MEDICINAL CHEMISTRY

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VOLUME I

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Preface to the Series

Chemists and pharmacologists concerned with the synthesis and evaluation of new compounds have long realized the need for a publication that would provide comprehensive and systematic summaries of available data on the biological properties of substances already studied. The correlation of structure and activity in such summaries stimulates the visualization of new molecular structures and leads to the synthesis and testing of new compounds.

The Division of Medicinal Chemistry of the American Chemical Society, at its business meeting in Chicago on September 11, 1946, decided to initiate plans for a series of books that would present reviews in the field of medicinal chemistry. This project was to be under the general supervision of an editorial board chosen from the membership of the division and in harmony with the rules of the national society.

After plans for the new publication had matured so that a definite proposal could be made, including discussion with prospective publishers, the board of directors of the American Chemical Society was asked for permission to proceed with the publication under the specific auspices of the Division of Medicinal Chemistry and the general guidance of the committee on publications of the society. Approval was granted by the board on April 19, 1948. It is a pleasure to express our indebtedness to the directors of the society for this expression of confidence and to Mr. Alden H. Emery, Dr. W. A. Hamor, and Mr. Arthur B. Hanson of the American Chemical Society, who have been most cooperative in advice on matters of general policy and contractual arrangements.

A chief objective of MEDICINAL CHEMISTRY is to include in each chapter references to all the compounds that have been tested for a particular type of pharmacological activity. Where it is necessary to limit one chapter to a segment of the field because of lack of space, a division is made, based on a chemical classification. It is expected that the additional areas will be treated in later volumes. The compounds are presented mostly in tabular form according to chemical groups or series. Associated with this comprehensive survey of compounds are discussions of the relationships between chemical structure and pharmacological action. Many references are given to groups of compounds, particularly in the patent literature, which have been claimed to have pharmacologi-

cal activity even if data to sustain this statement have not been published. Each chapter also contains brief discussions of methods of synthesis and pharmacological test procedures which aid the reader in judging the status of work in a given area. It is not feasible, within the space limitations, to give a comprehensive treatment of organic or analytical chemistry problems or, on the other hand, of the detailed pharmacology of single compounds. The interests of the chemist and pharmacologist, who are searching for new and useful molecular structures, seem best served by concentration on the comparison of the "screening" results. These preliminary data are employed in making decisions as to what compounds receive intensive study.

Those concerned with this publication will be pleased to have suggestions with regard to improvements for future volumes and comments on subject matter suitable for review. Suggestions from the members of the Division of Medicinal Chemistry are particularly solicited because this is a publication of their division.

C. M. SUTER

January, 1951

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CHAPTER 1

ANTITHYROID COMPOUNDS

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INTRODUCTION

General. Antithyroid compounds may be defined broadly as chemical compounds that depress thyroid function. They have potential use wherever control of thyroid function is desirable. In physiological research, they have proved to be tools superior to surgical thyroidectomy. Their main practical application to date has been in the treatment of hyperthyroidism, a disorder in which the thyroid produces excessive amounts of its hormone. The first compound to be extensively used in the treatment of this condition was thiouracil; in 1946 a summary of the results in 5745 cases was published by Van Winkle et al.[1] Since then, many thousands of other cases have been treated with this and related drugs, and hundreds of compounds have been tested in animals. Of the dozen or so that have received clinical trial, 6-propyl-2-thiouracil and 6-methyl-2-thiouracil are currently receiving the widest use in general medical practice.

Antithyroid compounds may exert their action by (1) blocking the formation of thyroid hormone or (2) opposing its action. Substances having the latter type of action have been reported, but so far none has proved useful in clinical practice. It is the former type that has seen rapid development since 1941.

