solution of sodium bicarbonate, yielding 0.44 g. Recrystallization from DMF gave the product of m.p. 201–203°, which was identified as L-leucinehydroxamic acid by mixture melting point with the specimen described above.

4-Methyl-2-(2-oxopentylamino)valerohydroxamic Acid (VI).—The hydrochloride of V (5.8 g.) was dissolved in 1 *N* sodium hydroxide (40 ml.) and treated with activated charcoal. The solution was neutralized with carbon dioxide to afford an oil, which was extracted with ether and dried over anhydrous sodium sulfate. Evaporation of the ether yielded 4.8 g. of the oily free base (V), and it was reduced with hydrogen–5% palladium on charcoal (0.5 g.) at 40-kg./cm.^{2} initial pressure in ethanol (60 ml.). A portion of the product crystallized out and was collected together with the catalyst by filtration. The product was separated from the catalyst by solution in 1 *N* sodium hydroxide (20 ml.) followed by immediate reprecipitation with 1 *N* hydrochloric acid, yielding 1.4 g. The ethanolic filtrate obtained above was concentrated under reduced pressure to dryness. The crystalline residue was thinned with ether for filtration, yielding 1 g. of product. Total yield was 2.4 g. (70%). This product was practically pure for use in the next step. An analytical sample was obtained by recrystallization from methanol, m.p. 170–175°.

Anal. Calcd. for $C_{11}H_{22}N_2O_3$: C, 57.36; H, 9.63; N, 12.13. Found: C, 57.13; H, 9.88; N, 12.38.

1-Hydroxy-3-isobutyl-6-propyl-2-pyrazinone (Ib).—A suspension of VI (0.8 g.) in methanol (30 ml.) was saturated with ammonia under cooling. The resultant clear solution was allowed to stand at room temperature for 2 days, and concentrated to dryness under reduced pressure. The residue was dissolved in a mixture of methanol (10 ml.) and 1 *N* sodium hydroxide (8 ml.), and again concentrated to dryness under reduced pressure. The dark brown oily residue was dissolved in water (20 ml.) and treated with activated charcoal. The solution was saturated with carbon dioxide to separate an oily or crystalline by-product, which was removed by treatment with activated charcoal. The clear solution was acidified to pH 2 with 3 *N* hydrochloric acid and kept at 0° overnight. The crystalline solid was collected and recrystallized from a small amount of acetone to yield a cluster of very small yellowish needles (0.1 g.), m.p. 129–131°. The product is soluble in sodium bicarbonate solution and gives a deep red color with a methanolic ferric chloride solution; it showed ultraviolet absorption at λ_{max}^{EtOH} 235 mμ (ϵ 6100) and 326 (7800).

Anal. Calcd. for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.65; N, 13.32. Found: C, 62.66; H, 8.91; N, 13.53.

Synthesis of *ortho* and *meta* Analogs of Thyropropionic Acid and of Their Iodinated Derivatives[1]

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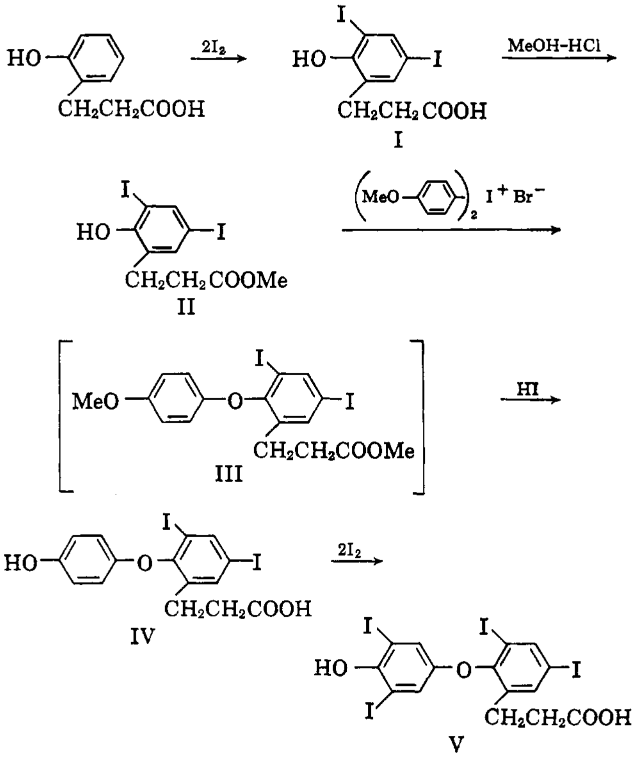
The synthesis of various analogs of desaminothyronine in which the aliphatic side chain is in *ortho* or *meta* position with respect to the ether bridge is described.

