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Thyroxine Analogs. 20.[1] Substituted 1- and 2-Naphthyl Ethers of 3,5-Diiodotyrosine

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The syntheses of 8 substituted 1- and 2-naphthyl ethers of 3,5-diiodotyrosine are reported. 3,5-Diiodo-4-(4-hydroxy-1-naphthoxy)-L-phenylalanine was equiactive with L-thyroxine and 3,5-diiodo-4-(6-hydroxy-2-naphthoxy)-L-phenylalanine showed 2% thyroxine-like activity in the rat antigoiter assay. All other isomeric compounds and analogs were without appreciable thyroxine-like effect. These results indicate that the potential for oxidation to a quinoid form, and steric restrictions on the position of the phenolic OH relative to the "inner" ring are requisites for thyromimetic activity.

The demonstration[2,3] that 1- and 2-naphthyl ethers of 3,5-diiodotyrosine possess thyromimetic activity showed that the phenolic or "outer" benzene ring of thyroxine is not a unique structural requirement. The particularly high activity of 3,5-diiodo-4-(4-hydroxy-1-naphthoxy)-DL-phenylalanine (3,5-diiodonaphthyronine[2]) may be attributed to the presence of a free OH positioned 1,4 with respect to an ether O through an aromatic ring system, and to the naphthalene nucleus being held in a fairly fixed position by steric effects, the most favored position being that in which the plane of the naphthalene ring is at right angles to the plane of the "inner" benzene ring.[4] Interaction of the 4′-OH and the "outer" aromatic ring system with a *specific* part of a biological receptor surface has been postulated[3] as an essential step in the production of the biological effects of thyroxine and its analogs. Efficient interaction between such a receptor surface and the 4′-OH-containing outer ring of 3,5-diiodonaphthyronine would be expected due to the relatively fixed orientation of the naphthalene nucleus. In addition, the nonhydroxylated ring of the naphthalene moiety may be envisaged as filling spatial, electronic, and lipophilic requirements in its interaction with the receptor surface.[5] Halogen atoms and alkyl groups may fulfil this activating function for a substituent on the outer benzene ring in other active thyroxine analogs.

Niemann[6] has postulated that the potential for reversible production of a quinoid form is a requisite feature of thyroxine's interaction with biological systems. In a test of this quinoid hypothesis, thyroxine-like activity was demonstrated for 3,5-diiodo-4-(3,5-diiodo-2-hydroxyphenoxy)-DL-phenylalanine (*"ortho*-thyroxine").[7] This work and the report of activity for a related 3′-OH analog[8] provided support for the concept that no specific relationship was required between the ether O and OH group of thyroxine analogs.

The present paper examines these structural and stereochemical concepts further by the synthesis and biological evaluation of a series of 1′- and 2′-naphthyl ethers of 3,5-diiodotyrosine bearing an OH group at various positions on the naphthalene nucleus. Possession of thyromimetic activity by such analogs would preclude the interaction between the OH group and a specific part of a receptor surface discussed above. In addition, 2 types of hydroxynaphthyl ethers are possible—those from which quinoid forms can be produced, *e.g.*, from the 4′-hydroxy-1′-naphthyl ether, and those from which they cannot, *e.g.*, from the 7′-hydroxy-2′-naphthyl ether (Scheme I) without the introduction of an additional O atom. Thus the activity of 3,5-diiodonaphthyronine is in agreement with Niemann's hypothesis.[6]

1′-Naphthyl ethers of 3,5-diiodo-L-tyrosine bearing Me and amino groups at the 4′ position were also synthesized. The unsubstituted 1′-naphthyl ether has been shown to be weakly thyromimetic,[2] but it was postulated that activity may be preceded by *in vivo* hydroxylation to 3,5-diiodonaphthyronine. The 4′-Me substituted analog was synthesized to investigate this possibility further by the introduction of a group which would block *in vivo* 4′-hydroxylation. The 4′-amino-

