Anal. Calcd. for $C_{25}H_{46}N_2O$: C, 76.86; H, 11.87; N, 7.17. Found: C, 77.23; H, 12.25; N, 7.27.

2. By Reductive Amination.—A solution of *allo*-pregnanolone acetate (VII, 28.8 g.), β-dimethylaminoethylamine (14.1 g.), and acetic acid (19.2 g.) in absolute ethanol (500 ml.) was hydrogenated over platinum oxide (3.0 g.) at 70.3 kg./cm.^{2} and 46°. After hydrogen uptake ceased (11 hr.), the catalyst was removed by filtration and washed with ethanol. Sodium hydroxide (25 g.) and water (100 ml.) were added to the filtrate and the solution refluxed on the steam bath for 1.5 hr. The solution was then concentrated to one half the original volume and slowly poured into ice water. The resulting gum was extracted with methylene chloride. The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was removed by distillation and the oily residue dissolved in isopropyl alcohol–ether (1:4, 500 ml.). A solution of hydrogen chloride in isopropyl alcohol was added dropwise with stirring until precipitation was complete. The precipitate was collected by filtration and washed with acetone and ether. The crude dihydrochloride (39 g.) was dissolved in ethanol–water (1:4) and the solution made basic with 20% sodium hydroxide solution. The resulting precipitate was washed with water and slowly recrystallized from acetone to afford 7.5 g. of material, m.p. 110–120°. Several recrystallizations from ethyl acetate gave pure VIa (3.1 g., 10%) identical in all respects with that obtained above. A second crop of material (12.3 g.) obtained from the initial recrystallization was recrystallized several times from ethyl acetate to give a lower melting isomer (VIII), m.p. 72–74°, $[\alpha]^{25}D$ +9.

Anal. Calcd. for $C_{25}H_{46}N_2O$: C, 76.86; H, 11.87. Found: C, 76.53; H, 11.74.

Thyroxine Analogs. VI.[1] Synthesis and Antigoitrogenic Activity of 3,5-Diiodo-4-(4′-Aminophenoxy)-L-Phenylalanines, Including the 4′-Amino Analog of 3,5,3′-Triiodo-L-Thyronine

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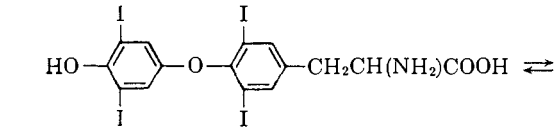
The synthesis of several analogs of thyroxine, in which the 4′-hydroxyl group has been replaced by an amino group, is described. The 4′-amino analogs of 3,5,3′-triiodo-L-thyronine and 3,5-diiodo-3′,5′-dimethyl-L-thyronine show thyroxine-like activity in the rat antigoiter assay.

One of the ways in which thyroxine might exert its biological effects is by interaction with oxidation-reduction systems. Niemann[2] has

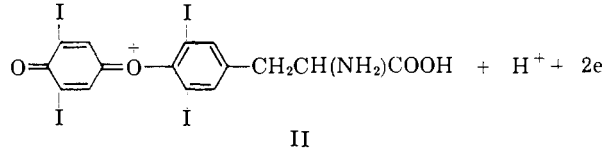
(1) Paper V, E. C. Jorgensen and P. A. Lehman, *J. Org. Chem.*, **26**, 897 (1961).

(2) C. Niemann, *Fortschr. Chem. org. Naturstoffe*, **7**, 167 (1950).

postulated that such an interaction might be mediated through a reversible conversion of thyroxine (I) to a quinoid form (II):



I

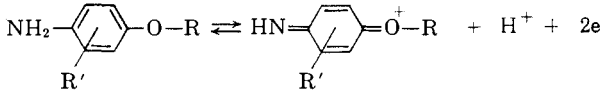


II

To date, analogs of thyroxine which have been shown to be thyromimetic have either possessed a hydroxyl group in the "prime" ring in such a position as to make it possible for a quinoid form like II (or the corresponding *o*-quinoid form) to be formed, or have had that position occupied by an ether or ester of the phenol, rendering biological conversion to the corresponding hydroxy compound a possible prerequisite for thyroxine-like activity. This fact lends some support to Niemann's hypothesis.