A three-phase sequence occurs with type 1 action: (*a*) suppression of thyroid hormone formation in the thyroid, (*b*) increased production by the pituitary of thyroid-stimulating hormone, and (*c*) morphological activation of the thyroid without physiological effect. Indicators of antithyroid effect are associated with *c*. The thyroid iodine content decreases, the gland becomes hyperemic, histological changes occur, and the weight of the gland increases. Effects due to decreased thyroid hormone formation other than *b* and *c* are decrease in basal metabolism and growth in animals, and inhibition of metamorphosis of tadpoles. The mechanism of thyroid hormone production is discussed later.

Historical. Since the start of the century a number of investigators have studied the thyroid gland and its functions and dysfunctions. Many attempts have been made to control excessive physiological activity of the gland by antithyroid substances. The earlier work is reviewed by Petrova.[2] According to this author, "antithyroidin," a preparation from the serum of thyroidectomized animals, received a good deal of attention in the period 1905–1915, and good results in the treatment of hyperthyroidism were claimed. Extracts from normal animal and

[1] Van Winkle, Jr., Hardy, Hazel, Hines, Newcomer, Sharp, and Sisk, *J. Am. Med. Assoc.*, **130**, 343 (1946).

[2] Petrova, *Advances in Modern Biol. U.S.S.R.*, **15**, 65 (1942).

human blood or urine, antibodies to thyroxine-like compounds which had been injected in rabbits, salts of copper, iron, or cobalt, arsenious acid, fatty substances, carbohydrates, halogen derivatives, and several alkaloids such as quinine were reported by various investigators to oppose the effect of thyroxine (or thyroid hormone) in animals, such as to reduce metabolic rate in animals or man or to inhibit tadpole metamorphosis. Apparently none of these has been satisfactory in the treatment of hyperthyroidism.

Astwood and co-workers [3] refer to 20 papers concerning substances that cause thyroid enlargement in animals. Diets high in protein, liver, fat, soybeans, or cabbage, and the feeding of nitriles, arsenic salts, or thiocyanates are included. Vitamins, particularly A and C, are important in thyroid function but have not been shown to have appreciable antithyroid action.[4]

The first observations leading to the development of the more generally useful antithyroid compounds, such as the thioureas and thiouracils, were published in 1941 and 1942. Mackenzie, Mackenzie, and McCollum (1941),[5] investigating the effect of sulfaguanidine on intestinal bacteria in rats, observed a marked effect on the rats' thyroids. Mackenzie and Mackenzie (1942) [6] observed similar effects from feeding several other sulfa drugs and from thiourea. While studying the taste sensation in rats, Richter and Clisby (1941, 1942) [7,8] observed that phenylthiourea caused marked enlargement and histological hyperplasia of the thyroid gland. After several years of investigation by Purves, Kennedy, and Griesbach of the goitrogenic or thyroid-enlarging effect of *Brassica* seeds in animals, Kennedy (1942) [9] suspected that a derivative of thiourea might be the antithyroid agent involved, and so he tested both allylthiourea and thiourea and found them to be active. Later (1943), simultaneous papers by the Mackenzies [10] and by Astwood, Sullivan, Bissell, and Tyslowitz [3] did much to elucidate the mechanism of the effect and also reported tests on several other compounds including thiourea. Shortly afterward, Astwood [11] published the results of testing 106 compounds in rats; one of these was 2-thiouracil. Also in 1943,[12] Ast-

[3] Astwood, Sullivan, Bissell, and Tyslowitz, *Endocrinology*, **32**, 210 (1943).
[4] Drill, *Physiol. Rev.*, **23**, 355 (1943).
[5] Mackenzie, Mackenzie, and McCollum, *Science*, **94**, 518 (1941).
[6] Mackenzie and Mackenzie, *Federation Proc.*, **1**, 122 (1942).
[7] Richter and Clisby, *Arch. Path.*, **33**, 46 (1942).
[8] Richter and Clisby, *Proc. Soc. Exptl. Biol. Med.*, **48**, 684 (1941).
[9] Kennedy, *Nature*, **150**, 233 (1942).
[10] C. G. Mackenzie and J. B. Mackenzie, *Endocrinology*, **32**, 185 (1943).
[11] Astwood, *J. Pharmacol. Exptl. Therap.*, **78**, 79 (1943).
[12] Astwood, *J. Am. Med. Assoc.*, **122**, 78 (1943).

wood reported the first successful clinical treatment of hyperthyroidism with thiourea and thiouracil.

