lized from acetic acid. Although this product (XVI A) gave a satisfactory analysis, ultraviolet spectra with strong absorption at 320 mμ in alkali indicated the presence of a phenolic impurity. This was confirmed by chromatography (Table IV) which gave three spots with R_f values of 0.22, 0.66 and 0.92. Comparison with an authentic sample showed the minor spot with R_f 0.22 to be *N*-acetyl-3,5-diiodo-DL-tyrosine. No authentic sample was available for comparison, but the other minor spot with R_f 0.92 was assumed to be *N*-acetyl-DL-thyroxine on the basis of the transformation of *N*-acetyl-3,5-diiodotyrosine to *N*-acetylthyroxine under similar conditions.[8] Both the R_f 0.92 spot and thyroxine-like activity were lost when the alternate synthetic Method B was applied. The spot varying between R_f 0.65–0.75 made up the major chromatographic component by both methods of synthesis, and on the basis of analytical and spectral data was assumed to be the desired cyclohexyl ether.

*N-Acetyl-3,5-diiodo-4-cyclohexyloxy-*DL*-phenylalanine*, (XVI B), Method B. *N*-Acetyl-3,5-diiodo-4-(3-cyclohexenyloxy)-DL-phenylalanine (XVII, 220 mg., 0.5 mmole) was dissolved in absolute ethanol (10 ml.), and shaken with hydrogen at atmospheric pressure and room temperature in the presence of platinum oxide (10 mg.) until the theoretical amount of hydrogen had been absorbed. The catalyst was filtered off, water was added to the hot solution which was then chilled until crystallization ceased. There was obtained 135 mg. (61%) of colorless prisms, m.p. 167–172°, which did not decolorize bromine water. Analytical and bioassay samples were prepared by recrystallization from aqueous acetone.

Ultraviolet absorption spectra in acidic and basic ethanolic solutions showed the presence of a small amount of phenolic contamination (λ_{max} 315 mμ in alcoholic alkali) and its absence in the starting material. This was confirmed by chromatography (Table IV) which showed one spot (R_f 0.71) for the starting material, and two for the hydrogenated product (R_f 0.29 and 0.75). The slower moving component was identified as *N*-acetyl-3,5-diiodo-DL-tyrosine, and its concentration in the preparation was estimated from the absorbance at 6%.

Acknowledgment. This work was supported in part by grant-in-aid funds from Smith Kline and French Laboratories and from Research Funds of the University of California Academic Senate. We are grateful to Mr. Michael Hrenoff for preparation of spectra.

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[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, SCHOOL OF PHARMACY, UNIVERSITY OF CALIFORNIA AT SAN FRANCISCO]

Thyroxine Analogs. V.[1] Synthesis of Some 1- and 2-Naphthyl Ethers of 3,5-Diiodo-DL-Tyrosine[2]

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In an investigation of the importance of aromatic character and steric requirements for the phenolic ring of thyroxine, a series of analogs was prepared replacing the benzene with the naphthalene ring.

The finding that a diverse series of aliphatic and alicyclic ethers substituted in the 4-position of 3,5-diiodotyrosine was devoid of either thyromimetic or thyroxine antagonistic properties,[1] together with the observation that such properties were displayed by a related series of alkyl-substituted phenyl ethers[4] led to the conclusion that aromaticity of the "prime" ring was a requisite for activity. In order to determine the effect of aromatic systems other than the benzenoid, synthesis of a series of naphthyl ethers was carried out.

The unsubstituted 1-naphthyl and 2-naphthyl ethers of 3,5-diiodo-DL-tyrosine were selected since they could be considered as sterically related to the 2′,3′-dimethylphenoxy[5] and the 3′,4′-dimethylphenoxy[6] analogs which have shown mimetic[4] and antagonistic[7] properties, respectively. The naphthalene ring of 3,5-diiodo-4-(1-naphthyl) ethers possesses a relatively fixed stereochemical orientation, being forced to occupy a position in space perpendicular to the plane of and distal to the alanine-bearing ring in order to provide a minimal interaction with the 3,5-diiodophenyl structure.[8] The 4-hydroxy-1-naphthoxy analog was of interest in providing comparison with its nonhydroxylated analog, and as a precursor to a halogenated derivative whose halogen substituent would occupy a

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(2) Reported in part before the Division of Medicinal Chemistry at the 138th National Meeting of the American Chemical Society, New York, N. Y., September 1960.