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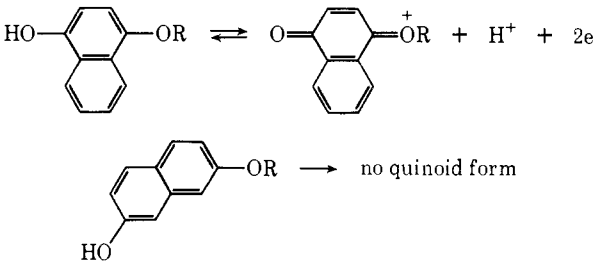
SCHEME I

POTENTIAL REVERSIBLE OXIDATION OF A 4-HYDROXY-1-NAPHTHYL ETHER (TOP). A 7-HYDROXY-2-NAPHTHYL ETHER (BOTTOM) AS AN ISOMER WHICH IS NOT OXIDIZED TO THE QUINOID FORM



R = -4-(3,5-diiodophenyl)alanine

substituted analog was of interest in view of the thyromimetic activity of other 4′-amino analogs of thyroxine.[9]

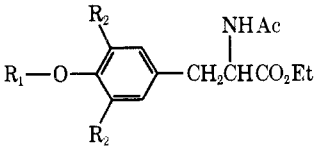
The syntheses of the thyroxine analogs followed methods previously described.[2,10,11] The required methoxynaphthols derived from symmetrical naphthalenediols, in which monomethylation could produce only a single product, were obtained by methylation under conditions of controlled pH and removal of the methoxynaphthol into an organic solvent phase as formed. Other methoxynaphthols and substituted naphthols were prepared by unambiguous methods described in the Experimental Section. The appropriate substituted naphthol was condensed in good yield with *N*-acetyl-3,5-dinitro-4-pyridiniumtyrosine ethyl ester methanesulfonate, although modifications of the normal conditions were necessary in some cases. The cryptophenolic nature[12,13] of 8-methoxy-1-naphthol required the use of boiling γ-picoline as the reaction solvent, and a long reaction time. The resulting substituted dinitrodiphenyl ethers (Table I, **1–12**) were hydrogenated to the diamines which were not isolated, but were bis-diazotized under anhyd conditions and converted to the diiodo compounds (Table I, **13–20**) by decomposition in an aq solution of I_2 and KI. Unexpectedly low yields of these diiodo compounds were obtained from some dinitro compounds. In a few cases no diiodo compound could be isolated, and the reactions were accompanied by the formation of intractable tars. In all cases chromatography on acid-washed alumina was necessary to isolate the pure diiodo intermediates. These were hydrolyzed to the appropriate amino acids (Table II).

Biological Results and Discussion.[9,14]—The rat antigoiter assay used was designed to detect activity relative to L-thyroxine of 0.2% or higher. The 4′-hydroxy-1′-naphthyl ether of 3,5-diiodo-L-tyrosine (Table II, **21**) was 100% as active as L-thyroxine while the 6′-hydroxy-2′-naphthyl ether of 3,5-diiodo-L-tyrosine (Table II, **27**) was 2% as active as L-thyroxine. The other isomeric 3,5-diiodonaphthyronines (Table II, **22**, **23**, **26**, **28**) and analogs (Table II, **24**, **25**) were inactive, or less than 0.2% as active as L-thyroxine.

The inactivity of all the hydroxynaphthyl ethers of 3,5-diiodotyrosine tested except the 6′-hydroxy-2′-naphthyl and 4′-hydroxy-1′-naphthyl ethers indicates that interaction of the OH group with a fairly specifically located part of a receptor surface is a necessary requisite for the thyroxine-like response. The weak activity of the 6′-hydroxy-2′-naphthyl ether agrees with the idea of such a specific interaction, since molecular models show that the 6′-OH in a 2′-naphthyl ether can

