[From the Departments of Biochemistry and Chemistry, University of Southern California]

THE SYNTHESIS OF SOME NEW THYROXINE ANALOGS[1]

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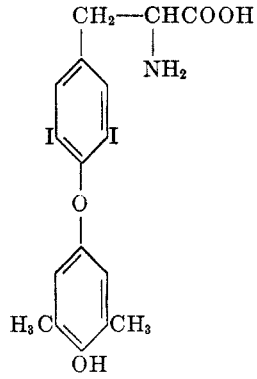
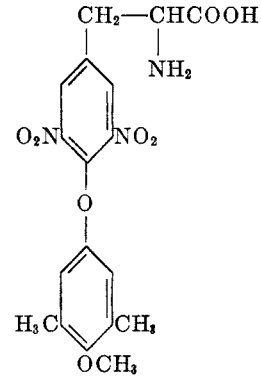
Our considerations of the relation between the structures of substituted diphenyl ethers and their thyroxine-like activities suggested the need for testing a series of thyroxine analogs such as I, II, and III. This paper reports the synthesis of these compounds. The results of our biological testing, and the correlation of structure and thyroxine activity will be reported elsewhere (1).



I



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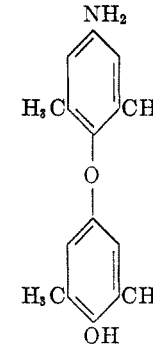
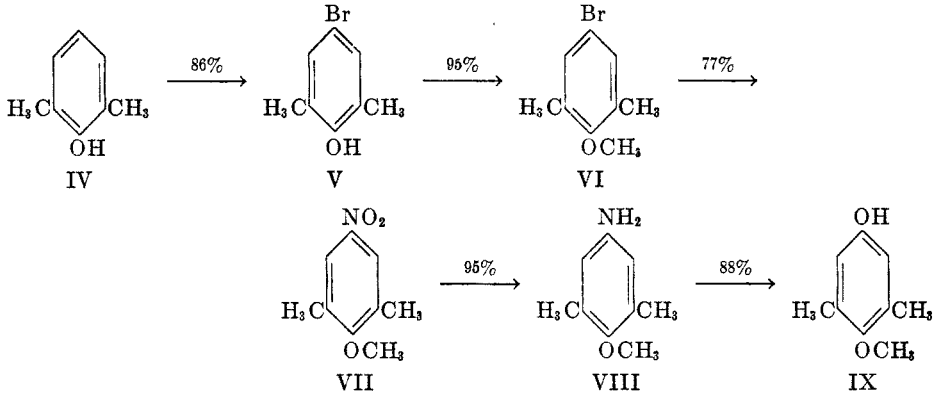


III

The syntheses of I, II, and III were effected by condensing the appropriate halves of the molecules of the required diphenyl ethers. The precursors VI and IX were obtained as shown below:



IV V VI

VII VIII IX

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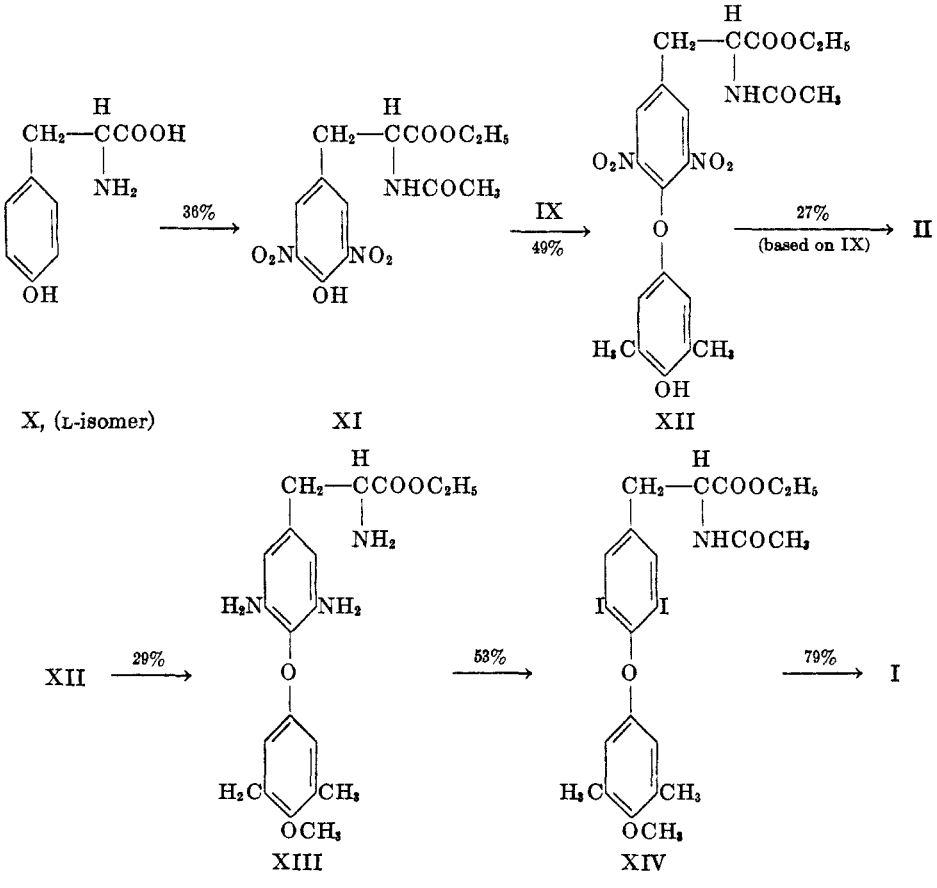
Compound VI was a liquid and was characterized by conversion to 2,6-dimethyl-3,4-dibromoanisole. In the sequence shown above, it will also be noted that VII was obtained by brominating IV to yield V, methylating V, and replacing the bromine atom of VI by nitration. While this procedure is less direct than those involving nitration of IV, followed by methylation (or methylation of IV, followed by nitration) it nevertheless gives the best yield, as described in the experimental section. The lowered yields in the more direct routes (recorded in the experimental part) are caused by side reactions, such as oxidation of IV to the known tetramethyldiphenoquinone (8). The alternate synthesis of VI from VIII, by the Sandmeyer method, is also recorded in the experimental section.

The application of the excellent technique of Lambooy (2) for hydrolysis of diazonium salts to phenols is also worthy of note. By its use VIII was converted to IX in 88% yield, an unusually high conversion for this type of reaction by usual techniques.

The precursor XI was prepared from L-tyrosine; and the syntheses of I and II were effected as follows.

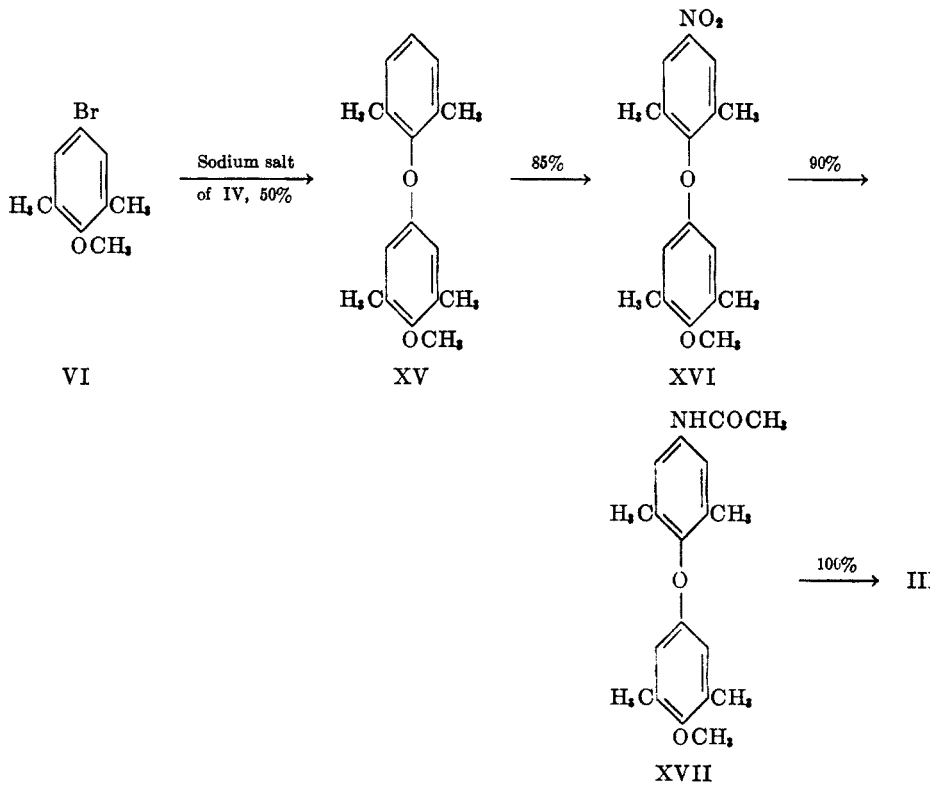


The acetylation technique employed in the conversion of X to XI was one which has previously been shown to involve a minimum of racemization (3). It will be noted, however, that our detailed procedures for the acetylation,