(3) In partial fulfillment of the requirements for the degree of Doctor of Philosophy, University of California, June 1960. Present address: Laboratorios "Hormona," S.A., Laguna de Mayrañ 411, Mexico D.F., Mexico.

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TABLE I. 3,5-DISUBSTITUTED-4-ARYLOXY-DL-PHENYLALANINE DERIVATIVES

No.	R	R'	R''	R'''	Yield, %[a]	M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
I	2-Naphthyl	NO_2	$COCH_3$	C_2H_5	71	117–119	$C_{23}H_{21}N_3O_8$	59.10	59.08	4.53	4.42
II	1-Naphthyl	NO_2	$COCH_3$	C_2H_5	49	154–156	$C_{23}H_{21}N_3O_8$	59.10	58.82	4.53	4.77
III	4-Methoxy-1-naphthyl	NO_2	$COCH_3$	C_2H_5	56	114–115	$C_{24}H_{23}N_3O_9$	57.94	58.13	4.66	4.93
IV	2-Naphthyl	I	$COCH_3$	C_2H_5	31	186–188	$C_{23}H_{21}I_2NO_4$	43.90	43.51	3.36	3.29
V	1-Naphthyl	I	$COCH_3$	C_2H_5	50	162–163	$C_{23}H_{21}I_2NO_4$	43.90	43.89	3.36	3.38
VI	4-Methoxy-1-naphthyl	I	$COCH_3$	C_2H_5	48	195–198	$C_{24}H_{23}I_2NO_5$	43.72	43.84	3.52	3.52
VII	2-Naphthyl	I	H	H	94	250–255 (dec.)	$C_{19}H_{15}I_2NO_3 \cdot H_2O$[b]	39.54	39.69	2.97	2.92
VIII	1-Naphthyl	I	H	H	76	209–215 (dec.)	$C_{19}H_{15}I_2NO_3 \cdot H_2O$[c]	39.54	40.16	2.97	2.97
IX	4-Methoxy-1-naphthyl	I	H	H	Low	195–205 (dec.)	$C_{20}H_{17}I_2NO_4$[d]	40.77	40.52	2.91	2.90
X	4-Methoxy-1-naphthyl	I	$COCH_3$	H	62	249–251 (dec.)	$C_{22}H_{19}I_2NO_5$[e]	41.86	42.02	3.03	3.16
XI	4-Hydroxy-1-naphthyl	I	H	H	80	258–264 (dec.)	$C_{19}H_{15}I_2NO_4$[f]	39.68	39.60	2.63	2.81
XII	3-Bromo-4-hydroxy-1-naphthyl	I	H	H	69	238–240 (dec.)	$C_{19}H_{14}BrI_2NO_4$[g]	34.89	35.11	2.16	2.47

[a] Yields are based on purified material. [b] Calcd.: I, 43.98. Found: I, 43.60. [c] Calcd.: I, 43.98. Found: I, 43.90. [d] Calcd.: I, 43.08. Found: I, 42.90. [e] Calcd.: I, 40.21. Found: I, 40.33. [f] Calcd.: I, 44.13. Found: I, 43.90. [g] Calcd.: Br, 12.22. Found: Br, 12.50.

relatively fixed position in space with respect to the rest of the molecule.

The synthetic sequence used was the Meltzer[9] modification of the method of Borrows, Clayton, and Hems.[10] A representative series of reactions with the 1-naphthols is shown in Fig. 1. The structures of the 2-naphthoxy analogs, obtained by a similar reaction sequence, are summarized in Fig. 2. Physical constants are listed in Table I.

