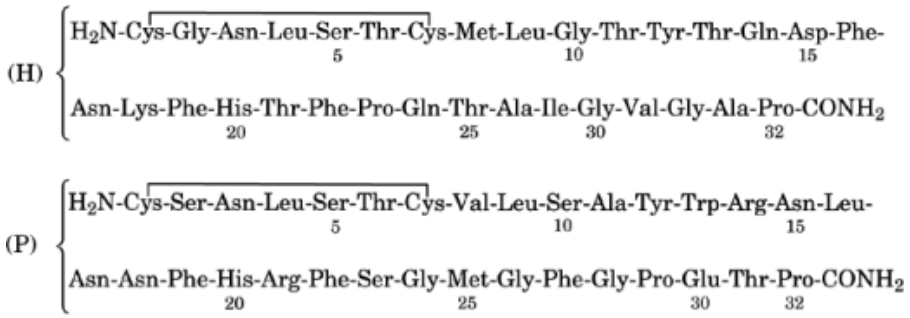


Fig. 6. Amino acid sequence of human (H) and porcine (P) calcitonins.

5. Commercial Preparations

5.1. Sodium Levothyroxine

As one of the active principles of the thyroid gland, sodium levothyroxine [55-03-8] (levothyroxine sodium) can be obtained either from the thyroid glands of domesticated animals (10) or synthetically. It should contain 61.6–65.5% iodine, corresponding to $100 \pm 3\%$ of the pure salt calculated on an anhydrous basis. Its chiral purity must also be ascertained because partial racemization may occur during synthesis and because *dl*-T_4 is available commercially. Sodium levothyroxine melts with decomposition at ca 235°C. It is prepared as pentahydrate [6106-07-6] from L-thyroxine and sodium carbonate (47).

Sodium L-thyroxine is a light yellow or buff-colored odorless, tasteless, hygroscopic powder that is stable when dry and protected from light. It is slightly soluble in water (1 g/700 mL) and ethanol (1 g/300 mL) and insoluble in most organic solvents. It is soluble in aqueous alkaline solutions (48). The sodium salt is reported to be better absorbed than the free acid although its bioavailability is still low (50%). Its plasma half-life is five days. An extensive compilation of its chemical, spectroscopic, and chromatographic characteristics is given in Reference 29.

5.2. Sodium Liothyronine

Sodium liothyronine [55-06-1] is the sodium salt of L-3,5,3′-triiodothyronine. It is made by the controlled iodination of L-3,5-diiodothyronine. It may be contaminated by starting material or L-T_4. The USP assay (49) describes a chromatographic separation specifying 3,5-T_2 2% max and T_4 5% max. Iodine content is specified at 95–101%. Chiral purity must also be ascertained. Detailed information on its chromatographic behavior is available (29).

5.3. Thyroglobulin

Thyroglobulin is obtained by fractionating hog thyroid glands until a preparation is obtained containing not less than 0.7% of organically bound iodine (50). It is a cream- to tan-colored powder with a characteristic odor and taste. It is stable in air but sensitive to light and is insoluble in water, alcohol, and other organic solvents (51). It is standardized by chemical and biological assay to contain a T_4:T_3 ratio of 2.5:1.

5.4. Thyroid

Glandulae Thyroideae siccatae is the cleaned, dried, and powdered thyroid gland previously deprived of connective tissue and fat from domesticated animals used for food by humans (52). It contains $0.20 \pm 0.03\%$ iodine

in organically bound form and is free of inorganic iodine. Batches of high or low iodine content should be adjusted to the specified concentration by blending or with a suitable diluent. It is dispensed in tablets of various strengths (15–300 mg).

5.5. Calcitonin

Calcitonin is available commercially from pork and salmon extracts (Calcimar, Armour) as well as by synthesis. Preparations are bioassayed on the basis of their calcium-lowering activity in comparison to the potency of pure pork calcitonin of which ca 4 μg is equivalent to 1 MRC unit (Medical Research Council, U.K.). For clinical use, vials containing 400 units in 4 mL are available. The recommended daily dosage is 100 units to be administered subcutaneously or intramuscularly because its plasma half-life is short (4–12 min).

5.6. Antithyroid Drugs

5.6.1. Propylthiouracil

This compound is a white, powdery, crystalline substance of starch-like appearance with a bitter taste. It is slightly soluble in water, chloroform, and ethyl ether, sparingly soluble in ethanol, and soluble in aqueous alkaline solutions (53). An extensive compilation of its chemical, spectral, and chromatographic properties is available (43). It is assayed titrimetrically with NaOH (53).

5.6.2. Methimazole

This compound is a white to pale buff crystalline powder with a faint characteristic odor. It is soluble in water, ethanol, and chloroform (1 g/5 mL) and only slightly soluble in other organic solvents. A detailed chemical, analytical, spectral, and chromatographic description is available (44). It is assayed titrimetrically with NaOH (54).

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