nitration, and esterification techniques used in the synthesis of XI from X differ somewhat from the procedures described by Chalmers and co-workers (4), and gave a somewhat lower over-all yield than the one recorded by these workers. These variations were adopted because we were unable to attain a required intermediate (3,5-dinitro-N-acetyl-L-tyrosine), in a suitable state of purity and in the expected yield by the literature method. We therefore followed our alternate procedure, which could be repeated at will, and which led to this intermediate in much cleaner form. The product XI agreed well, in melting point and optical rotation, for the L-compound, as recorded by Chalmers, *et al.* (4).

In the synthesis of XII, the condensation of XI and IX, through the pyridinium tosylate of XI, was effected by the general method of Ullmann and Nadai (5), as adapted by Chalmers and co-workers (4) for the preparation of dinitrodiphenyl ethers. This condensation and the steps which follow have been shown by the latter workers to proceed without racemization. For optimal yield, we found it desirable to remove excess *p*-toluenesulfonyl chloride and pyridine from the crude pyridinium tosylate.

By refluxing XII with a mixture of hydrochloric and acetic acids, II was obtained in 27% yield (based on XI); while reduction of XII led to XIII. Tetrazotization of the latter, and treatment with potassium iodide-iodine solution led to XIV. In the latter step, a useful technique (4) was to carry out the reaction in the presence of chloroform, to continuously extract XIV from the reaction mixture—thus avoiding further reactions of the product. Compound III was obtained by the following sequence:



VI XV XVI XVII

The condensation of the sodium salt of IV and VI, using copper bronze at 235°, is of the Ullmann type (6). It was found that optimal yields were obtainable when VI was used in excess, the unreacted portion being recovered; and the yield of XV was based on the amount of VI consumed in the reaction.

Nitration of XV to XVI proceeded smoothly, using acetyl nitrate as nitrating agent. Accompanying cleavage, as has often been observed on nitration of polymethylated diphenyl ethers (7), was not observed in our work, and a correspondingly high yield (85%) of XVI was obtained. Reduction of XVI with hydrogen, using Raney nickel catalyst and acetic acid as solvent, gave the acetylated product (XVII), obtained in 90% yield upon dilution of the acetic acid solution after removal of the catalyst. This procedure gives slightly greater yields than does hydrogenation of the nitro compound XVI directly to the amine. The conversion of XVII to III was readily effected.

EXPERIMENTAL[3]

2,6-DIMETHYL-4-METHOXYPHENOL (IX)

Bromination of IV *to* V. 2,6-Dimethylphenol (1 mole, 122 g.) was dissolved in 250 ml. of glacial acetic acid. The solution was kept at 10°, and 160 g. of bromine (1 mole), in 250 ml. of glacial acetic acid, was added with constant stirring. After complete addition, 13 g. of sodium bisulfite in 1.3 l. of water was added, with stirring. Compound V crystallized from the reaction mixture as long white needles (96%). Recrystallization from petroleum ether (boiling range 89–98°) gave 172.5 g. (86%); m.p. 78–79°; lit. (8) 79.5°.

Conversion of V *to* VI. Compound V was best converted to VI, as follows: To a stirred, refluxing solution of V (40.2 g., 0.2 mole) in 20 ml. of absolute ethanol, there was slowly added a solution of sodium ethoxide (made from 9.2 g. sodium in 200 ml. of absolute alcohol) and 26 g. (0.2 mole) of methyl sulfate. The addition of the reagents was best made in small alternate portions. After refluxing for four hours, the procedure of adding the sodium ethoxide and methyl sulfate was repeated exactly as above. The mixture was stirred and refluxed for 12 hours, and most of the alcohol was distilled from the reaction flask (while heating on the steam-bath, with continued stirring). The remaining slurry was diluted with 1.5 l. of water and extracted with chloroform. The chloroform was aspirated, and the product distilled at 86° and 3 mm., at a bath temperature of 110°. The yield was 40 g. (95%).