3,5-Dinitro-DL-tyrosine-*N*-acetyl ethyl ester in pyridine was converted to the methanesulfonyl ester, which without isolation was allowed to react with the appropriate phenol (1-naphthol, 2-naphthol, or 4-methoxy-1-naphthol) to form the dinitrodiaryl ether (I–III). This was converted to the corresponding diiododiaryl ether (IV–VI) by catalytic reduction, tetrazotization, and iodination, and was hydrolyzed to the free amino acid (VII–IX, XI). The method of Bredereck, Henning, and Rau[11] was used in the preparation of 4-methoxy-1-naphthol by monomethylation of 1,4-naphthalenediol in significantly higher yield than by previously reported methods.[12,13]

Hydrolysis of IV and V with hydrochloric and acetic acids was used to obtain the free amino acids of the 1-naphthyl (VIII) and 2-naphthyl (VII) ethers, hydriodic and acetic acids being used to convert the *N*-acetyl ethyl ester of the 4-methoxy-1-naphthyl ether (VI) to the free amino acid of the 4-hydroxy-1-naphthyl ether (XI).[14] In an attempt to remove the protective groups of the alanyl side chain in the 4-methoxy-1-naphthoxy analog (VI) by hydrochloric and acetic acid hydrolysis without cleavage of the methyl ether, a partially demethylated product was obtained as shown spectrally by the appearance of phenolic absorption (λ_{max} 350 mμ) in alcoholic alkali. This was purified with difficulty to yield a small amount of 4-methoxy-1-naphthyl amino acid (IX). Cleavage of simple methyl naphthyl ethers has been reported under similar conditions of acidic hydrolysis.[15] Aqueous alkaline hydrolysis yielded the *N*-acetyl-4-methoxy-1-naphthoxy (X) analog free of phenolic contamination as determined spectrally.

The desired benzolog of triiodothyronine, 3,5-diiodo-4-(3-iodo-4-hydroxy-1-naphthoxy)-DL-phenylalanine could not be obtained. Iodination of 3,5-diiodo-4-(4-hydroxy-1-naphthoxy)-DL-phenylala-

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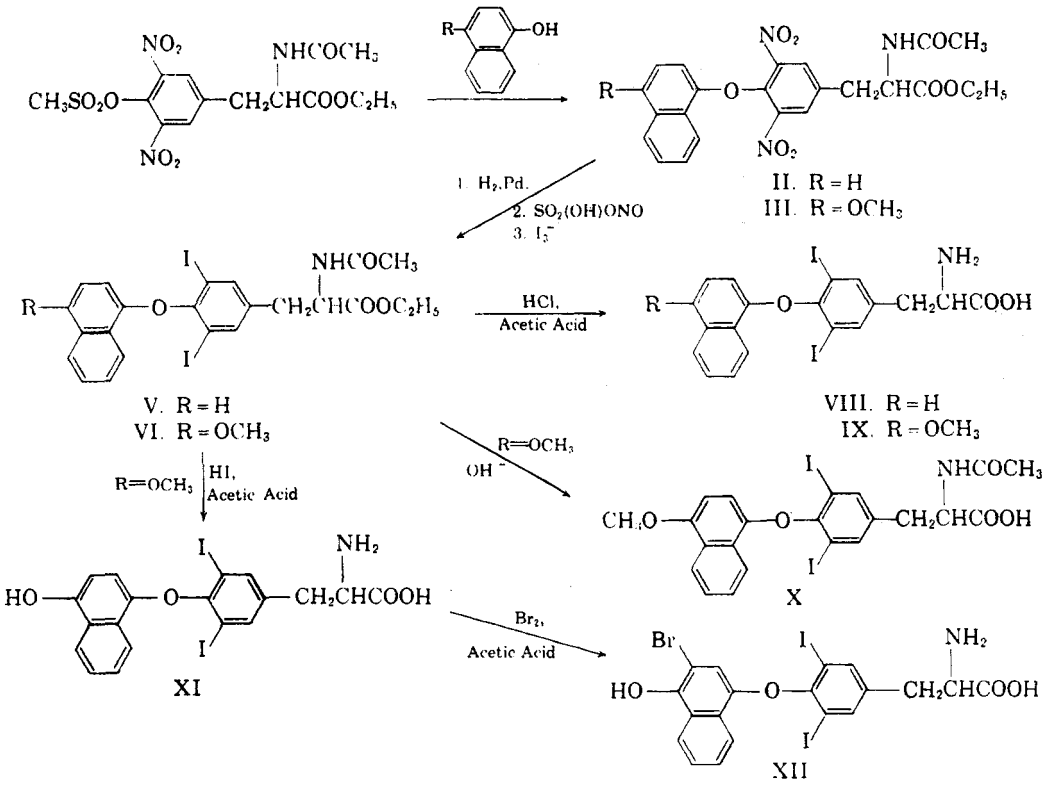
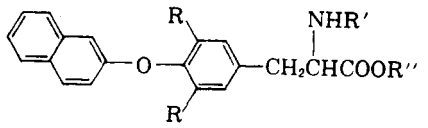