However, all that may be required for thyromimetic activity is a hydroxyl group in a fixed position in the "prime" ring, capable of forming a phenoxide ion. This might, by virtue of its charge, interact with a center of low electron density on the biological receptor, initiating a series of molecular changes which finally result in thyroxine-like response.

One way of distinguishing between these two possibilities would be to examine the biological activity of molecules in which the hydroxyl group is replaced by a group which is capable of undergoing oxidation to a quinone-like intermediate, but not able to produce an ion of the phenoxide type. A substituent which fulfills these requirements is the amino group: the resulting molecule can undergo oxidation to an imino-quinoid form but cannot form an anion. The present paper

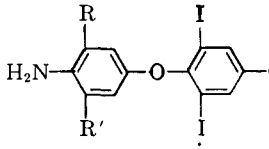


describes the synthesis and biological evaluation of four analogs of thyroxine of this type.

Barnes and co-workers[3] made several unsuccessful attempts to

(3) J. H. Barnes, R. C. Cookson, G. T. Dickson, J. Elks, and V. D. Poole, *J. Chem. Soc.*, 1448 (1953).

prepare the 4′-amino analog (III) of DL-thyroxine by iodination of



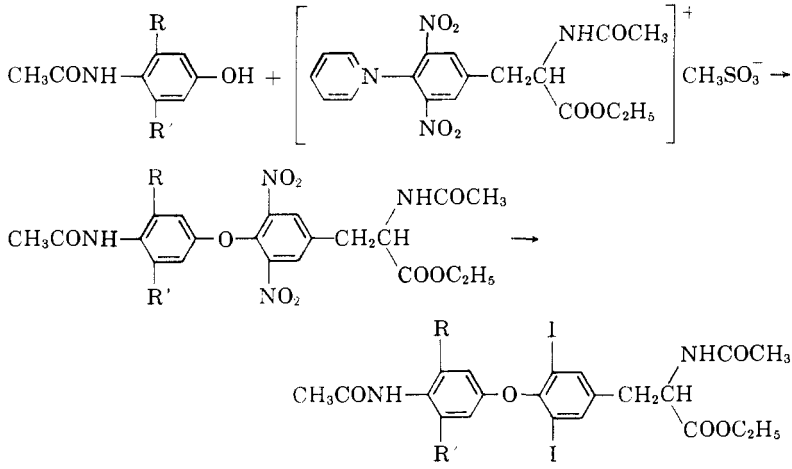
III, R = R′ = I
IV, R = R′ = H
V, R = CH_3, R′ = H
VI. R = R′ = CH_3
VII, R = I, R′ = H

the corresponding des-iodo compound (DL-IV). In view of the lack of success of their efforts, and since the 4′-amino analog of 3,5-diiodothyronine (IV) itself does not seem to have been evaluated biologically, our research was initially directed toward a synthesis of this compound (as its L-isomer) and toward the related 4′-amino analogs possessing 3′-methyl (V) and 3′,5′-dimethyl (VI) substituents with a view to testing these for thyromimetic activity. The rationale for this was the finding that 3,5-diiodothyronine,[4] 3,5-diiodo-3′-methylthyronine[5] and 3,5-diiodo-3′,5′-dimethylthyronine[6] possess thyroxine-like activity. The activity of the 4′-amino analogs could be compared to the activities of these compounds, thus providing a direct evaluation of the effect of replacing the 4′-hydroxyl group by an amino group.

The analogs IV to VI were synthesized by the Meltzer[7] modification of the method of Barnes, *et al.*[3] 4-Acetamidophenol and its 3-methyl and 3,5-dimethyl congeners reacted in good yield with 3,5-dinitro-4-pyridinium-L-tyrosine-N-acetyl ethyl ester methanesulfonate. The resulting substituted dinitrodiphenyl ethers (VIIIa, b, c) were converted to the diamines by hydrogenation: these were not isolated but tetrazotized under anhydrous conditions and converted to the diiodo compounds (IXa, b, c) by treatment with iodine and potassium iodide, in the presence of chloroform to remove the product as formed.