The most comprehensive review of the field of the newer antithyroid compounds is Astwood's *Harvey Lecture* (1945).[13] He discusses the development of these agents since 1941, including mode of action, physiological effect, relation of chemical structure to activity, and clinical applications. The biological effects of antithyroid compounds [14] and the relation of structure to activity [15] have received attention. Other pertinent reviews are those of Riker and Wescoe,[16] Lukens,[17] and Lawson and Rimington.[18] A collection of papers presented at a conference on "Thyroid Function as Disclosed by New Methods of Study," held by The New York Academy of Sciences in 1947, has been published;[19] much valuable information on antithyroid compounds is included.

Scope of This Review. The accumulation of results of screening of compounds for antithyroid action and the listing of these in a standard form to aid in comparison is a major objective of this article.* Most of the data have been obtained from tests in rats and have been found susceptible of comparative treatment in spite of a considerable variation in testing procedures and conditions. The screening procedure of McGinty and Bywater [20] is given as a standard. The use of other species of animals is discussed briefly. A new method of determining relative activities directly in man [21] and monkey [22] is given, and the results on a number of compounds are compared with the results from rat testing.

Another major objective is to discuss the correlation of chemical structure with activity. Modes of action and various biochemical and physical chemical data are involved. Toxicities are not considered, since suitable data are not available except for the few compounds that have been used clinically.

* *Chemical Abstracts* for the period 1942–1948 (Vols. 36–42) has been searched for antithyroid compounds under *antihormones, goiter, hyperthyroidism, thyroid, thyrotoxicosis,* and *uracil.* Volume 42 was read through November, 1948.

[13] Astwood, *Harvey Lectures,* **Ser. 40,** 195–235 (1944–1945), Science Press, Lancaster, Pa., 1945.

[14] Charipper and Gordon, *Vitamins and Hormones,* **5,** 274–315, Academic Press, New York, 1947.

[15] Roblin, *Chem. Revs.,* **38,** 255 (1946).

[16] Riker and Wescoe, *Am. J. Med. Sci.,* **210,** 665–80 (1945).

[17] Lukens, *Ann. Rev. Physiol.,* **9,** 69–102 (1947).

[18] Lawson and Rimington, *Ann. Repts. Progress Chem.* (*Chem. Soc. London*), **44,** 247–54 (1948).

[19] Means, Albert, Astwood, Chaikoff, Dempsey, De Robertis, Goldsmith, Leblond, McGinty, Rawson, Reineke, Salter, and Taurog, *Ann. N. Y. Acad. Sci.,* **50,** 279–508 (1949).

[20] McGinty and Bywater, *J. Pharmacol. Exptl. Therap.,* **84,** 342 (1945*a*).

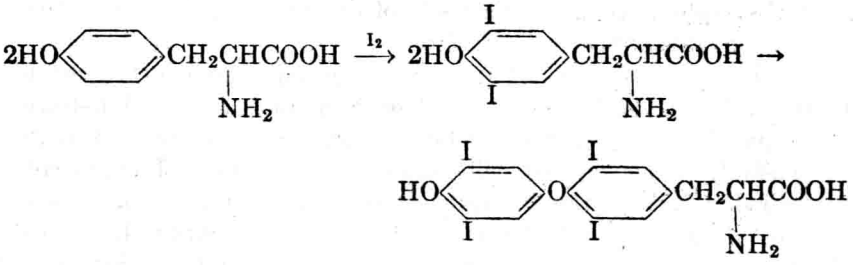
[21] Stanley and Astwood, *Endocrinology,* **41,** 66 (1947).