The liquid product VI was characterized by bromination to 2,6-dimethyl-3,4-dibromoanisole, m.p. 109–110°. The bromination was effected in good yield, in glacial acetic acid.

Anal. Calc'd for $C_9H_{10}Br_2O$: C, 36.76; H, 3.40.

Found: C, 36.64; H, 3.31.

Alternate synthesis of VI. Nitration of IV, followed by methylation and reduction (hydrogen-Raney nickel) gave 4-amino-2,6-dimethylanisole (see below). The corresponding sulfate (see below) (2.49 g., 0.01 mole) was dissolved in 20 ml. of water. Excess acid (2 ml. of conc'd sulfuric) was added, and the mixture was cooled to 0° and diazotized with a solution of 0.7 g. (0.01 mole) of sodium nitrite in 5 ml. of water. After five minutes, 0.1 g. of urea was added; and when foaming subsided, the solution of the diazonium salt was added to a refluxing solution of 48% hydrobromic acid (20 ml.), to which 2.8 g. (0.02 mole) of cuprous oxide had been added. When the addition was complete, the solution was refluxed for ten minutes more, then chilled and extracted with chloroform. The chloroform layer

[3] The microanalyses were performed by Mr. J. Pirie of this laboratory. Melting points were not corrected. 2,6-Dimethylxylenol was the Eastman Kodak product; L-tyrosine was obtained from the Nutritional Biochemicals Corporation.

was dried over calcium chloride and the solvent removed *in vacuo* at room temperature. The product was distilled, giving 1.4 g. (75%). The dibromo derivative was prepared and found to be identical with the one made from VI by the procedure described just above.

2,6-Dimethyl-4-nitroanisole (VII). *Method 1.* 2,6-Dimethylphenol was converted to 4-nitro-2,6-dimethylphenol (50% yield) by nitration of IV in glacial acetic acid, in accord with the method of Auwers and Markowitz (8). M.p. 169–170°, in agreement with the recorded value. The low yield is caused by oxidation of the xylenol to the corresponding diphenoquinone.

The nitrophenol was methylated by the same procedure as was used for preparation of VI from V. The yield in this step was 85% (over-all yield from IV, 42%), m.p. 89–91°.

Anal. Calc'd for $C_9H_{11}NO_3$ (VII): C, 59.67; H, 6.07.

Found: C, 59.75; H, 5.90.

Method 2. To 50 ml. of acetic anhydride was added, with stirring, at 5°, 0.1 mole (24.7 g.) of 2,6-dimethyl-4-bromoanisole (VI) and 1 ml. of conc'd sulfuric acid. With constant stirring, 6.5 ml. of conc'd nitric acid, dissolved in 60 ml. acetic anhydride, was added dropwise, keeping the temperature below 20°. When addition was complete, the reaction mixture was warmed to room temperature and added, dropwise, with stirring to 200 ml. of chilled 3 *N* hydrochloric acid. The product was collected, washed with water, and pressed dry. The oily crystals were recrystallized from methanol, giving 14 g. (77.5%) of VII, m.p. 88°. This is the preferred method for synthesis of VII.

Method 3. 2,6-Dimethylanisole was prepared by methylating IV, similarly as described for the methylation of V to VI, above. From 122 g. of IV, there was obtained 140 g. (85%) of 2,6-dimethylanisole, boiling at 181°, in accord with the value of Ullmann (9). The latter product (15.4 g., 0.112 mole) was dissolved in 100 ml. of acetic anhydride and nitrated, below 20°, by slowly adding 7.15 ml. of conc'd nitric acid (*d.*, 1.52), dissolved in 30 ml. of acetic anhydride. After addition was complete, the mixture was stirred for an additional hour and poured into 2 l. of water. After refrigerating ten hours, the product was collected, pressed free of oil, and recrystallized from 95% ethanol (with charcoal). Yield, 3.9 g. (20.5%); m.p. 89–91°.

