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HALO-THIOURACILS

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10 Claims. (Cl. 167—65)

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This invention relates to improved therapeutic agents, more particularly to novel therapeutic compounds which display thyroid inhibiting action.

As is known, hyperthyroidism is characterized by an excessive or depraved functional activity of the thyroid gland and markedly affects the basal metabolism. The gland itself is overactive, may be enlarged and the cells of the gland may be hyperplastic, hypertrophied and hyperemic. In the past, iodine, in the form of Lugol's solution has been employed for the treatment of hyperthyroidism. The use of iodine has not been especially satisfactory particularly because the effects of the iodine administration are but temporary.

In view of the shortcomings of the iodine treatment many investigators have sought other therapeutic agents which would be more efficacious. It has been demonstrated (R. H. Williams, Arch. Internal Medicine 1944, 77, 479) that thiouracil is effective in suppressing the activity of the thyroid gland, presenting the advantage of a considerably greater depressor action on the gland than that obtained with iodine. Further research and clinical investigation (J. W. Shirer and M. Cohen, Annals of Internal Medicine 1945, 23, 790) indicate that thiouracil, when not toxic to the individual, was found to control clinical hyperthyroidism in the pre-operative patient. These authors point out, however, that the gland treated with thiouracil presented greater surgical difficulties than the iodine-treated gland, displaying increased vascularity and friability. Furthermore, it was ascertained that a very toxic patient prepared for operation with thiouracil may have a post-operative course which at times approaches thyroid crisis.

One of the major disadvantages attending the administration of thiouracil is the continued hyperemia of the gland. Experience has shown that a degeneration of the thyroid cells themselves may occur with the administration of thiouracil. In view of these limitations and deleterious effects of thiouracil the profession has largely reverted to iodine as the drug of choice in the preparation of thyreo toxic patients for operation.

Thus, the problem which is still posed is the discovery of an agent which is non-toxic, possesses a marked depressing action on the function of the thyroid gland and which minimizes or eliminates the deleterious after-effects hereinbefore noted, such as hyperemia and cellular degeneration. As a result of intensive investigation it has been found that compounds fulfilling these

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difficultly attainable criteria can be produced. The invention to be described stems from the concept of retaining the desirable effective depressing action of thiouracil but by modification of the molecular structure, by introduction of beneficially functioning groups, minimizing or eliminating the described undesired effects. Considered more specifically, the invention is based on the discovery that a series of halogenated derivatives of 2-thiouracil exert a profound antagonistic action on the thyroid function with minimal undesired secondary effects. In view of the specificity of action of compounds of this type it will be appreciated that the effect of the several compounds will vary in degree of intensity in respect to thyroid inhibition resulting in qualitative and quantitative differences.

The invention can be more readily comprehended and evaluated from a consideration of typical or preferred methods of synthesizing the compounds of this new series and the effect of such compounds on test animals.

As noted previously, the novel therapeutic agents comprehended by the present invention comprise selected halogen derivatives of 2-thiouracil. In producing the new compounds it has been found advantageous to utilize as the starting material intermediate compounds such as alkylated or benzylated 2-thiouracil; then by the steps of halogenation and subsequent dealkylation or debenzylation to produce the desired compound which may be suitably purified to the desired degree.

One of the members of the new group of compounds is 5-chloro-2-thiouracil. The method of producing this compound is typical of the type of synthesis contemplated and is illustrative of that available for producing other specifically different members of the series. In this production a suitable alkyl derivative of thiouracil, such as 2-methyl thiouracil or 2-ethyl thiouracil may be employed. Such compound is dissolved in a suitable solvent, such as glacial acetic acid containing a catalyst such as ferric chloride. Halogenation is then carried out by adding to this solution, at room temperature, a suitable chlorinating agent, such as sulphur monochloride or chlorine gas dissolved in glacial acetic acid or carbon tetrachloride. In carrying out the chlorination two equivalents of chlorine are added slowly to the mother liquor. The temperature will rise to approximately 60° C. and should be maintained at this level at which time about a 25% excess of chlorine is added. The reaction is continued until there is no further evolution of hydrogen chloride gas.