Hydrolysis to the appropriate amino acid (IV-VI) was achieved by the use of a mixture of hydrochloric acid and acetic acid. As expected, the methyl groups in the 3′,5′-dimethyl compound hindered cleavage of the 4′-acetamido group. The hydrolysis finally was accomplished by increasing the reaction time from the 2 hours, required in the case of unsubstituted and monomethyl compounds, to 48 hours. The dimethylamino acid (VI) and the amino acid without methyl substitution in the outer ring (IV) formed monohydrates stable to prolonged drying.

(4) H. A. Selenkow and S. P. Asper, Jr., *Physiol. Rev.*, **35**, 426 (1955).
(5) C. S. Pittmann, H. Shida, and S. B. Barker, *Endocrinology*, **68**, 248 (1961).
(6) T. C. Bruice, R. J. Winzler, and N. Kharasch, *J. Biol. Chem.*, **210**, 1 (1954).
(7) R. I. Meltzer, D. M. Lustgarden, and A. Fischman, *J. Org. Chem.*, **22**, 1577 (1957).



VIIIa, R = R′ = H
VIIIb, R = CH_3, R′ = H
VIIIc, R = R′ = CH_3

IXa, R = R′ = H
IXb, R = CH_3, R′ = H
IXc, R = R′ = CH_3

In their attempts to iodinate 3,5-diiodo-4-(4′-aminophenoxy)-DL-phenylalanine (DL-IV), Barnes, *et al.*,[3] used iodine and iodine monochloride under a variety of unspecified conditions. In our hands, the latter reagent proved to be a successful means of introducing one iodine atom into the molecule. Essentially a procedure developed by Block[8] for the iodination of 4-aminophenylalanine was used. Very slow addition of iodine monochloride in dilute acid to an acid solution of the amino acid, and avoidance of the presence of excess reagent, led to precipitation of the triiodo amino acid VII. The amino group would be largely protonated in the prevailing acid conditions, but its *meta*-orienting (deactivating) effect would be overcome by the small amount of free amino group present which would direct the entering iodine atom into the *ortho* position. Consequently, the 3′-iodo compound was expected to be the sole product, and this was confirmed by paper chromatography.

Experimental

All melting points were taken in capillary tubes in an oil bath, and are corrected. Optical rotations were measured with a Rudolph polarimeter. Microanalyses were carried out by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley.

4-Acetamidophenols.—4-Aminophenol was acetylated by the method of Lumière, *et al.*,[9] yielding prisms m.p. 166–168° (lit.[9] m.p. 168°). 3-Methyl-4-

(8) P. Block, *J. Org. Chem.*, **21**, 1237 (1956).
(9) A. Lumière, L. Lumière and H. Barbier, *Bull. soc. Chim.*, [3], **33**, I, 783 (1905).

acetamidophenol was prepared from the corresponding amino compound by the method of Proskouriakoff and Titherington[10] as prisms which crystallized from water as a hydrate (m.p. 70–80°) which could be dehydrated by prolonged drying (m.p. 127–129°; lit.[10] m.p. 130°). 3,5-Dimethyl-4-aminophenol was prepared by Albert's method[11] by adding 3,5-dimethylphenol to diazotized sulfanilic acid and reducing the resultant azo compound with sodium hydrosulfite. The aminophenol produced as needles (m.p. 182–184°) was acetylated by suspending the compound (20 g.) in water (200 ml.) and shaking with acetic anhydride (4 ml.). The phenol dissolved and the solution became warm. After 30 min., the mixture was cooled to 0° when 20 g. (90%) of white prisms separated, m.p. 180–182° (lit.[12] m.p. 178–180°).