2,6-Dimethyl-4-aminoanisole (VIII). Compound VII (60.3 g., 0.33 mole) in 500 ml. of anhydrous ether was reduced at 40 p.s.i. hydrogen pressure with Raney nickel catalyst. The hydrogenation mixture was filtered and the cold filtrate acidified by adding, dropwise, 16.9 ml. of conc'd sulfuric acid (98% of theoretical quantity). The suspension of the amine sulfate was refrigerated for six hours, and the amine salt was collected, washed with dry ether, and dried *in vacuo*. Yield, 83 g.; 95%. The free amine, VIII, was obtained by liberating it from the sulfate with dilute aqueous ammonia. To purify the product, the crude amine was dissolved in 95% alcohol and precipitated by adding dilute aqueous ammonia The recovery of the white needles of the amine (m.p. 63°) was good.

Anal. Calc'd for $C_9H_{13}NO$ (VIII): C, 71.49; H, 8.67; N, 9.26.

Found: C, 71.55; H, 8.63; N, 9.48.

To obtain IX. 2,6-Dimethyl-4-methoxyanilinium hydrogen sulfate (salt of VIII) (24.9 g., 0.1 mole) was dissolved in one liter of water to which 80 ml. of conc'd sulfuric acid had been added. The solution was cooled in an ice-bath, and diazotized by adding 6.9 g. (0.1 mole) of sodium nitrite in 200 ml. of water. After five minutes, a solution of 0.5 g. of urea was added and the diazonium salt solution was added dropwise to a boiling solution of 400 ml. of water and 300 ml. of sulfuric acid, following the excellent technique of Lambooy (2). Best results were obtained when — following addition of each 100 ml. of diazonium solution — there was added 100 ml. of water to the steam-distillation pot, to prevent increasingly higher concentrations of sulfuric acid. The final volume of sulfuric acid solution (at the end of the steam distillation) should be about 200 ml. greater than the original volume of solution with which the apparatus was first charged. The steam-distillant was acidified with hydrochloric acid and extracted with ether. The ether extract was then concentrated, extracted with 10% sodium hydroxide solution, and the phenol (IX) was precipitated by acidifying with hydrochloric acid. Drying over sodium hydroxide in a vacuum

desiccator gave 10.6 g. (88%) of IX. Colorless plates, m.p. 84–85°. The melting point was not changed by recrystallization from a mixture of alcohol, diluted with water.

Anal. Calc'd for $C_9H_{14}O_3$: C, 71.02; H, 7.95.
Found: C, 70.81; H, 7.88.

3,5-DINITRO-4-(3′,5′-DIMETHYL-4′-HYDROXYPHENOXY)-L-TYROSINE (II)

3,5-Dinitro-N-acetyl-L-tyrosine. L-Tyrosine (109 g., 0.6 mole) was suspended in 600 ml. of water and acetylated by adding 450 ml. (4.85 moles) of acetic anhydride in 10-ml. portions, maintaining the reaction mixture at 90–95°. Aspiration of the solvent from the heated (steam-bath) reaction mixture left N-acetyl-L-tyrosine as a glass. This was dissolved in 80 ml. of hot acetic acid, chilled to 0°, and taken up in 500 ml. of conc'd sulfuric acid. With rapid stirring, there was now slowly added 106 ml. of conc'd nitric acid (*d.* 1.42; 1.66 moles), keeping the temperature at −6 to −10°. When the addition was complete, the reaction mixture was stirred for an additional hour at the sub-zero temperature, then warmed to 10° and stirred for 15 minutes. The mixture was next poured on 2 kg. of crushed ice, intermixed with *ca.* 300 g. of pulverized solid carbon dioxide, the purpose of the latter being to help refrigerate the mixture as well as to "blow off" excess nitrous fumes. The resulting suspension was refrigerated for 12 hours, and filtered. The yellow residue was discarded, and the filtrate was diluted to 6 l. and refrigerated for 48 hours to obtain complete crystallization. The crystalline product was collected, washed with water, and dried *in vacuo* at 50°. There was obtained 100 g. (60%) of 3,5-dinitro-N-acetyl-L-tyrosine, m.p. 189–190° (after recrystallizing from ethanol). This corresponds to the literature value (4).