[22] McGinty and Wilson, *Endocrinology,* **44,** 546 (1949).

The papers on syntheses of antithyroid compounds are only briefly discussed because the methods used are mostly old. The field of compounds which oppose the action of the thyroid hormone has been little developed and is not included.

MECHANISM OF THYROID HORMONE PRODUCTION AND THE NATURE OF HYPERTHYROIDISM

The thyroid gland accumulates iodide from the blood and synthesizes the thyroid hormone, which is either thyroxine or a protein-like substance containing thyroxine as one of its units. A good deal of evidence [23] indicates that first tyrosine is iodinated, and then from two molecules of diiodotyrosine one molecule of thyroxine is formed:



A brief survey of generally accepted theories of thyroid operation may be useful at this point. As mentioned before, the pituitary controls the activity of the thyroid by means of its thyrotropic hormone. If the pituitary is surgically removed, the thyroid becomes inactive and stores its hormone along with its colloid, a jelly-like protein material presumably present as a carrier for the hormone. Similarly, in an intact animal with a functioning thyroid, a lessened demand for thyroid hormone, arising, for example, from exposure of the animal to a warmer environment, causes storage. Exposure to cold, on the other hand, creates a demand for thyroid hormone, and the pituitary releases an increased amount of thyrotropic hormone, which in turn stimulates the thyroid. Colloid is released from storage, thyroid cells change in size and shape (histological activation), and the gland as a whole becomes larger and hyperemic. It can now absorb more iodine and synthesize hormone at a faster rate (physiological activation).

In human beings, a chronic insufficiency of iodine in the diet or possibly the presence of naturally occurring antithyroid compounds results in a deficiency of thyroid hormone, with a resulting increase in size of the gland, known as simple goiter, also called "*colloid*" *goiter*. This con-

[23] Harington, *Proc. Roy. Soc. London*, **132**, 223 (1944).

dition is different from the acute state of activation principally in that colloid is stored, but it probably develops out of the phenomena described above for an acute state.[24] Increased efficiency of handling what iodine is available usually allows sufficient hormone production for a normal existence. If the structural alterations of the gland have not reached an irreversible state, its excessive size can be reduced by addition of iodine to the diet. It is also possible that the more efficient gland will produce too much hormone when iodide is fed, resulting in a form of hyperthyroidism.[25]

Hyperthyroidism usually arises from other, although obscure, causes. It is known variously as *toxic goiter, thyrotoxicosis, Graves' disease*, etc., and is characterized by an overactive gland, usually moderately oversized, which produces and releases excessive amounts of hormone. The clinical symptoms are mainly a result of the effects of the greater than normal amounts of hormone released.

Paradoxically, hyperthyroidism can be controlled to a certain extent by increasing the intake of iodine. Use of the radioactive-iodide-tracer technique in rats has shown that blood-plasma concentrations of iodide considerably above normal will inhibit the formation of organically bound iodine; this synthesis is restored as the iodide level of the plasma returns to usual ranges.[26] Although adequate in preventing the normal gland from making excessive amounts of hormone when the iodide intake is excessive, this mechanism is limited in its ability to control hyperactive glands. Clinically, iodide is useful in the treatment of mild cases of hyperthyroidism and in preparing the more serious cases for operation. A better control of hyperthyroidism results from the use of antithyroid drugs, which prevent the synthesis of thyroid hormone.

MODE OF ACTION OF ANTITHYROID COMPOUNDS

Aniline Derivatives, Mercapto Compounds, and Aminoheterocycles. It was early shown that administration of sulfaguanidine or thiourea to young rats caused (1) histologic activation and enlargement of their thyroid glands and (2) a decrease in basal metabolic rates of the animals. These effects were not prevented by feeding excess iodide, but administration of thyroxine or thyroid hormone inhibited them completely. Also, the first of these effects failed to appear in animals whose pituitaries had been removed, showing the necessity of the thyrotropic hormone in the process.[10,3] The iodine content of the thyroid glands of

[24] Marine, *J. Am. Med. Assoc.*, **104**, 2334 (1935).