4′-Acetamidoaryl Ethers of 3,5-Dinitro-L-tyrosine-N-acetyl Ethyl Ester.—(Table I, VIIIa-c): To 3,5-dinitro-L-tyrosine-N-acetyl ethyl ester[13] (17.0 g., 0.05 mole) in dry pyridine (125 ml.), redistilled methanesulfonyl chloride (6.3 g., 0.055 mole) was added and the mixture heated under reflux for 2 min. After some cooling, the appropriate 4-acetamidophenol (0.1 mole) was added and the mixture heated under reflux for 20 min. The cooled reaction mixture was poured into water (200 ml.) and extracted with ethyl acetate. The ethyl acetate extract was washed successively with 2 *N* hydrochloric acid, water, 0.3 *N* sodium hydroxide and water, dried (sodium sulfate) and the solvent was removed by distillation. The resulting orange gums were crystallized from 95% ethanol (except compound VIIIa, Table I. which was crystallized from aqueous acetone).

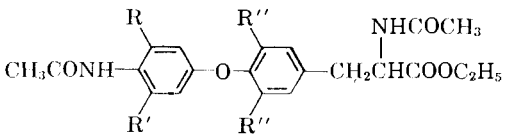
4′-Acetamidoaryl Ethers of 3,5-Diiodo-L-tyrosine-N-acetyl Ethyl Ester.—(Table I, IXa-c): 3,5-Dinitro-4-(4′-acetamidoaryloxy)-L-phenylalanine-N-acetyl ethyl ether (Table I, VIII a-c, 0.02 mole) dissolved in acetic acid (300 ml.) was shaken with hydrogen (31.6–35 kg./cm.^{2} initial pressure) in the presence of palladium on charcoal (10%, 1.0 g.) until hydrogenation was complete (30–60 min.). Nitrogen was passed over the cooled solution, concentrated sulfuric acid (40 ml.) was added, and the mixture was filtered through Celite. The solution was added during 1 hr. from a pressure-equalized dropping funnel under nitrogen to a well-stirred mixture of nitrosylsulfuric acid (prepared by adding sodium nitrite (6.0 g., 0.09 mole) in small portions to sulfuric acid (60 ml.) at 60–70°, and diluted when cool with acetic acid (60 ml.) under nitrogen and kept at −5°. After addition was complete, the orange tetrazonium solution was stirred for an additional hr. at −5°, and then poured rapidly into a well-stirred mixture of iodine (22 g., 0.083 mole), sodium iodide (30 g., 0.20 mole) and urea (6.0 g.) in water (400 ml.) and chloroform (800 ml.) at room temperature. The mixture was stirred for 1 hr., then the chloroform phase was removed and the aqueous layer was extracted with chloroform. The combined chloroform extracts were washed with water, 10% aqueous sodium bisulfite, water, sodium bicarbonate and water. Removal of solvent from the dried solution (sodium sulfate) yielded a buff solid which was crystallized from 95% ethanol.

In some runs with two of the compounds (IXa,b) a brown tar was precipitated during the decomposition of the tetrazonium compound. This was washed with water, dissolved in ethanol and treated with a solution of sodium bisulfite in aqueous ethanol. The solution was allowed to stand for a few min., then evapo-

(10) A. Proskouriakoff and R. J. Titherington, *J. Am. Chem. Soc.*, **52**, 3983 (1930).
(11) H. E. Albert, *ibid.*, **76**, 4985 (1954).
(12) Agfa, German Patent 291499; *Chem. Zentr.*, **87** I, 956 (1916).
(13) J. C. Clayton, G. F. H. Green, and B. A. Hems, *J. Chem. Soc.*, 2467 (1961).