After the completion of the reaction the solution is cooled. On cooling a portion of the chlorinated product will precipitate. This precipitate is then separated from clear liquor and the latter is evaporated under reduced pressure until all of the acetic acid is evolved. The residue thus obtained is combined with the first precipitate and is treated with a mixture of pyridine and water. The resulting mixture is then permitted to evaporate spontaneously. The residue from this evaporation may then be purified in any desired manner as by recrystallization from either water, alcohol or glacial acetic acid.

It is found that with such a procedure a yield of about 20% of the 5-chloro-2 alkyl thiouracil is secured. Utilizing such a procedure 5-chloro-2 methyl thiouracil, 6-methyl-5-chloro-2 ethyl thiouracil and 6-methyl-5-chloro-2-isopropyl thiouracil have been prepared. The compound 5-chloro-2-methyl thiouracil was found to have a melting point of 258–260° C. and on analysis was found to contain 20.6% chlorine (calculated 20.02) and 15.80% nitrogen (calculated 15.87). The compound 6-methyl-5-chloro-2-ethyl thiouracil was determined on analysis to have a melting point of 185° C. containing 17.50% chlorine (calculated 17.32) and 13.7% nitrogen (calculated 13.69). Upon analysis of the compound 6-methyl-5-chloro-2-isopropyl thiouracil it was found to have a melting point of 160° C. containing 16.39% chlorine (calculated 16.21%).

As intimated previously these alkylated halogenated thiouracil intermediates are utilized to produce the desired ultimate compound. This is achieved by removal of the alkyl or equivalent group attached to the thiono group. This dealkylation may be effectively accomplished in any suitable manner. In a specific illustrative procedure utilizing, for example, the intermediate 5-chloro-2-methyl thiouracil the compound 5-chloro-2-thiouracil may be procured in purified form by the following procedure. This intermediate is dissolved in boiling glacial acid to which has been added 25% by volume of acetic anhydride. A 50% solution of hydriodic acid in glacial acetic acid and acetic anhydride is then added to the reacting liquor preferably through a reflux. The hydriodic acid should be added slowly, as by dropwise addition, while heating and refluxing. To insure complete dealkylation it is desirable to use about a 10% excess of the hydriodic acid over the stoichiometrical requirements. After addition of the hydriodic acid boiling and refluxing is continued for a period of about one-half hour after which the liquor is cooled and then subjected to reduced evaporation. The residue is washed with water and any excess iodine is removed by adding a small amount of ammonium hydroxide to the water mixture and heating if necessary. On subsequent cooling and acidification with acetic acid the compound precipitates. This may be further purified in any suitable manner as by redissolution and recrystallization.

With such a method high yields of the 5-chloro-2-thiouracil compound are produced. Upon analysis this compound was found to have a melting point (with decomposition) about 264° C. and was found to contain 21.83% chlorine (calculated 21.80%); 17.29% nitrogen (calculated 17.22%) and 19.58% sulphur (calculated 19.76%).

By invoking the principles described and general procedure outlined above a series of specifically different halogen substituted 2 thiouracils may be prepared which display thyroid inhibitory action. Thus, by utilizing the intermediate compound 6-methyl-5-chloro-2-ethyl thiouracil and dealkylating this in the manner described the compound 6-methyl-5-chloro-2-thiouracil may be prepared in the desired state of purity. This product decomposes above 260° C. and on analysis was found to contain 20.34% of chlorine (calculated 20.20%).

The invention, as previously indicated, comprehends the production not only of the chloro derivatives of 2 thiouracil but also other halogen derivatives such as the corresponding bromo and iodo compounds. For example, the compound 5-bromo-2-thiouracil has been produced by a similar procedure used for this production of 5-chloro-2-thiouracil. This was produced by the dealkylation of the intermediate compound 5-bromo-2-methylthiouracil with yields of up to 49% of the compound. The intermediate compound, as will be appreciated, may be produced by the suitable bromination of the 2-alkyl thiouracil in a manner analogous to the production of the described 5-chloro-2-alkyl thiouracil. The compound 5-bromo-2-thiouracil melts, with decomposition, at 268–270° C., on analysis it was found to contain 38.70% bromine (calculated 38.60%), 13.44% nitrogen (calculated 13.52%), 15.33% sulphur (calculated 15.48%).

Likewise the compound 6-methyl-5-bromo-2-thiouracil was prepared by specific dealkylation of the corresponding intermediate 6-methyl-5-bromo-2-methyl thiouracil in the same manner as has been previously described. This product melts, with decomposition, at 260° C. and was found to contain 36.18% bromine (calculated 36.15).