[25] Selye, *Textbook of Endocrinology*, p. 719, University of Montreal, Canada, 1947.

[26] Wolff and Chaikoff, *Endocrinology*, **42**, 468 (1948); **43**, 174 (1948); *J. Biol. Chem.*, **172**, 855 (1948); **174**, 555 (1948).

thiouracil- or sulfadiazine-treated rats was found to be very low.[27] Subsequently, various compounds were studied to determine their action on surviving thyroid slices *in vitro* [28-31] and on the thyroid in the living rat [32-36] and rabbit,[37] using chemical analyses and radioactive-iodine-tracer techniques. These studies demonstrated that the action of sulfanilamides and other anilines, thiourea, thiouracil, and other mercapto compounds is to inhibit the synthesis in the thyroid gland of organic iodine compounds and thus of the thyroid hormone. The subsequent activation of the thyroid by the pituitary mechanism is futile, since the gland cannot synthesize thyroid hormone in the presence of the drugs.

More detailed study in rats of the effects of varying iodide intake as well as drug dose has shown differences within this class of compounds.[38] Iodide inhibits to a certain extent the action of thiouracil on the thyroid histology, whereas it increases this action of sulfaguanidine. Small doses of iodide inhibit the goitrogenic (thyroid weight increase) effect of thiouracil by 50 to 100%, depending on the dose of the thiouracil, but larger doses of iodide have no greater effect. Iodide has no effect on the goitrogenic action of large doses of sulfaguanidine but *increases* this effect from low doses of the sulfa drug. *p*-Aminobenzoic acid is more like thiouracil. These differences are more understandable if one considers the possible modes of action that have been proposed.

One likely mode of action concerns iodine reactions. Iodine reacts rapidly with tyrosine in a neutral or alkaline environment to form diiodotyrosine.[39,40] This in turn can be oxidized to thyroxine in small yields, under certain conditions; iodination of tyrosine-containing protein also produces thyroxine.[23] Since the reaction of thiourea with iodine has long been known, it has been suggested by several investigators [37,41-43] that thiourea and other thio compounds having antithyroid activity react with iodine liberated within thyroid cells and

[27] Astwood and Bissell, *Endocrinology*, **34**, 282 (1944).
[28] Franklin and Chaikoff, *J. Biol. Chem.*, **148**, 719 (1943).
[29] Franklin, Chaikoff, and Lerner, *J. Biol. Chem.*, **153**, 151 (1944*a*).
[30] Franklin, Lerner, and Chaikoff, *Endocrinology*, **34**, 265 (1944*b*).
[31] Taurog, Chaikoff, and Franklin, *J. Biol. Chem.*, **161**, 537 (1945).
[32] Keston, Goldsmith, Gordon, and Charipper, *J. Biol. Chem.*, **152**, 241 (1944).
[33] VanderLaan and Bissell, *Endocrinology*, **39**, 157 (1946*a*).
[34] McGinty and Sharp, *Endocrinology*, **39**, 74 (1946).
[35] Taurog, Chaikoff, and Feller, *J. Biol. Chem.*, **171**, 189 (1947).
[36] VanderLaan and VanderLaan, *Endocrinology*, **40**, 403 (1947).
[37] Baumann, Metzger, and Marine, *Endocrinology*, **34**, 44 (1944).
[38] C. G. Mackenzie, *Endocrinology*, **40**, 137 (1947).
[39] Li, *J. Am. Chem. Soc.*, **64**, 1147 (1942).
[40] Li, *J. Am. Chem Soc.*, **67**, 1065 (1945).
[41] Campbell, Landgrebe, and Morgan, *Lancet*, **246**, 630 (1944).
[42] Williams, Weinglass, and Kay, *Am. J. Med. Sci.*, **207**, 701 (1944).
[43] Chapman, *Quart. J. Pharm. Pharmacol.*, **17**, 314 (1944).

prevent iodination of tyrosine in thyroid protein. In support of this theory, Miller et al.[44] and Calvo and Goemine [45] have shown that tyrosine is not iodinated *in vitro* in the presence of thiouracil or thiourea.