TABLE I

4′-ACETAMIDOARYL ETHERS OF 3,5-DINITRO- AND 3,5-DIIODO-L-TYROSINE-N-ACETYL ESTER



No.	R	R′	R″	Yield, %	M.p., °C.	Optical rotation $[\alpha]^{22}D$	C	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Iodine, % Calcd.	Iodine, % Found
VIIIa	H	H	NO_2	68	169–172	−9.9[a]	1.03	$C_{21}H_{22}N_4O_9$	53.15	53.40	4.67	4.90	—	—
VIIIb	CH_3	H	NO_2	58	223–224	−13.7[a]	1.03	$C_{22}H_{24}N_4O_9$	54.09	54.17	4.95	5.04	—	—
VIIIc	CH_3	CH_3	NO_2	40	224–225	−15.0[a]	1.04	$C_{23}H_{26}N_4O_9$	54.96	54.87	5.22	5.18	—	—
IXa	H	H	I	47	245–246	+24.2[b]	0.81	$C_{21}H_{22}I_2N_2O_5$	39.64	39.96	3.49	3.61	39.89	39.58
IXb	CH_3	H	I	65	241.5–243	+18.4[b]	1.05	$C_{22}H_{24}I_2N_2O_5$	40.63	40.92	3.72	3.92	39.03	39.26
IXc	CH_3	CH_3	I	47	232–233	+11.9[b]	1.06	$C_{23}H_{26}I_2N_2O_5$	41.58	41.69	3.95	3.76	38.20	38.40

[a] Solvent, glacial acetic acid. [b] Solvent, anhydrous pyridine.

rated to dryness under reduced pressure, shaken thoroughly with water and the resulting brown, impure diiodo compound was filtered off and, after treatment with Norit A, was crystallized from 95% ethanol.

3,5-Diiodo-4-(4′-aminophenoxy)-L-phenylalanine (IV).—3,5-Diiodo-4-(4′-acetamidophenoxy)-L-phenylalanine-N-acetyl ethyl ester (IXa, 1.8 g.), glacial acetic acid (60 ml.) and concd. hydrochloric acid (40 ml.) were heated under reflux for 2 hr. The solvent was removed under reduced pressure and the resulting solid redissolved in hot 95% ethanol. An equal volume of water was added and the solution heated to boiling, then hot 10% aqueous sodium acetate was added to bring the pH to 5.0. Very pale buff needles were produced on cooling (1.3 g., 86%). They were taken up in ethanol and the isoelectric precipitation was repeated twice more. The amino acid was obtained as the monohydrate, m.p. 238–244° dec., resistant to prolonged drying at 100° (1 mm.) $[\alpha]^{22}D$ +77° ± 16° (*c* 0.93, 1:1 mixture of *N* hydrochloric acid and ethanol).

Anal. Calcd. for $C_{15}H_{14}I_2N_2O_3 \cdot H_2O$: C, 33.36; H, 2.99; I, 46.99. Found: C, 33.54; H, 2.93; I, 46.92.

3,5-Diiodo-4-(3′-methyl-4′-aminophenoxy)-L-phenylalanine (V).—3,5-Diiodo-4-(3′-methyl-4′-acetamidophenoxy)-L-phenylalanine-N-acetyl ethyl ester (IXb, 4 g.) was hydrolyzed using the above method, and the amino acid was isolated as clusters of tiny white needles (3.3 g., 100%). After two more isoelectric precipitations the compound melted at 262–264° dec. $[\alpha]^{28}D$ +25° (*c* 1.19, 1:1 mixture of *N* hydrochloric acid and ethanol).

Anal. Calcd. for $C_{16}H_{16}I_2N_2O_3$: C, 35.70; H, 3.00; I, 47.15. Found: C, 35.42; H, 3.07; I, 46.88.

3,5-Diiodo-4-(3′,5′-dimethyl-4′-aminophenoxy)-L-phenylalanine (VI).—The method described above was used to obtain this compound from 3,5-diiodo-4-(3′,5′-dimethyl-4′-acetamidophenoxy)-L-phenylalanine-N-acetyl ethyl ester (IXc, 2.0 g.) except that hydrolysis was continued for 48 hr. The amino acid (1.6 g., 96%) was isolated as described, and after a total of three isoelectric precipitations was obtained as the buff monohydrate, m.p. 224–227° dec., which could not be dehydrated by prolonged drying at 100° (1 mm.) $[\alpha]^{28}D$ + 18° (*c* 1.00, 1:1 mixture of *N* hydrochloric acid and ethanol).

Anal. Calcd. for $C_{17}H_{18}I_2N_2O_3 \cdot H_2O$: C, 35.80; H, 3.53; I, 44.50. Found: C, 36.01; H, 3.54; I, 43.96.