TABLE I

NAPHTHYL ETHERS OF *N*-ACETYL-3,5-DINITRO-L-TYROSINE ETHYL ESTER AND OF *N*-ACETYL-3,5-DIIODO-L-TYROSINE ETHYL ESTER

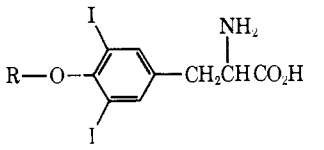


No.	R_1[a] = substd naphthyl	R_2	Mp, °C	Yield, %	Optical rotation[b]
1	2′-MeO-1′	NO_2	93–95	56	+47.9
2	4′-MeO-1′	NO_2	131–132	63	+48.6
3	5′-MeO-1′	NO_2	130–131	41	DL
4	6′-MeO-1′	NO_2	151–152	58	+44.2
5	7′-MeO-1′	NO_2	160–162	60	+57.2
6	8′-MeO-1′	NO_2	125–127	17	+69.8
7	4′-Me-1′	NO_2	161–162	70	+51.0
8	4′-AcNH-1′	NO_2	223–224	60	+9.2
9	3′-MeO-2′	NO_2	118–119	71	+44.6
10	5′-MeO-2′	NO_2	116–118	57	+46.2
11	6′-MeO-2′	NO_2	206–207	55	+21.2
12	7′-MeO-2′	NO_2	164–165	69	+44.6
13	4′-MeO-1′	I	135–137	16	+45.6
14	5′-MeO-1′	I	169–170	4	DL
15	7′-MeO-1′	I	126–128	15	+70.4
16	4′-Me-1′	I	123–125	72	+62.2
17	4′-AcNH-1′	I	250–251	29	+44.6
18	3′-MeO-2′	I	180–182	21	+55.4
19	6′-MeO-2′	I	147–149	18	+51.6
20	7′-MeO-2′	I	171–173	5	+54.0

[a] Compds 1–**6**, **9–12** ($C_{24}H_{23}N_3O_9$), **7** ($C_{24}H_{23}N_3O_8$), **8** ($C_{25}H_{24}N_4O_9$), **13–15**, **18–20** ($C_{24}H_{23}I_2NO_5$), **16** ($C_{24}H_{23}I_2NO_4$), **17** ($C_{25}H_{24}I_2NO_5$). All compds were analyzed for C and H, and in addn, **14–20** for I. The values obtd were within 0.4% of the calcd values. [b] $[\alpha]^{26}D$ (*c* 1.0, $CHCl_3$).

TABLE II

NAPHTHYL ETHERS OF 3,5-DIIODO-L-TYROSINE



No.	R_1[a] = substd naphthyl	Mp, °C dec	Yield, %	Optical rotation[b]	Antigoiter activity[c]
21	4′-HO-1′	>300	52	+32.7	100
22	5′-HO-1′	225–227	83	DL	0
23	7′-HO-1′	210–212	87	+25.0	0
24	4′-Me-1′	245–247	91	+63.2	0
25	4′-H_2N-1′	245–247	90	+30.0	0
26	3′-HO-2′	261–263	87	+20.8	0
27	6′-HO-2′	252–254	78	+13.6	2
28	7′-HO-2′	278–281	93	+26.6	0

[a] Compds **21–23**, **26–28** ($C_{19}H_{15}I_2NO_4$), **24** ($C_{20}H_{17}I_2NO_3$), **25** ($C_{19}H_{16}I_2N_2O_3$). All compds were analyzed for C, H, I. The values obtd were within 0.4% of the calcd values. [b] $[\alpha]^{26}D$ (*c* 0.5, 1 *N* HCl–EtOH, 1:1 v/v). [c] Relative to L-thyroxine as 100 on a molar basis. [d] The L compd has been described, without a report of biological activity, C. M. Buess, T. Giudici, N. Kharasch, W. King, D. D. Lawson, and N. N. Saha, *J. Med. Chem.*, **8**, 469 (1965).

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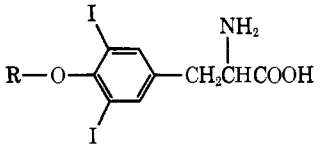
(13) Ng. Ph. Buu-Hoi and D. Lavit, *J. Chem. Soc.*, 2412 (1956).
(14) Detailed biol results are given in Table III.