A particularly effective compound of this group of therapeutic agents is 5-iodo-2-thiouracil. This may be prepared in the same manner as 5-bromo-2-thiouracil by dealkylation of the corresponding alkyl intermediate. However, in producing this compound it is preferred to utilize as the intermediate an aryl substituted intermediate such as 5-iodo 2-benzyl thiouracil. This may be produced, as will be appreciated, in the general manner previously outlined i. e., by iodization of the 2-benzyl thiouracil analogue.

The compound 5-iodo-2-benzyl thiouracil may be debenzylated in the manner described for the dealkylation of the 5-chloro-2 methyl thiouracil observing the precaution however that the temperature of reaction should not exceed 100° C. for if the temperature is allowed to rise above this iodine is lost from the ring. On drying the final product care must be taken to keep the temperature below 80° C. The drying may be accomplished by drying for a period of about two hours at a temperature somewhat below 80° C. but is best accomplished by drying in a vacuum over a dessicating agent such as phosphorus pentoxide. It is also particularly to be noted that this compound is sensitive to light and therefore must not be unnecessarily exposed. This compound has a melting point, with decomposition, of 270° C. and analysis showed an iodine content of 50.06% (calculated 49.95) and a sulphur content of 12.77% (calculated 12.62).

While, as noted, the compound 5-iodo-2-thiouracil may be prepared by utilizing the procedure hereinbefore described it has been found that increased yields of the desired product may be attained by using a modification of this procedure. This modified procedure insures a more careful control of the reaction and involves the evolution of hydrogen iodide from a vessel sepa-

rate from the main reaction vessel and its controlled addition to the solution of the 5-iodo-2-benzyl thiouracil.

The value of this modified method will be apparent from a consideration of the specific procedure. The apparatus consists of a main reaction vessel equipped with a reflux provided with a water jacket or other suitable indirect heat exchange unit to control the temperature. With the reaction vessel is associated a second vessel in which hydrogen iodide is generated and which is fed by means of suitable conduit to the liquid in the main reaction vessel. The vessel in which the hydrogen iodide is generated is provided with means to feed thereto a controlled amount of a solution of hydriodic acid. The hydrogen iodide generator and reaction vessel are thus connected in a closed circuit.

As an illustrative example 64.4 grams of 5-iodo-2-benzyl thiouracil were deposited in the reaction vessel and dissolved by adding 400 cc. of glacial acetic acid containing 10 cc. of acetic anhydride and the reaction vessel was connected tightly with the reflux condenser. The second vessel or generator was charged with 95 cc. of acetic anhydride and the vessel connected to a vessel such as a dropping funnel or equivalent containing 75 cc. of a 50% solution of hydriodic acid which was added slowly, as by dropwise addition, to the acetic anhydride in the generator. The mixture in the generator soon became hot and the hydrogen iodide which evolved passed continuously through the connecting conduit into the reaction flask just above the level of liquid therein. As the hydrogen iodide contacted the solution of the 2 benzyl derivative, a ring of the debenzylated product formed under the inlet conduit. This operation was continued until all of the hydriodic acid was added to the generator vessel. The hydrogen iodide remaining in the generator was driven over into the reaction vessel by heating the generator. It was ascertained that the reaction is complete when no more precipitate forms in the main reaction vessel. During the reaction vapors evolved were condensed in the condenser and returned to the reaction vessel as reflux. The upper end of the reflux is preferably connected with a vent leading to a drying chamber.

The reaction vessel was cooled and the precipitate separated by pouring or decanting off the supernatant liquor. The precipitate of the 5-iodo-2-thiouracil was then thoroughly washed, as for example on a Buchner funnel. The precipitate was then extracted twice with hot glacial acetic acid to remove unreacted material and then washed thoroughly by alternate washes with alcohol and water. The product was then further purified by dissolving it in warm dilute sodium hydroxide and after cooling was reprecipitated by careful acidulation with acetic acid.

Utilizing this procedure 37 grams of purified 5-iodo-2-thiouracil were obtained.

The supernatant liquid separated from the precipitate was concentrated in vacuo and 7.4 grams of the unreacted 5-iodo-2-benzyl thiouracil were recovered. This obviously may be utilized for further debenzylation.

As pointed out previously, the 5-iodo-2-thiouracil is carefully dried, preferably in a vacuum over P_2O_5.