Niemann, *et al.*, reported the synthesis of two analogs of thyroxine, *o*- and *m*-thyroxine, in which the phenolic hydroxyl is in the *ortho* or *meta* position with respect to the ether bridge.[3-5] Attempts to synthesize another analog of thyroxine, in which the aliphatic side chain is in the *meta* position with respect to the ether bridge, were reported by Jackson.[6,7] The present paper describes the synthesis of various desamino analogs of thyroxine (V, IX, and XIV) in which the propionic acid side chain is either in the *ortho* or in *meta* position with respect to the ether bridge. These analogs were needed as reference substances for the identification of reaction products obtained in the earlier reported reactions[8] between 4-hydroxy-3,5-diiodophenylpyruvic acid and the acids I, VI, and X.

The *ortho* analog V of thyropropionic acid was synthesized according to the sequence of reactions shown in Scheme I. Conversion of the phenol II to the diphenyl ether IV was carried out essentially according to the method of Ziegler and Maar.[9] The *ortho* analog V was obtained in good yield.

SCHEME I



The *meta* analogs IX and XIV were synthesized in a similar manner as shown in Scheme II.

Depending on the amount of iodine used in the iodination of *m*-hydroxyphenylpropionic acid, either the diiodo acid VI or the triiodo acid X was obtained.

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[3] C. Niemann, *Fortschr. Chem. Org. Naturstoffe*, **7**, 167 (1950).

[4] C. Niemann and J. F. Mead, *J. Am. Chem. Soc.*, **63**, 2685 (1941); *cf.*, also, T. C. Bruice, *J. Org. Chem.*, **19**, 333 (1954).

[5] C. Niemann and C. E. Redemann, *J. Am. Chem. Soc.*, **63**, 1549 (1941).

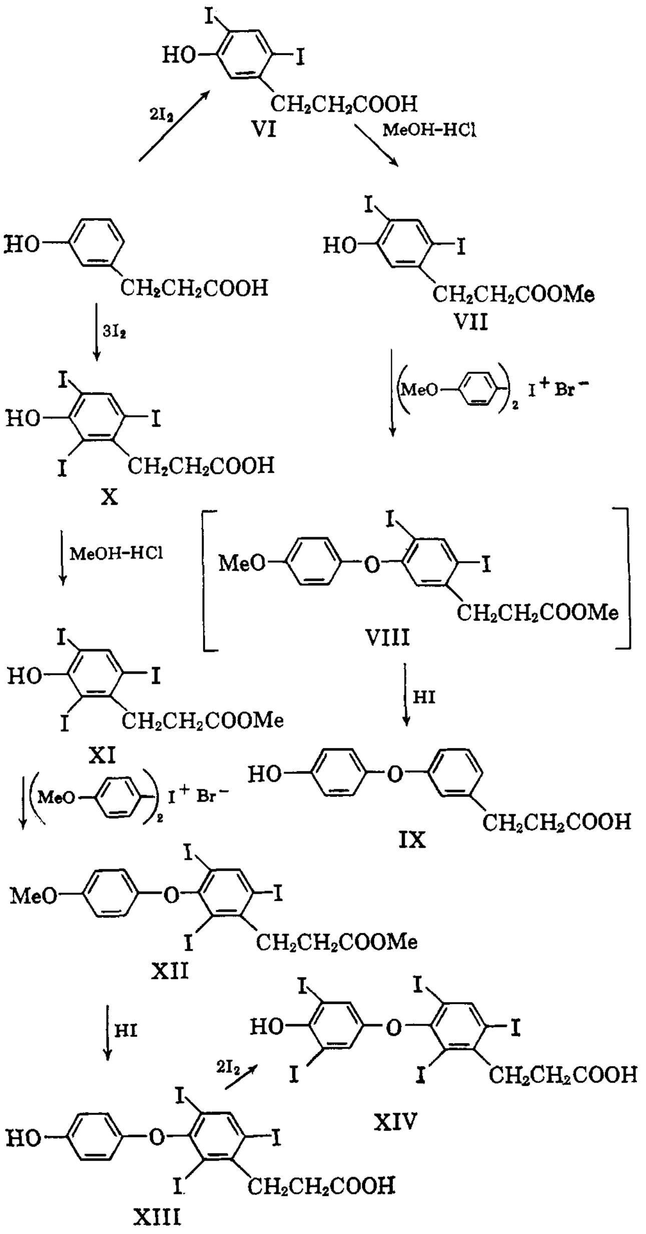
[6] E. L. Jackson, *ibid.*, **77**, 4860 (1955).