TABLE III

RAT ANTIGOITER ASSAY OF SUBSTITUTED NAPHTHYL ETHERS OF 3,5-DIIODO-L-TYROSINE[a]



Assay number	Food	Compound injected	Daily dose per 100 g, μg	Molar ratio	Thyroid weight per 100 g mg	±std dev	Approximate activity
I	Untreated				7.0	1.2	
	Thiouracil, 0.3%				22.5	4.7	
	Thiouracil, 0.3%	Thyroxine[b]	2.0	0.67	13.3	5.0	100
	Thiouracil, 0.3%	Thyroxine	3.0	1.0	11.9	6.2	100
	Thiouracil, 0.3%	Thyroxine	4.5	1.5	6.5	1.4	100
	Thiouracil, 0.3%	R = 5′-hydroxy-1′-naphthoxy[c]	195.0	100	23.9	6.3	0
	Thiouracil, 0.3%	R = 3′-hydroxy-2′-naphthoxy	195.0	100	26.1	8.0	0
	Thiouracil, 0.3%	R = 6′-hydroxy-2′-naphthoxy	195.0	100	6.0	1.3	>1.5
	Thiouracil, 0.3%	R = 7′-hydroxy-2′-naphthoxy	195.0	100	18.5	3.0	0
II	Untreated				6.6	0.8	
	Thiouracil, 0.3%				20.2	3.9	
	Thiouracil, 0.3%	Thyroxine[b]	2.0	0.67	14.4	3.5	100
	Thiouracil, 0.3%	Thyroxine[b]	3.0	1.0	10.3	4.0	100
	Thiouracil, 0.3%	Thyroxine	4.5	1.5	6.1	3.0	100
	Thiouracil, 0.3%	R = 7′-hydroxy-1′-naphthoxy[d]	195.0	100	23.1	5.9	0
	Thiouracil, 0.3%	R = 6′-hydroxy-2′-naphthoxy[e]	48.8	25	21.4	3.2	<3
	Thiouracil, 0.3%	R = 4′-methyl-1′-naphthoxy[e]	194.0	100	25.4	5.4	0
	Thiouracil, 0.3%	R = 4′-amino-1′-naphthoxy[f]	194.5	100	21.1	6.5	0
III	Untreated				7.0	1.2	
	Thiouracil, 0.3%				22.5	4.7	
	Thiouracil, 0.3%	Thyroxine[b]	2.0	0.67	13.3	5.0	100
	Thiouracil, 0.3%	Thyroxine	3.0	1.0	11.9	6.2	100
	Thiouracil, 0.3%	Thyroxine	4.5	1.5	6.5	1.4	100
	Thiouracil, 0.3%	R = 4′-hydroxy-1′-naphthoxy	2.58	1.33	8.7	1.3	100

[a] Six rats in each control and experimental group. [b] Sodium L-thyroxine pentahydrate. [c] DL isomer. [d] Dissolved in a 1:1:8 mixt of EtOH–propylene glycol–0.9% aq NaCl contg sufficient NaOH to make the soln 0.01 *N*. [e] Dissolved in 40% propylene glycol in 0.9% aq NaCl contg sufficient NaOH to make the soln 0.02 *N*. [f] Dissolved in 20% EtOH in 0.9% aq NaCl contg sufficient NaOH to make the soln 0.01 *N*.

occupy a position close to that occupied by the 4′-OH in 3,5-diiodonaphthyronine. Additionally, the 6′-hydroxy-2′-naphthyl ether is capable of oxidation to a quinoid form, and its thyromimetic activity thus lends further support to Niemann's hypothesis.[6] However, the inactivity of other hydroxylated analogs which could also be oxidized to quinoid forms (the 5′-hydroxy- and 7′-hydroxy-1′-naphthyl and 3′-hydroxy-2′-naphthyl ethers of 3,5-diiodotyrosine) suggests that capability of oxidation to a quinoid form alone is insufficient to impart activity. This potential must be accompanied by steric restrictions which could permit interaction between a receptor surface and an OH or amino group[9] located at a fairly closely defined position with respect to the inner ring, before a thyromimetic response can be initiated.