The above product was converted to the ethyl ester as follows: The dinitro acid (31.3 g., 0.1 mole) was finely ground and suspended in 90 ml. of pure, dry benzene in a 250-ml. flask, and 15 ml. of thionyl chloride, purified as suggested by Fieser (10), was added. The flask was fitted with a drying tube and set aside for five days at 25°. The insoluble, crystalline product was collected, washed thoroughly with dry benzene, and dried *in vacuo* over sodium hydroxide. It was then ground finely and refluxed in 300 ml. of absolute ethanol for one hour. The alcoholic solution was filtered, concentrated, chilled, and the sides of the flask scratched, yielding yellow needles of the ethyl ester, m.p. 110°. The crude product was recrystallized from 95% ethanol, giving 19.9 g. (61%) of XI, m.p. 118–119°. The recorded value (4) is 120–121°. The observed value for $[\alpha]_5^{20}$ was −6.45° (with *c*, 6.2 g. per 100 ml. of solution), in dioxane; the recorded value (4) is −6.75°.

Ethyl 3,5-dinitro-4-(3′,5′-dimethyl-4′-methoxyphenoxy)-N-acetyl-L-phenylalanate (XII). Ethyl 3,5-dinitro-N-acetyl-L-tyrosinate (8.61 g., 0.03 mole) and pure *p*-toluenesulfonyl chloride (16.1 g., 0.06 mole) were suspended in 50 ml. of acetone and brought to gentle reflux. There was now added, dropwise, a solution of 10.6 g. (0.1 mole) of sodium carbonate in 60 ml. of water, during one hour. Refluxing was continued for an additional half hour, the solution was concentrated to small volume, and the resulting oil was extracted with petroleum ether to remove the last traces of the *p*-toluenesulfonyl chloride. The residue was taken up in chloroform and washed with 2 *N* sodium carbonate solution and water. The chloroform was evaporated to dryness and the residue dried over phosphorus pentoxide. To the crude tosylate of XI there was added 20 ml. of dry pyridine, and the anhydrous mixture was heated on the steam-bath for half an hour. The unreacted pyridine was pumped off, and to the tarry residue was added 9.13 g. (0.06 mole) of IX. The mixture was heated at 140° for one hour, the residue taken up in chloroform and washed with 1 *N* sodium hydroxide, 1 *N* hydrochloric acid, and water. The chloroform was removed and the brown, semi-solid product repeatedly extracted with petroleum ether until no clouding was observed on concentrating and cooling the successive extract portions. The combined extracts were concentrated and "seeded" with a crystal of product obtained in an earlier run. The crude product was used directly for conversion to II, as described below. In one of the runs, however, recrystallization from aqueous alcohol (with charcoaling) gave 7.1 g. (49%) of XII; pale yellow needles, m.p. 115.5–116°.

Anal. Calc'd for $C_{22}H_{25}N_3O_9$: C, 55.57; H, 5.30; N, 8.84.
Found: C, 55.69; H, 5.32; N, 9.07.

Conversion of XII *to* II. The crude product, obtained by concentrating the final extracts in the preparation of XII, in a run as described above, was dissolved in 10 ml. of a solution of glacial acetic acid and conc'd hydrochloric acid (1:1, by volume) and refluxed for two hours. On cooling, a voluminous mass of green needles was deposited. The crude product was collected, dissolved in the minimum of a 50% aqueous acetic acid solution, and decolorized by treating with charcoal. Addition of conc'd hydrochloric acid to the filtrate gave yellow needles. These were collected, washed with water, and dried at 100°; m.p. 244°. Yield, 27%, based on amount of XI used.

Anal. Calc'd for $C_{18}H_{19}N_3O_8$: C, 53.33; H, 4.72; N, 10.36.
Found: C, 53.42; H, 4.72; N, 10.15.

3,5-DIIODO-4-(3′,5′-DIMETHYL-4′-HYDROXYPHENOXY)-L-PHENYLALANINE

Ethyl 3,5 - diamino - 4 - (3′,5′ - dimethyl - 4′ - methoxyphenoxy) - N - acetyl - L - phenylalanate (XIII). Ethyl 3,5-dinitro-N-acetyl-L-tyrosinate (see above) was condensed with IX, by the same procedure as used in the synthesis of XII from IX and XI (see above). The dark residue obtained from the condensation of the tosylate of the tyrosinate and IX was extracted with a large volume of boiling petroleum ether, concentrated to a small volume, and diluted with 95% ethanol. The solution was then heated to 50° and shaken with hydrogen at 40 p.s.i., with a Raney nickel catalyst. The catalyst was collected, and the filtrate concentrated by aspiration. This yielded a white solid which was taken up in 50% aqueous acetic acid, filtered, and carefully neutralized by adding solid ammonium carbonate. Refrigeration for several hours gave 3.6 g. (29% based on XI). Recrystallization from mixtures of ethanol and dilute aqueous ammonia gave the pure product, m.p. 124–125°.