[7] E. L. Jackson, *J. Org. Chem.*, **25**, 2227 (1960).

[8] A. Nishinaga and T. Matsuura, *ibid.*, **29**, 1812 (1964).

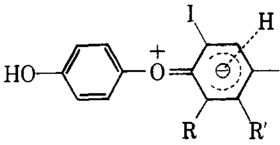
[9] H. Ziegler and C. Maar, *ibid.*, **27**, 3335 (1962). See also G. Hillmann, *Z. Naturforsch.*, **11B**, 419 (1956); P. F. Bevilacqua, J. T. Plati, and W. Wenner, U. S. Patent, 2,895,927 (July 21, 1959).

SCHEME II



The positions of the iodine atoms in VI were determined by n.m.r. spectroscopy of the methyl ester VII. The n.m.r. spectrum showed two singlets at δ = 8.10 and 8.23 p.p.m. which must be assigned to two *para* hydrogens.[10] The positions of the iodine atoms are the same as those in diiodo-*m*-tyrosine, obtained by iodination of *m*-tyrosine.[6] When the diphenyl ether VIII was treated with hydriodic acid in order to remove the two methyl groups, complete deiodination took place at the same time. In contrast, when the triiodinated diphenyl ether XII was treated in the same manner, only little if any deiodination took place. The elemental analysis of XIII shows that this compound was not completely pure. It could, however, be converted by further iodination to the desired pentaiodinated *meta* analog XIV of desaminothyroxine. The ease with which VIII is deiodinated and the resistance to deiodination of III and XII are reminiscent to the finding of Meltzer, *et al.*,[11] that the methyl ether of 3-iodothyropropionic acid is easily deiodinated while similar compounds in which the 3- and 5-positions are substituted by iodine, do not loose these iodine atoms under the same conditions Shiba, *et al.*,[12] found that the diphenyl ether in which the propionic ester side chain of VIII is replaced by a N-acetylalanine ethyl ester side chain was easily deiodinated by hydriodic acid, but that the corresponding triiodinated diphenyl ether, analogous to XII, was resistant to deiodination.

All these findings suggest that substitution in both positions *ortho* to the ether bridge of iodinated thyronines and their analogs may be a prerequisite for resistance to deiodination in the nonphenolic ring. A possible explanation for the lesser ease of deiodination of III and XII compared with VIII is the following.[13] Examinations of models suggest that two bulky substituents in both *ortho* positions to the ether bridge restrict a free rotation of the C–O bond. Accordingly, the π-electrons cannot interact with the ring to form a π-complex (XVa or XVb) which is considered as an intermediate in the deiodination of the iodinated thyronines. In contrast, VIII which has one substituent in the *ortho* positions can more easily form a π-complex (XVc) because of free rotation of the C–O bond.



XVa, R = I; R′ = CH_2CH_2COOMe
b, R = CH_2CH_2COOMe; R′ = H
c, R = H; R′ = CH_2CH_2COOMe

Experimental[14]

3-(2-Hydroxyphenyl)propionic Acid.—A solution of 29.2 g. (0.2 mole) of coumarin in 110 ml. of ethyl acetate was hydrogenated in the presence of 0.9 g. of 10% palladium-charcoal. After absorption of 1 mole of hydrogen, the catalyst was filtered and the filtrate was evaporated. The residue was heated on a boiling water bath together with 50 ml. of 40% sodium hydroxide solution until the oily material was dissolved. The mixture was acidified with 6 *N* hydrochloric acid and extracted with ether. Evaporation of the ether extract yielded a crystalline residue, which was recrystallized from benzene to give 30 g. (90%) of needles, m.p. 88–89°, lit.[15] m.p. 82–84°.

3-(2-Hydroxy-3,5-diiodophenyl)propionic Acid (I).—A solution of 5.5 g. (33 mmoles) of the acid obtained above, in 70 ml. of a 20% aqueous methylamine solution was iodinated (ice cooling) with a solution of 17.1 g. (133 mmoles) of iodine and 15 g. of potassium iodide in 50 ml. of water. After stirring for 30 min. at room temperature, the mixture was acidified with dilute hydrochloric acid. The precipitate formed was crystallized from benzene to give 10.6 g. (76%) of needles, m.p. 128.5–129°.

Anal. Calcd. for $C_9H_8I_2O_3$: C, 25.86; H, 1.93. Found: C, 25.97; H, 1.98.

Methyl 3-(2-Hydroxy-3,5-diiodophenyl)propionate (II).—A solution of 4.60 g. (11 mmoles) of the acid I in 15 ml. of methanol

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(10) *Cf.* L. M. Jackman, "Applications of Nuclear Magnetic Resonance in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959, p. 62.