3,5-Diiodo-4-(3′-iodo-4′-aminophenoxy)-L-phenylalanine (VII).—A solution of iodine monochloride (1 g.) in concd. hydrochloric acid (0.75 ml.) and water (4.5 ml.) was added dropwise, very slowly, to a solution of 3,5-diiodo-4-(4′-aminophenoxy)-L-phenylalanine (IV, 0.75 g.) in water (100 ml.) containing hydrochloric acid (5 ml.). As the addition proceeded a buff solid was precipitated. After 3 hr. and the addition of 16. ml. of iodine monochloride solution the precipitation ceased, and the buff solid was filtered off. This was dissolved in ethanol containing 6 *N* hydrochloric acid, treated with Norit A, filtered and the pH of the filtrate adjusted to 3.5 with 10% sodium acetate. This isoelectric precipitation was repeated twice more, and produced a pink solid (0.3 g., 32%), m.p. 224–225° dec.[14] Paper chromatography on Whatman No. 1 paper using a 4:1:5 mixture

(14) Some preparations of this amino acid were very dark in color, and appreciable lightening could not be effected with Norit. Considerable purification was achieved by making a dilute solution of the crude product in hot ethanol containing 6 *N* hydrochloric acid, and adjusting the pH to 4.0 by addition of sodium acetate in hot 90% ethanol (5% w./v.). The resulting dark precipitate was filtered off, and the pH of the filtrate was raised to 4.5 by adding more sodium acetate solution. Dilution of the solution with water caused precipitation of the amino acid as a pink solid.

of 1-butanol, acetic acid and water as developer revealed a single spot, R_f 0.91. (Starting material had R_f 0.74. Compounds detected by quartz envelope ultraviolet light.) A solution of the compound in a 1:1 mixture of N hydrochloric acid and ethanol was too opaque for optical rotation measurements.

Anal. Calcd. for $C_{15}H_{13}I_3N_2O_3$: C, 27.73; H, 2.02; I, 58.58. Found: C, 27.60; H, 2.29; I, 58.90.

Biological.—The rat antigoiter assay was based on that of Dempsey and Astwood[15] and was designed to detect activity relative to L-thyroxine of 0.2% or higher.

Rat Antigoiter Assay.—The compounds were dissolved in 0.9% aqueous sodium chloride containing 0.01 N sodium hydroxide, and were refrigerated between injections. Concentrations were such that a volume of 0.125 ml. was injected daily per 100 g. of body weight. Long–Evans strain male rats weighing initially 125 ± 25 g. were fed powdered Simonsen rat food either alone (normal controls) or containing 0.3% thiouracil. Following one day on this diet, daily subcutaneous injections of the test compounds were carried out for 10 days. On the 11th day the rats were sacrificed by chloroform inhalation, the thyroid glands excised, cleaned under a dissecting microscope, and weighed to the nearest 0.1 mg. L-Thyroxine-treated rats as well as rats receiving the 0.9% alkaline saline vehicle subcutaneously were run concurrently as controls. Reversal of the thiouracil-induced increase in thyroid weight (goiter) by the test compounds was compared with the reversal produced by standard doses of L-thyroxine as a measure of thyroxine-like activity. Assay conditions and results are collected in Table II.

Discussion

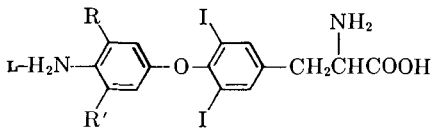
The three doses of L-thyroxine (2.0, 3.0 and 4.5 mcg./100 g. of body weight) all produced thyroid weights significantly lower ($P > 0.99$) than the thiouracil control, and were therefore active dose levels. The 3.0 mcg. per 100 g. body weight dose of L-thyroxine produced a thyroid weight not significantly different from the normal controls ($P > 0.95$), 2.0 mcg. of L-thyroxine produced incomplete reversal (different from normal controls, $P > 0.99$), and the 4.5 mcg. dose of L-thyroxine produced a thyroid weight significantly lower than the normal controls ($P > 0.95$), therefore constituted an over-dose.