These results are apparently in conflict with the thyroxine-like activity reported for the 2′-OH isomer of thyroxine, "*ortho*-thyroxine." However, a reexamination of this and related compounds[15] indicates the probability that metabolic 4′-hydroxylation is responsible for the production of an active metabolite.

The unsubstituted 1′- and 2′-naphthyl ethers of 3,5-diiodotyrosine have previously been shown[2,3] to be thyromimetic. Their biological activities have been presumed to be preceded by *in vivo* hydroxylation to the 4′-OH- and 6′-OH-substituted compounds, resp,[3] and such a postulate receives support from the inactivity of the 4′-methyl-1′-naphthyl ether of 3,5-diiodotyrosine (Table II, **24**) in which hydroxylation at the 4′ position is prohibited. The unsubstituted naphthyl ethers had low activities—3.3% of L-thyroxine for the 1′-naphthyl and 0.2% of L-thyroxine for the 2′-naphthyl ether. This order would be expected if the activities are due to the sort of hydroxylation discussed above, since the present work shows that the 4′-hydroxy-1′-naphthyl and 6′-hydroxy-2′-naphthyl ethers of 3,5-diiodotyrosine have much higher activities than the corresponding 4′-deoxy analogs.

That the 4′-amino-1′-naphthyl ether of 3,5-diiodotyrosine is not thyromimetic at the dose level tested might be expected from the fact that the most active 4′-amino-substituted thyroxine analog yet synthesized,[9] the 4′-amino analog of L-triiodothyronine, has an activity of about 2% that of L-thyroxine.

Experimental Section[16]

Substituted Naphthols. (a) Methoxynaphthols from Symmetrical Naphthalenediols.[17]—The diol (10 g, 0.062 mole) was suspended in Et_2O (100 ml) contg Me_2SO_4 (7.5 ml) under N_2.

(15) P. E. Berteau, Ph.D. Dissertation, University of California, San Francisco, Calif., 1964.

(16) Melting points (cor) were determined with a Thomas-Hoover capillary melting point app. Microanalyses were performed by the Microanalytical Laboratory, University of California, Berkeley, Calif. Optical rotations were measured with a Rudolph polarimeter. Where analyses are indicated only by symbols of the elements, anal. results were within 0.4% of the theor values.

(17) H. Brederick, I. Hennig, and W. Rau, *Chem. Ber.*, **86**, 1085 (1953).

Aq NaOH (30%) was added dropwise with vigorous stirring to maintain the pH between 10 and 10.5. After addn of about 10 ml of aq NaOH, the pH remained const and the Et_2O layer was removed to give an oil which crystd from heptane: 4-methoxy-1-naphthol, mp 126–128° (lit.[18] 124–125°); 5-methoxy-1-naphthol, mp 137–138° (lit.[19] 135–136°); 8-methoxy-1-naphthol, mp 55–57° (lit.[13] 55–56°); 3-methoxy-2-naphthol, mp 107–108° (lit.[20] 108°); 6-methoxy-2-naphthol, mp 148–149° (lit.[21] 136–137°) (*Anal.* ($C_{11}H_{10}O_2$) C, H); 7-methoxy-2-naphthol, mp 114–115° (lit.[22] 116–117°).

(**b**) By the method of Byrde,[23] 6-methoxy-1-naphthol, mp 82–84° (lit.[23] 85°), 7-methoxy-1-naphthol, mp 104–106° (lit.[23] 100–102°)(*Anal.* ($C_{11}H_{10}O_2$) C, H), and 5-methoxy-2-naphthol, mp 59–60° (lit.[24] unstable oil) (*Anal.* ($C_{11}H_{10}O_2$) C, H), were prepd by decompn of the appropriate methoxynaphthalene diazonium salt in dil acid under N_2. Purification of the crude phenol was effected by chromatog on acid-washed alumina with elution by C_6H_6–Et_2O (9:1), unlike the alk extn of Byrde;[23] it crystd from heptane as colorless needles.