(11) R. I. Meltzer, S. Farber, E. Merrill, and A. Caro, *J. Org. Chem.*, **26**, 1413 (1961).

(12) T. Shiba, A. Höfer, and H. J. Cahnmann, *ibid.*, **29**, 3171 (1964).

(13) This interpretation of the differences in ease of deiodination of the iodothyronines was called to our attention by a referee. A more detailed discussion of the interpretation is given by E. C. Jorgensen and J. A. W. Reid, *J. Org. Chem.*, **29**, 3396 (1964).

(14) The microanalyses were made by Mr. J. Goda and his associates; of this faculty. Melting points were determined in capillary tubes and are uncorrected. Paper chromatographic procedures were same as those described earlier [T. Matsuura and H. J. Cahnmann, *J. Am. Chem. Soc.*, **81**, 871 (1959)].

(15) E. Marui, *Sci. Rept. Tohoku Univ., First Ser.*, **17**, 693 (1928).

was saturated with hydrogen chloride at 0°. After standing at room temperature for 1 day, the mixture was poured into ice–water. The precipitate deposited was collected by filtration and dried. Crystallization from benzene–isooctane gave 3.35 g. (78%) of prisms, m.p. 73–74°.

Anal. Calcd. for $C_{10}H_{10}I_2O_3$: C, 27.78; H, 2.31. Found: C, 27.73; H, 2.52.

3-[2-(4-Hydroxyphenoxy)-3,5-diiodophenyl]propionic Acid (IV).—A mixture of 1.30 g. (3 mmoles) of the ester II, 2.61 g. (6 mmoles) of *p*-anisyliodonium bromide,[9] 0.42 ml. (3 mmoles) of triethylamine, and 0.45 g. of copper powder in 3 ml. of methanol was stirred at room temperature for 5.5 hr. After standing overnight, the mixture was filtered and the filtrate was evaporated to dryness. The residue was shaken with benzene and 1 *N* hydrochloric acid. The benzene layer was washed with water, 1 *N* sodium hydroxide solution, water, and 5% aqueous acetic acid, then evaporated. The residue was subjected to steam distillation until no more *p*-iodoanisol distilled over. The residual mixture was extracted with ether and the ether extract was evaporated. The residue was refluxed for 2 hr. in a mixture of 5 ml. of acetic acid and 5 ml. of hydriodic acid (*d* 1.7). When the reaction mixture was diluted with water, needles deposited which were collected by filtration: m.p. 166–169°, yield 1.07 g. (70%). Recrystallization from ethyl acetate–benzene yielded needles, m.p. 172–174°.

Anal. Calcd. for $C_{15}H_{12}I_2O_4$: C, 35.32; H, 2.37. Found: C, 35.77; H, 2.61.

3-[2-(4-Hydroxy-3,5-diiodophenoxy)-3,5-diiodopenyl]propionic Acid (V).—A solution of 0.255 g. (0.5 mmole) of the acid IV in 10 ml. of a 20% aqueous methylamine solution was iodinated in the usual manner with 0.28 g. (2.1 mg.-atoms) of iodine and 0.4 g. of potassium iodide dissolved in 2 ml. of water. Acidification of the mixture with dilute hydrochloric acid deposited crystals of the methylamine salt, which were dissolved in 1 *N* sodium hydroxide. The solution was evaporated under reduced pressure and acidified with hydrochloric acid to yield a precipitate which, on recrystallization from benzene, gave 0.26 g. (68%) of plates, m.p. 182–184°. Paper chromatography of this substance showed a single spot.

Anal. Calcd. for $C_{15}H_{10}I_4O_4$: C, 23.66; H, 1.32; I, 66.68. Found: C, 24.47; H, 1.62; I, 65.43.

3-(3-Hydroxy-4,6-diiodophenyl)propionic Acid (VI).—A solution of 3.32 g. (20 mmoles) of 3-(3-hydroxyphenyl)propionic acid[16] in 45 ml. of a 20% aqueous methylamine solution was cooled in an ice bath and a solution of 10.2 g. (80 mg.-atoms) of iodine and 10 g. of potassium iodide in 30 ml. of water was added over a period of 50 min. After stirring at room temperature for 30 min., the mixture was acidified with 6 *N* hydrochloric acid to yield 8.47 g. of precipitate. Fractional crystallization of the precipitate from ethyl acetate–benzene gave 5.63 g. (67%) of the acid VI as needles, m.p. 146–148°; after recrystallization from benzene, m.p. 148–150°.

Anal. Calcd. for $C_9H_8I_2O_3$: C, 25.86; H, 1.93. Found: C, 26.12; H, 1.97.