Fig. 1. 1-Naphthoxy series



I. R = NO_2, R′ = $COCH_3$, R″ = C_2H_5
IV. R = I, R′ = $COCH_3$, R″ = C_2H_5
VII. R = I, R′ = H, R″ = H

Fig. 2. 2-Naphthoxy series

nine (XI) with iodine monochloride in dioxane,[16] with sodium triiodide in ethylamine[17] and in ammonia, or with iodine in acetic acid,[18] resulted in products which showed by analysis that the required iodination had not occurred, or that iodine had been lost. However, bromination was effected in warm acetic acid to give the corresponding 3-bromo analog (XII).

In the rat antigoiter assay of Dempsey and Astwood,[19] these analogs demonstrated the following thyroxine-like activities relative to L-thyroxine (100%): 2-naphthyl (VII), 0.2%; 1-naphthyl (VIII), 3.3%; 4-methoxy-1-naphthyl (X), 4.9%; 4-hydroxy-1-naphthyl (XI), > 100%; 3-bromo-4-hydroxy-1-naphthyl (XII), 29%. A detailed discussion of these and related biological results will be submitted for publication elsewhere.

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EXPERIMENTAL

All melting points were taken on a Fisher-Johns melting point apparatus and are given uncorrected. Microanalyses were carried out by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley. All compounds were dried for at least 24 hr. over phosphorus pentoxide at 3 mm. and 100°.

4-Methoxy-1-naphthol.[11] In a three necked flask equipped with a stirrer, dropping funnel, *p*H-meter electrodes and supplied with nitrogen were placed 1,4-naphthalenediol (80 g., 0.5 mole) and anisole (300 ml.). The water bath was held at 40°, and with strong stirring, dropwise addition of 20% sodium hydroxide was begun. Dimethyl sulfate (63 ml., 0.65 mole) was added in three equal portions at intervals of 10 min. The addition of the base was adjusted to maintain the *p*H between 10.0 and 10.5 and was continued until a drop in *p*H was no longer observed when the addition was stopped. This occurred after 115 ml. of sodium hydroxide had been added over 3 hr. The reaction mixture was acidified to *p*H 3 with 2*N* sulfuric acid, the aqueous phase extracted with ether, and the ether solution extracted until colorless with 2*N* sodium hydroxide. The basic extract was covered with ether, cooled, and re-acidified as quickly as possible to minimize air oxidation. The aqueous layer was extracted with ether, the combined ether extracts were dried over calcium chloride and reduced nearly to dryness with gentle warming under a stream of nitrogen. The brown residue was taken up in hot 95% ethanol from which it crystallized on standing. The resulting purple-brown tinged product was recrystallized from alcohol-water with Norit A to give 49 g. (56%) of pink needles, m.p. 126–128° (lit.[18] m.p. 124–125°). A second run in 150 ml. of anisole and 125 ml. of ether gave 48.2 g. (55.4%).