All compounds were tested at a single level of 100 times (molar basis) the 3.0 mcg. dose of L-thyroxine. Both the 4′-amino (IV) and 4′-amino-3′-methyl (V) analogs produced thyroid weights which were the same as the thiouracil controls, and different from the 3.0 mcg. level of L-thyroxine ($P > 0.99$), and were therefore inactive at this level. The 4′-amino-3′,5′-dimethyl (VI) produced a thyroid weight significantly lower ($P > 0.95$) than the thiouracil control, and not significantly different ($P > 0.99$) from the 2.0 mcg. dose of L-thyroxine. This compound is, therefore, about 0.7% as active as L-thyroxine. The 4′-amino-3′-iodo analog (VII) produced a thyroid

(15) E. Dempsey and E. B. Astwood, *Endocrinology*, **32**, 509 (1943).

TABLE II

RAT ANTIGOITER ASSAY OF 3,5-DIIODO-4-(4′-AMINOPHENOXY)-L-PHENYLALANINES



Food	Compound injected	Daily dose per 100 g., mcg.	Molar ratio	No. of rats	Thyroid weight per 100 g. mg.	± s.d.	Approximate activity
Untreated	—	—	—	6	5.6	0.7	—
Thiouracil, 0.3%	—	—	—	6	22.0	5.9	—
Thiouracil, 0.3%	Thyroxine[a]	2.0	0.67	6	11.2	4.1	100
Thiouracil, 0.3%	Thyroxine[a]	3.0	1.0	6	8.5	3.2	100
Thiouracil, 0.3%	Thyroxine[a]	4.5	1.5	6	4.6	0.7	100
Thiouracil, 0.3%	R = R′ = H[b] (IV)	183	100	6	21.7	4.7	0
Thiouracil, 0.3%	R = CH_3[b] R′ = H (V)	182	100	6	19.6	3.8	0
Thiouracil, 0.3%	R = R′ = CH_3[b] (VI)	193	100	6	13.8	6.1	0.7
Thiouracil, 0.3%	R = I, R′ = H (VII)	220	100	6	5.0	1.5	>1.5

[a] Sodium L-thyroxine pentahydrate. [b] Monohydrate.

weight significantly lower than that produced by both the thiouracil control ($P > 0.99$) and by 3.0 mcg. of L-thyroxine ($P > 0.95$), and not significantly different from the maximal reversal produced by 4.5 mcg. of L-thyroxine. This 4′-amino analog of 3,5,3′-triiodo-L-thyronine is, therefore, at least 1.5% as active as L-thyroxine. Additional graded dose assays will be required to fix the exact level of activity. The thyromimetic activity shown by two 4′-amino analogs of thyroxine indicates that the amino group is capable of functioning in place of the phenolic hydroxyl group in reversing thiouracil-induced goiter in the rat. This would support a mechanism of action related to electron transport, and present evidence against a mechanism involving simple interaction between phenoxide ion and biological receptor. The additional requirement for appropriate substitution *ortho* to the amino group (iodine or dimethyl) for minimal activity, when supplemented by additional examples, may help to clarify the role of the "prime ring" and its substituents in the thyroxine-like response.

Acknowledgment.—This work was supported by a U.S.P.H.S. research grant A4223, National Institute of Arthritis and Metabolic Diseases, which we gratefully acknowledge. P.S. thanks the Wellcome Trust, London, for the award of a travel scholarship.

Studies on Monoamine Oxidase Inhibitors. I. The Autoxidation of β-Phenylisopropylhydrazine as a Model Reaction for Irreversible Monoamine Oxidase Inhibition

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The cupric ion catalyzed autoxidation of β-phenylisopropylhydrazine has been studied by preparative and kinetic methods under conditions resembling those existing in biological systems. The data obtained point to a radical mechanism for the autoxidation, initiated by transfer of one electron from the hydrazine group to a cupric ion. A mechanism for irreversible monoamine oxidase inhibition is proposed, involving transfer of one electron from the hydrazine to the enzyme and subsequent oxidation of the hydrazine radical by molecular oxygen.