(**c**) 2-Methoxy-1-naphthol was synthesized as an oil by treatment of 2-methoxy-1-naphthylmagnesium bromide with O_2 followed by decompn with dil acid.[25]

(**d**) Attempts to prep 3-methoxy-1-naphthol by decompn of the diazonium sulfate in dil H_2SO_4, by decompn of the diazonium fluoroborate in AcOH, by the action of O_2 or of trimethyl borate[26] on 3-methoxy-1-naphthylmagnesium bromide followed by acid decompn, yielded only small amts of 2-methoxy-1,4-naphthoquinone, yellow needles from aq EtOH, mp 183–184° (lit.[27] 184–185°). *Anal.* ($C_{11}H_8O_3$), C, H.

(e) 4-Acetamido-1-naphthol, mp 186–187° (lit.[28] 187°), and 4-methyl-1-naphthol, mp 82–83° (lit.[29] 85°), were prepd by the lit. methods.

Substituted Naphthyl Ethers of *N*-Acetyl-3,5-dinitro-L-tyrosine Ethyl Ester (Table I, 1–12).—A 2-fold excess of the appropriate substituted naphthol was condensed with *N*-acetyl-3,5-dinitro-L-tyrosine ethyl ester by standard methods.[2,10,11] Formation of the 8′-methoxy-1′-naphthyl ether (**6**) required γ-picoline as solvent heated under reflux for 1.5 hr, and a 1:1 molar ratio of phenols, in place of pyridine and standard reaction conditions. Crystd from aq EtOH.

Substituted Naphthyl Ethers of *N*-Acetyl-3,5-diiodo-L-tyrosine Ethyl Ester (Table I, 13–20).—The dinitro compds (**1–12**) were hydrogenated, bis-diazotized, and decompd in aq I_3^- soln by standard methods.[2,10,11] The crude products were chromatogd on acid-washed alumina and crystd from aq EtOH. All yields were low due to tar formation, and no diiodo compds could be isolated from the dinitro intermediates **1, 4, 6, 10**.

Substituted Naphthyl Ethers of 3,5-Diiodo-L-tyrosine (Table II, 21–28).—The diiodo methoxynaphthyl ethers (**13–15, 18–20**) were hydrolyzed to the amino acids (Table II, **21–23, 26–28**) using HI in AcOH.[2,10] Compds **16** and **17** were hydrolyzed with HCl in AcOH.[9] The free amino acids were isolated by isoelectric pptn.

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Biosynthesis of Coenzymes Q by Malarial Parasites. 2. Coenzyme Q Synthesis in Blood Cultures of Monkeys Infected with Malarial Parasites (*Plasmodium falciparum* and *P. knowlesi*)†

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The incorporation of [^{14}C]*p*-hydroxybenzoic acid into coenzymes Q by cultures of normal monkey blood and monkey blood infected with malarial parasites has been measured. The host blood cells and the corresponding parasites are: rhesus monkey blood with *Plasmodium knowlesi*, and night monkey (*Aotus trivirgatus*) blood with *P. falciparum*. Only coenzyme Q_{10} was labeled in normal *Aotus* blood cultures, while coenzymes Q_8, Q_9, and Q_{10} were labeled in *Aotus* blood cultures infected with *P. falciparum*. Effects of incubation time and of parasitemia on incorporation were compared for rhesus blood cultures infected with *P. knowlesi* and *Aotus* blood cultures infected with *P. falciparum*. No correlation of extent of incorporation with growth stage could be demonstrated for rhesus blood infected with *P. knowlesi*.

It was demonstrated[1] that rhesus monkey blood cells which are infected with *Plasmodium knowlesi* incorporate [^{14}C]*p*-hydroxybenzoic acid into coenzymes Q_8, Q_9, and Q_{10} (I, n = 8, 9, and 10) while normal rhesus blood cells synthesize only coenzyme Q_{10} from the same labeled precursor. These data agreed with the results on the identification of coenzymes Q from normal duck blood and duck blood infected with *P. lophurae*.[2] The recent discovery that a new world monkey (*Aotus trivirgatus*) is susceptible to infection with *P. falciparum*[3] provided an opportunity to study the biosynthesis of coenzyme Q by this important human parasite. This

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† Coenzyme Q. 114.
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