Aryl ethers of 3,5-dinitro-DL-tyrosine-N-acetyl ethyl ester

(I–III). To 3,5-dinitro-DL-tyrosine-*N*-acetyl ethyl ester[20] (17.0 g., 0.05 mole) dissolved in dry pyridine (100 ml.) by gentle warming, methanesulfonyl chloride (6.3 g., 0.055 mole) was added and the mixture refluxed for 2 min. The phenol (1-naphthol, 2-naphthol, or 4-methoxy-1-naphthol; 0.15 mole) was added and the mixture heated under reflux for 6 min. The reaction mixture was poured into 200 ml. of cold water, extracted with benzene, and the benzene extract was washed successively with 2*N* hydrochloric acid, water, 0.3*N* sodium hydroxide, and water. At this point, the product usually crystallized from the benzene solution and was removed by filtration. A second crop was obtained by evaporation of the filtrate (air current) to remove the last traces of pyridine, and by extraction of the resultant tarry residue with hot benzene. The combined material was recrystallized from 95% ethanol.

*Aryl ethers of 3,5-diiodo-*DL*-tyrosine-N-acetyl ethyl ester* (IV–VI). 3,5-Dinitro-4-aryloxy-DL-phenylalanine-*N*-acetyl ethyl ester (I–III, 0.01 mole) dissolved in acetic acid (100 ml.) was shaken for 1 hr. in the presence of palladium-on-charcoal (10%, 1.0 g.) and hydrogen (45 p.s.i. initial pressure). In each case the hydrogen uptake was from 90 to 98% of the theoretical. Concentrated sulfuric acid (20 ml.) was added with cooling, the catalyst removed by filtration through Celite, and the solution of the diamine placed in a pressure-equalized dropping funnel under nitrogen. This solution was added during 1 hr. to a well stirred mixture under nitrogen of nitrosylsulfuric acid (sodium nitrite, 2.76 g., 0.04 mole, added in small portions to sulfuric acid, 30 ml., at 60–70°, and diluted when cool with acetic acid, 30 ml.) kept at −5°. Concentrated sulfuric acid was added as needed to prevent freezing. After the addition was complete, the orange tetrazonium solution was stirred for an additional hour at −5° and then poured rapidly into a well stirred mixture of iodine (10.7 g., 0.042 mole), sodium iodide (15 g., 0.10 mole) and urea (1.56 g., 0.026 mole) diluted with water (150 ml.), underlayed with chloroform (150 ml.), and cooled in an ice bath. After stirring 1 hr. below 10°, it was stirred another hour while allowing the mixture to reach room temperature and then an additional half hour while raising the temperature to 35–40°. If a solid residue was present, the mixture was filtered, the chloroform phase removed, and the aqueous layer extracted with chloroform. The combined chloroform extracts were washed with water, 10% aqueous sodium bisulfite, water, sodium bicarbonate, and water, dried over calcium chloride, filtered, and the chloroform removed at reduced pressure. The residue was dissolved in a minimum volume of chloroform and after rapid adsorption and development with chloroform on a short column of acid-washed alumina, the residue from evaporation of the first eluate was crystallized from absolute ethanol.

*Aryl ethers of 3,5-diiodo-*DL*-tyrosine* (VII–IX). 3,5-Diiodo-4-aryloxy-DL-phenylalanine-*N*-acetyl ethyl ester (IV–VI) was heated under reflux for 3 hr. with glacial acetic acid and concentrated hydrochloric acid (10 ml. of each per g. of ester). The mixture was diluted while warm with an equal volume of hot water and the *p*H adjusted to 5 with 2*N* sodium hydroxide. The resulting precipitate was crystallized from aqueous acetic acid.