Anal. Calc'd for $C_{22}H_{29}N_3O_5$: C, 63.59; H, 7.04; N, 10.11.
Found: C, 63.52; H, 7.17; N, 9.88.

Ethyl 3,5-diiodo-4-(3′,5′-dimethyl-4′-methoxyphenoxy)-N-acetyl-L-phenylalanate (XIV). The diamino compound (XIII; 1.04 g., 0.0025 mole) was dissolved in 2.0 ml. of glacial acetic acid. The solution was chilled (15°) and 1.5 ml. of conc'd sulfuric acid was added. The resulting solution was now added to a cold (0°) solution of nitrosylsulfuric acid, and the container rinsed with 0.5 ml. of glacial acetic acid, the rinsing being added to the reaction mixture. [The nitrosyl chloride was prepared as follows: Sodium nitrite (0.44 g., 0.0066 mole) was dissolved in 3.25 ml. of conc'd sulfuric acid at 70°, and the cooled solution was diluted with 6.5 ml. of glacial acetic acid]. After stirring for one hour at 0°, the solution of the tetrazonium salt was added dropwise, with rapid stirring, to a mixture of sodium iodide (2.1 g., 0.014 mole), iodine, (1.74 g., 0.0068 mole), and urea (0.26 g., 0.00434 mole) in 34 ml. of water, which was underlaid by 20 ml. of chloroform, the purpose of the latter being to extract the product as it was formed. The mixture was stirred for one hour and then warmed to 40°. The chloroform layer was separated, and the aqueous layer extracted with fresh chloroform. The combined chloroform extracts were washed with water, and the remaining free iodine removed by treatment with an aqueous solution of sodium metabisulfite (2.6 g.) through which a stream of sulfur dioxide was passed until the color of iodine was discharged. After washing with water, and drying over calcium chloride, the chloroform solution was evaporated, and the resulting tar extracted with boiling petroleum ether (88–98° range). The extract was aspirated to dryness, and the pink solid, so obtained, recrystallized several times from 95% alcohol (with charcoal). The colorless product melted at 149–150°; 0.82 g., 53%.

Anal.: Calc'd for $C_{22}H_{25}I_2NO_4$: C, 41.46; H, 3.96; N, 2.20.
Found: C, 41.60; H, 4.01; N, 2.41.

To obtain I. Compound XIV (0.6 g., 0.001 mole) was refluxed four hours with 5 ml. of a mixture (1:1, by volume) of 57% hydriodic acid and glacial acetic acid. Cooling the reaction mixture gave white needles, which clustered in the form of rosettes. These were col-

lected and dried over phosphorus pentoxide. This product (the hydroiodide of I) melted at 255–257°; 0.54 g., 79.5%. The conversion to I was effected by dissolving the hydroiodide in dilute ammonia and heating, under reduced pressure, until the odor of ammonia was no longer detectable. This treatment, together with a charcoal treatment, was repeated several times. The product was amorphous and melted at 230–235° (dec.).

Anal. Calc'd for $C_{17}H_{17}I_2NO_4$: C, 36.91; H, 3.10; N, 2.53.

Found: C, 35.80; H, 3.70; N, 2.72.

3,5-DIMETHYL-4-(3′,5′-DIMETHYL-4′-HYDROXYPHENOXY)ANILINE

3,5-Dimethyl-4-(3′,5′-dimethyl-4′-methoxyphenoxy)benzene (XV). Compound IV (6.46 g., 0.0529 mole), VI (4.4 g., 0.228 mole), potassium hydroxide (5.6 g., 0.10 mole), and copper-bronze (50 mg.) were heated together, at 190°, in a flask fitted with an air-condenser, the latter having a side-arm (attached to a receiver) one foot above the heated flask. When the vigorous reaction had subsided, and water was no longer being distilled, the organic layer was separated from the distillate and returned to the reaction flask. The temperature was then raised to 235° for three hours, and the mixture extracted with boiling chloroform. The residue was powdered and repeatedly extracted with chloroform. The combined extracts were washed with dilute potassium hydroxide and water, then dried. The solvent was aspirated and the residual liquid fractionated. Unreacted VI, containing also some product (total weight 9.3 g.) distilled at a bath temperature of 70–140° at 3 mm., while the major product was obtained at a bath temperature of 150–200° (3 mm.). The latter fraction was chilled, seeded (with product from a previous run), and recrystallized from aqueous alcohol. This reaction was run in batch-procedure, the recovered starting material (VI), carrying also some product, being used in the successive batch. This procedure made careful fractionation of successive batches unnecessary. The final yield of product (3.0 g.) represented a 50% yield (taking recovered starting material into account), m.p. 57.5–58.5°.