Other iodo derivatives of 2 thiouracil may also be utilized for thyroid inhibitory effects such as the alkyl derivatives of 5-iodo-2-thiouracil as, for example, 6-methyl 5-iodo 2-thiouracil. This may be prepared from the intermediate 6-methyl-5-iodo-2 methyl thiouracil by the dealkylation method described herein and observing the precautions mentioned. This compound melts at 270° C. (with decomposition) and was found on analysis to contain 47.25% iodine (calculated 47.17).

In order to determine the efficacy of compounds of the described type in the treatment of hyperthyroidism and to respectively evaluate the different halogen derivatives a series of experiments were conducted on animals. The tests were carried out by subcutaneously injecting into rats equivalent molar concentrations of the described compounds in a non-toxic vehicle, namely, sesame. In these tests 2-thiouracil, in sesame oil, was employed as a control and evaluative base. The injections, consisting of 2 mg. per 100 gm. rat, were carried out daily for three periods on different groups of animals, mainly five consecutive days, ten consecutive days and fifteen consecutive days. At the end of each period the animals so treated were sacrificed, the thyroids removed and prepared for histological examination and analysis of the halogen content. The compounds tested were the three halogen homologues of 2 thiouracil. All the compounds tested displayed thyroid inhibitory action.

The results of these tests are tabulated in the following table.

Table I

Average of groups	Cellular change	Colloid change	Hyperemia	Gammas per glands Iodine content
2 thiouracil (control)	Hypertrophy some degeneration.	decreased	present	1
5 chloro-2 thiouracil	slight hypertrophy	do	do	1.5
5 bromo-2 thiouracil	moderate hypertrophy also degeneration.	moderate decrease.	do	1.5
5 iodo-2 thiouracil	none	slight decrease.	absent	1-2

From an inspection of the table it will be observed that the use of the halogen derivatives of 2 thiouracil resulted in less fibrosis of the gland than that which obtained when the control 2-thiouracil was used. It is particularly to be observed that no fibrosis was noted in the animals receiving the 5 iodo-2 thiouracil. The normal value for this colony of rats, with reference to thyroid iodine, is from 3 to 5 gammas per gland. All of the compounds which were administered decreased the iodine content, including the rats receiving the 5-iodo-2 thiouracil.

It is obvious from the data advanced that the described group of compounds are effective thyroid inhibitors. It is also apparent that the iodo substituted 2 thiouracils, such as 5-iodo-2-thiouracil, are the ideal drugs of choice since

these depress thyroid activity, reduce hyperemia without fibrosis or cellular degeneration and at the same time decrease the iodine value, reflected by iodine usage.

While the illustrative tests described involved the use of the 5-halogen-2-thiouracil compounds it has been determined, as noted, that alkyl derivatives of these compounds also function effectively in suppressing thyroid activity.

While typical examples of a characteristic group of compounds possessing thyroid inhibiting action have been given it is to be understood that the invention comprehends the broad concept of modifying the effect of 2-thiouracil by the introduction into the molecule of beneficially functioning radicals, particularly the halogens.

I claim:

1. A new composition of matter possessing marked suppressive action on thyroid activity having as its active ingredient an iodo 2-thiouracil.

2. A new composition of matter possessing marked suppressive action on thyroid activity having as its active ingredient a mono-iodo-2-thiouracil.

3. As a new therapeutic agent, 5 iodo-2-thiouracil.

4. As a new therapeutic agent, 6 alkyl 5-halo-2-thiouracil.

5. As a new composition of matter having marked suppressive action on thyroid activity having as its active ingredient, 6 alkyl 5-iodo-2 thiouracil.

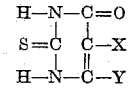
6. As a new composition of matter having marked suppressive action on thyroid activity having as its active ingredient, 6-methyl-5-iodo 2 thiouracil.

7. As a new composition of matter having marked suppressive action on thyroid activity having as its active ingredient, 5-bromo 2 thiouracil.

8. As a new composition of matter having marked suppressive action on thyroid activity having as its active ingredient 5-chloro 2 thiouracil.

9. A therapeutic agent comprising 5-iodo 2 thiouracil suspended in a vegetable oil.

10. A new therapeutic agent having thyroid activity suppressing action comprising a compound of the formula



where X is a halogen and Y is a member of the group consisting of hydrogen and alkyl.

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