In the case of the 4-methoxy-1-naphthoxy ether (VI) the hydrolysis was inadvertently allowed to proceed for 5 hr. The high melting product (*ca.* 250°) could not be purified to the point of correct analysis, even after repeated isoelectric precipitations. (Calcd. for $C_{20}H_{17}I_2NO_4$: C, 40.77; H, 2.91; I, 43.08. Found: C, 39.44; H, 2.98; I, 40.98.) By slow crystallization from aqueous acetic acid, a small amount of a lower melting material was obtained whose analysis was correct for the methoxyamino acid (IX). Ultraviolet spectra of the crude material in alcoholic alkali showed λ_{max} 350 mμ, indicating that demethylation to the 4-naphthol (XI) had taken place.

*N-Acetyl-3,5-diiodo-4-(4-methoxy-1-naphthoxy)-*DL*-phenylalanine* (X). To 3,5-diiodo-4-(4-methoxy-1-naphthoxy)-DL-phenylalanine-*N*-acetyl ethyl ester (VI, 660 mg., 1.0 mmole) suspended in absolute ethanol (12 ml.) was added 2.0 ml. of 40% aqueous sodium hydroxide (800 mg., 20 mmoles). The mixture was stirred at room temperature for 1 hr. The resulting clear, orange colored solution was diluted with an equal volume of warm water and acidified to *p*H 3 with 2*N* hydrochloric acid. The orange oil which precipitated was crystallized from ethanol-water and from aqueous acetone to give 393 mg. (62%) of pink feathery crystals, m.p. 249–251° dec. Ultraviolet spectra: λ_{max} 310, 317, 331 mμ in both alcoholic hydrochloric acid and alcoholic sodium hydroxide.

*3,5-Diiodo-4-(4-hydroxy-1-naphthoxy)-*DL*-phenylalanine* (XI). 3,5-Diiodo-4-(4-methoxy-1-naphthoxy)-DL-phenylalanine-*N*-acetyl ethyl ester (VI, 3.3 g., 5.0 mmoles) was refluxed under nitrogen for 4 hr. with glacial acetic acid (40 ml.) and hydriodic acid (57%, 30 ml.). The reaction mixture was distilled to near dryness on a water bath at 50° under reduced pressure (5 mm.). The residue was dissolved in hot absolute ethanol, decolorized with sodium metabisulfite, diluted with hot water, and adjusted to *p*H 4.9 with hot 2*N* aqueous sodium acetate. The resulting light yellow powder weighed 2.3 g. (80%); m.p. 258–264° dec. Ultraviolet spectra: λ_{max} 309 mμ in aqueous hydrochloric acid; λ_{max} 351 mμ in aqueous sodium hydroxide.

Omission of the sodium metabisulfite treatment or neutralization with aqueous sodium hydroxide instead of aqueous sodium acetate resulted in a blue solid which only partially melted at 300°. Preliminary examination of its electron spin resonance spectrum both in the solid state and in concentrated sulfuric acid indicated the presence of a moderate concentration of free radicals.

*3,5-Diiodo-4-(3-bromo-4-hydroxy-1-naphthoxy)-*DL*-phenylalanine* (XII). To 3,5-diiodo-DL-naphthyronine[14] (XI, 575 mg., 1.00 mmole) dissolved in glacial acetic acid (30 ml.) and concentrated hydrochloric acid (5 drops), was added dropwise, at 50–60°, a glacial acetic acid (5 ml.) solution of bromine (176 mg., 1.10 mmoles). After stirring an additional 15 min., the solution was decolorized with sodium metabisulfite, diluted with water, and adjusted to *p*H 3.7 with 20% aqueous sodium acetate. The resultant precipitate was collected, washed with water and dissolved in ethanol acidified with a few drops of concentrated hydrochloric acid. The solution was warmed, diluted with an equal volume of water, and neutralized to *p*H 5.0 with 20% sodium acetate. The precipitate was washed with water and dried; yield, 450 mg. (69%); m.p. 238–240° dec. Ultraviolet spectra: λ_{max} 309 mμ in aqueous hydrochloric acid; λ_{max} 351 mμ in aqueous sodium hydroxide.

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