Another mode of action may be the inhibition of an oxidative enzyme system which liberates iodine in the thyroid cell. On histochemical evidence, Dempsey [46] proposed that a peroxidase was the enzyme involved. Neither Astwood [13] nor Glock [47] was able to isolate the enzyme by chemical means. De Robertis and Grasso,[48] like Dempsey, used histochemical reagents to indicate the presence of peroxidase activity in normal rat thyroid cells. This was absent in normal colloid but present in both cells and colloid of rat thyroids which had been stimulated by low environmental temperature or thyrotropic hormone. Because thiourea inhibited the peroxidase activity and sulfanilamide did not, it was concluded that the antithyroid activity of thiourea is due to direct inhibition of the enzyme, but sulfonamide action must be due to competition for iodine freed by the enzyme. Since the sulfonamides have a low order of reactivity with iodine,[44] and since Randall [49] has shown that thiol compounds can be substrates for a peroxidase-hydrogen peroxide system, these conclusions are in doubt. Randall suggests that thiol compounds may reduce the peroxide as it is formed in the thyroid gland.

Inhibition of enzymes such as cytochrome oxidase, xanthine oxidase, phosphatase, and a proteolytic enzyme concerned with release of the hormone from the gland has been proposed by various authors. Although a direct action of the compounds on the pituitary seems to be excluded as a primary effect, it has been suggested [50] that thiouracil may have another action, since *in vitro* experiments indicate that it can reactivate the thyrotropic hormone after the latter has been inactivated by thyroid tissue. The reader is referred to the review of Charipper and Gordon [14] for a discussion of these possibilities.

Mackenzie [38] concludes from his work that (1) the most likely mode of action of thiourea and thiouracil is reaction with iodine; (2) the sulfonamides inhibit an enzyme; (3) *p*-aminobenzoic acid is more like thiourea than the sulfanilamides in its behavior but possibly competes with iodide as an enzyme substrate, since it does not react readily with iodine *in vitro*.

[44] W. H. Miller, Roblin, and Astwood, *J. Am. Chem. Soc.*, **67**, 2201 (1945).
[45] Calvo and Goemine, *Arch. Biochem.*, **10**, 531 (1946).
[46] Dempsey, *Endocrinology*, **34**, 27 (1944).
[47] Glock, *Nature*, **154**, 461 (1944).
[48] De Robertis and Grasso, *Endocrinology*, **38**, 137 (1946).
[49] Randall, *J. Biol. Chem.*, **164**, 521 (1946).
[50] Rawson, Albert, McArthur, Merrill, Lennon, and Riddell, *Endocrinology*, **39**, 74 (1946).

With few exceptions, the active compounds that appear in Tables 1–14 are (1) mercapto and thio compounds capable of ready reaction with iodine, (2) sulfanilamide derivatives, or (3) other anilines or aminoheterocycles. It is tempting to speculate that these classes might be correlated with Mackenzie's three types of action.

In introduction to the next section, it is useful to state here that the compounds just described do not prevent the accumulation of a small amount of iodide by the thyroid; they do inhibit the conversion of this iodide to organically bound forms.