Anal. Calc'd for $C_{22}H_{20}O_2$: C, 79.65; H, 7.87.

Found: C, 79.83; H, 7.67.

3,5-Dimethyl-4-(3′,5′-dimethyl-4′-methoxyphenoxy)nitrobenzene. 3,5-Dimethyl-4-(3′,5′-dimethyl-4′-methoxyphenoxy)benzene (1.28 g., 0.005 mole) was dissolved in 1 ml. of hot acetic anhydride and thrown out as a fine suspension by cooling and shaking. The latter was cooled to 0°, and 0.32 ml. of cold nitric acid (*d.*, 1.43; 0.005 mole), dissolved in 4 ml. of acetic anhydride was added dropwise, keeping the temperature below 20°. After refrigerating for three hours, the solution was diluted with 50 ml. of water; and after the acetic anhydride had completely hydrolyzed, the product was collected and recrystallized from methanol (1.05 g., 85%); m.p. 111–112°.

Anal. Calc'd for $C_{17}H_{19}NO_4$: C, 67.75; H, 6.35; N, 4.65.

Found: C, 67.61; H, 6.55; N, 4.83.

3,5-Dimethyl-4-(3′,5′-dimethyl-4′-methoxyphenoxy)aniline. The nitro derivative, prepared just above (6.47 g., 0.0215 mole) was dissolved in 40 ml. of 95% ethanol and shaken at 40 p.s.i. hydrogen pressure, with a Raney nickel catalyst. When hydrogen uptake was complete, the catalyst was removed, and the filtrate concentrated, *in vacuo*, to a small volume. The product was obtained as square plates. After recrystallizing from 95% ethanol, there was obtained 4 g. (70%) of product, m.p. 89–90°.

Anal. Calc'd for $C_{17}H_{21}NO$: C, 75.24; H, 7.80; N, 5.16; Mol. wt., 271.

Found: C, 75.16; H, 7.90; N, 5.31; Mol. wt. (Rast method), 296.

N-Acetyl 3,5-dimethyl-4-(3′,5′-dimethyl-4′-methoxyphenoxy)aniline. When glacial acetic acid was used as the solvent in the above hydrogenation, there was obtained (after removal of catalyst, concentration of the solvent, addition of water and recrystallization from ethanol), 6.1 g. (90%) of the N-acetyl derivative, m.p. 177–178°. The identical product was also obtainable by treating the above amine with boiling acetic anhydride.

Anal. Calc'd for $C_{19}H_{23}NO_2$: N, 4.47; Mol. wt., 314.

Found: N, 4.70, 4.66; Mol. wt. (Rast method), 306.

3,5-Dimethyl-4-(3′,5′-dimethyl-4′-hydroxyphenoxy)aniline. The above amine (2.71 g.,

0.01 mole) or its N-acetyl derivative (3.14 g., 0.01 mole) was refluxed for 16 hours with 25 ml. of a mixture prepared from equal volumes of glacial acetic acid and 57% hydriodic acid. The reaction mixture was filtered through a glass-wool plug, diluted with 75 ml. of water, and neutralized by adding solid ammonium carbonate. The precipitated product was collected, washed with water, and recrystallized from 50% aqueous alcohol. There resulted 2.6 g. (quantitative yield) of the desired product, m.p. 150–151°.

Anal. Calc'd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44.
Found: C, 74.66; H, 7.60; N, 5.41.

SUMMARY

The syntheses of three new thyroxine-like compounds, in which methyl and nitro groups replace iodine, are described. The end-products were: 3,5-diiodo-4-(3′,5′-dimethyl-4′-hydroxyphenoxy)-L-phenylalanine; 3,5-dinitro-4-(3′,5′-dimethyl-4′-methoxyphenoxy)-L-phenylalanine; and 3,5-dimethyl-4-(3′,5′-dimethyl-4′-hydroxyphenoxy)aniline.

LOS ANGELES, CALIFORNIA

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