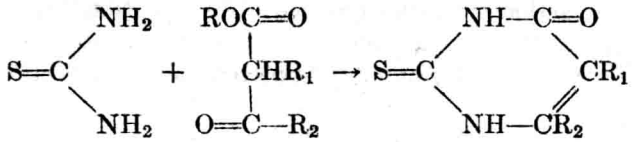
Nitriles and Thiocyanates. A less active class consists of those compounds whose action is readily reversed by increased amounts of iodide in the diet. Acetonitrile and thiocyanate ion are the outstanding examples. The action of nitriles received early attention [51] in relation to the goitrogenic effect of cabbage diets.[52] More recently several clinicians [53,54] have observed goiters in hypertensive patients after administering thiocyanate. Astwood [11] tested thiocyanate in rats and found an antithyroid effect. Rawson et al.[54] showed that the early (1932) suggestion of Marine and associates [51] that the mode of action of these compounds was through action on cellular oxidation systems of tissues in general, thus lowering the metabolism of the entire organism, was unlikely; they suggested an interference with iodine metabolism in the thyroid gland. Franklin et al.[29] showed that thiocyanate inhibited the uptake of iodide by surviving thyroid slices, and Wolff et al.[55] found that in the living rat accumulation of radioactive iodine by the thyroid was also inhibited, provided potassium thiocyanate in high concentration was present in the circulation at the time of iodine administration. Following chronic treatment with potassium thiocyanate, iodine uptake by the thyroid may be diminished or increased depending on the time interval between the last dose of potassium thiocyanate and administration of iodine. Thiocyanate interferes with the accumulation of iodine by thyroid glands under the influence of propylthiouracil;[33] this accumulated iodine has been shown to be in the form of iodide.[36,35] Similarly, using a radioactive-iodine technique, Stanley and Astwood [56] showed that thiocyanate would rapidly discharge iodide taken up by thyroids in human beings in which hormone synthesis had been inhibited by various antithyroid drugs.

[51] Marine, Baumann, Spence, and Cipra, *Proc. Soc. Exptl. Biol. Med.*, **29**, 772 (1932).
[52] Chesney, Clawson, and Webster, *Bull. Johns Hopkins Hosp.*, **43**, 261 (1928).
[53] Barker, Lindberg, and Wald, *J. Am. Med. Assoc.*, **117**, 1591 (1941).
[54] Rawson, Hertz, and Means, *Ann. Internal Med.*, **19**, 829 (1943).
[55] Wolff, Chaikoff, Taurog, and Rubin, *Endocrinology*, **39**, 140 (1946).
[56] Stanley and Astwood, *Endocrinology*, **42**, 107 (1948).

SYNTHESES OF ANTITHYROID COMPOUNDS

The majority of compounds tested for antithyroid activity were not first made for the purpose, having long been known. Their syntheses deserve no special comment. The several papers on series of compounds made specifically for antithyroid testing are concerned with derivatives of 2-thiouracil, 2-thiohydantoin, or 2-thioimidazole.

Anderson, Halverstadt, Miller, and Roblin [57] prepared a group of 2-thiouracils, mostly 5- and 6-alkyl derivatives. They used seven known methods of making β-oxo esters and reacted these with thiourea in alcohol in the presence of sodium ethylate to form 2-thiouracils, as illustrated in equation 1.



(1)

When R_2 was alkyl or aryl, yields of the intermediate β-oxo esters averaged 40 to 60%, and yields in the condensation step averaged 40 to 70%; when R_2 was H and R_1 was alkyl, the intermediate formyl esters were not isolated, and the over-all yield of the thiouracil was only 4 to 10%. A second paper from this group [58] concerns more 6-substituted 2-thiouracils, including several heterocycle derivatives. Some of the same compounds were reported by Jackman, Bergmann, and Archer [59] in a simultaneous paper and by Gilman and Broadbent [60] in a later paper; yields of the heterocycles were low in all cases. Other thiouracils in these papers were 6-cycloalkyl, substituted alkyl, aryl, aralkyl, and several 2,6-disubstituted derivatives; yields were best with the cycloalkyl compounds.[59]

The synthesis of 6-cyclopropyl-2-thiouracil, a compound with high antithyroid activity (see Table 1), is described by Spitzmiller.[61] Cyclopropyl methyl ketone was carbethoxylated with ethyl carbonate and sodium ethylate in 58% yield, and the resulting keto ester was allowed to react with thiourea and sodium ethylate to give a 43% yield of the thiouracil. Jackman et al.[59] carbethoxylated the ketone in the presence of sodium amide to give a 57% yield of the keto ester, and treated this with thiourea and sodium ethylate, yielding 60% of 6-cyclopropyl-2-thiouracil.

[57] Anderson, Halverstadt, Miller, and Roblin, *J. Am. Chem. Soc.*, **67**, 2197 (1945).
[58] W. H. Miller, Dessert, and Anderson, *J. Am. Chem. Soc.*, **70**, 500 (1948).
[59] Jackman, Bergmann, and Archer, *J. Am. Chem. Soc.*, **70**, 497 (1948*a*).
[60] Gilman and Broadbent, *J. Am. Chem. Soc.*, **70**, 2755 (1948).
[61] Spitzmiller, *J. Am. Chem. Soc.*, **69**, 2073 (1947).

As indicated in the papers summarized above, the generally preferred methods of making the intermediate β-oxo esters are illustrated by the equations 2–5.

$$RCO_2C_2H_5 + CH_3CO_2C_2H_5 \xrightarrow{NaOC_2H_5} RCOCH_2CO_2C_2H_5 \quad (2)$$

$$RCOCl + CH_3COCHNaCO_2C_2H_5 \rightarrow RCOCH(COCH_3)CO_2C_2H_5 \xrightarrow{NH_3} RCOCH_2CO_2C_2H_5 \quad (3)$$

$$RCOCl + C_2H_5O_2CCH(MgOC_2H_5)CO_2C(CH_3)_3 \rightarrow C_2H_5O_2CCH(COR)CO_2C(CH_3)_3 \xrightarrow{\Delta} RCOCH_2CO_2C_2H_5 + CO_2 + CH_2{=}C(CH_3)_2 \quad (4)$$

$$RCOCH_3 + (C_2H_5)_2CO_3 \xrightarrow{NaNH_2} RCOCH_2CO_2C_2H_5 \quad (5)$$

Method 2 works well when $RCO_2C_2H_5$ cannot condense with itself, as is the case with ethyl nicotinate. Method 3 is not suitable when the product has a boiling point close to that of ethyl acetoacetate, which is a by-product. Method 4 is valuable because a single product is obtained but is limited by the relative unavailability of ethyl *t*-butyl malonate. Method 5 is convenient when the ketone is available. A variation of this method wherein sodium hydride was used as the condensing agent has been described.[62, 63]

The syntheses of several 5-halogeno- and 5-halogeno-6-methyl-2-thiouracils were accomplished by halogenation of either S-methyl or S-benzyl-2-thiouracil or the 6-methyl derivative, followed by splitting off of the 2-substituent with hydrogen iodide.[64]

A paper by Jackman et al.[63] described the preparation of twelve 5-alkyl-2-thiohydantoins and eight 4-alkyl-2-thioimidazoles. The thiohydantoins were made in 21 to 60% yields by the reaction of amino acids and ammonium thiocyanate in acetic anhydride followed by acid hydrolysis of the crude acetyl derivatives (equation 6).

$$RCH(NH_2)CO_2H + NH_4SCN \xrightarrow{Ac_2O} \begin{matrix} & & NH{-}C{=}O \\ & S{=}C & \\ & & N{-}CHR \\ & CH_3CO & \end{matrix} \xrightarrow[HCl]{H_2O} \begin{matrix} & & NH{-}C{=}O \\ & S{=}C & \\ & & NH{-}CHR \end{matrix} \quad (6)$$

[62] Soloway and La Forge, *J. Am. Chem. Soc.*, **69**, 2677 (1947).
[63] Jackman, Klenk, Fishburn, Tullar, and Archer, *J. Am. Chem. Soc.*, **70**, 2884 (1948*b*).
[64] Barrett, Goodman, and Dittmer, *J. Am. Chem. Soc.*, **70**, 1753 (1948).