Methyl 3-(3-Hydroxy-4,6-diiodophenyl)propionate (VII).—A solution of 5.0 g. (1.2 mmoles) of the acid VI in 50 ml. of absolute methanol was saturated with hydrogen chloride at 0°. After standing at room temperature overnight, the mixture was poured into ice–water. The precipitate formed was collected by filtration yielding 3.08 g. (61%). Recrystallization from benzene gave needles, m.p. 113.5–115°.

Anal. Calcd. for $C_{10}H_{10}I_2O_3$: C, 27.78; H, 2.31. Found: C, 28.27; H, 2.60.

3-[3-(4-Hydroxyphenoxy)phenyl]propionic Acid (IX).—A mixture of 1.30 g. (3 mmoles) of the ester VII, 2.61 g. (6 mmoles) of *p*-anisyliodonium bromide,[9] 0.42 ml. (3 mmoles) of triethylamine and 0.45 g. (3 mg.-atoms) of copper powder in 3 ml. of methanol was stirred for 2.5 hr. and then allowed to stand for 2 days. The reaction mixture was worked up as described in the preparation of IV. The crude acid IX (0.30 g., 40%) gave after recrystallization from ethyl acetate–benzene 0.26 g. of plates, m.p. 155–156°.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 70.15; H, 5.34.

3-(3-Hydroxy-2,4,6-triiodophenyl)propionic Acid (X).—A solution of 17.2 g. (135 mg.-atoms) of iodine and 20 g. of potassium iodide in 50 ml. of water was added, over a period of 10 min., to 3.65 g. (22 mmoles) of 3-(3-hydroxyphenyl)propionic acid dissolved in 60 ml. of a 20% aqueous methylamine solution. The mixture was allowed to stand at 10° overnight. After the addition of a small amount of sodium bisulfite, the mixture was acidified with 6 *N* hydrochloric acid. A precipitate formed which was collected by filtration and crystallized from aqueous ethanol to give 10.3 g. (87%) of plates, m.p. 223° dec.

Anal. Calcd. for $C_9H_7I_3O_3$: C, 19.87; H, 1.30. Found: C, 20.32; H, 1.44.

Methyl 3-(3-Hydroxy-2,4,6-triiodophenyl)propionate (XI).—The acid X was esterified as described in the preparation of the ester VII. Crystallization from ethyl acetate–methanol gave prisms, m.p. 163–164°, yield 2.09 g. (82%).

Anal. Calcd. for $C_{10}H_9I_3O_3$: C, 21.53; H, 1.63. Found: C, 21.67; H, 1.84.

Methyl 3-[3-(4-Methoxyphenoxy)-2,4,6-triiodophenyl]propionate (XII).—A mixture of 1.68 g. (3 mmoles) of the ester XI, 2.61 g. (6 mmoles) of *p*-anisyliodonium bromide,[9] 0.42 ml. (3 mmoles) of triethylamine, 0.45 g. (3 mg.-atoms) of copper powder, and 10 ml. of methanol was stirred for 6 hr. and then allowed to stand overnight. The reaction mixture was worked up as described in the preparation of IV. The crystalline residue obtained after steam distillation gave, on recystallization from methanol–benzene, needles, m.p. 144–145°.

Anal. Calcd. for $C_{17}H_{15}I_3O_4$: C, 30.75; H, 2.28. Found: C, 31.00; H, 2.23.

3-[3-(4-Hydroxyphenoxy)-2,4,6-triiodophenyl]propionic Acid (XIII).—The crude methyl ester XII was refluxed with a mixture of equal volume of acetic acid and hydriodic acid (*d* 1.7) for 2 hr. The reaction mixture was diluted with water, decolorized with sodium bisulfite, and filtered, giving crystals, m.p. 214–216°; yield from XII was 64%. Recrystallization from ethyl acetate–benzene gave fine needles, m.p. 220–222°.

Anal. Calcd. for $C_{15}H_{11}I_3O_4$: C, 28.31; H, 1.73; I, 59.87. Found: C, 29.73; H, 2.17; I, 57.65.

3-[3-(4-Hydroxy-3,5-diiodophenoxy)-2,4,6-triiodophenyl]propionic Acid (XIV).—A solution of 0.43 g. (3.4 mg.-atoms) of iodine and 1.0 g. of potassium iodide in 3 ml. of water was added to 0.51 g. (0.8 mmole) of the acid XIII dissolved in 15 ml. of a 20% aqueous methylamine solution. The reaction mixture was treated as described in the preparation of V. The crude acid, 0.65 g. (91%), m.p. 257–259° dec., gave, after recrystallization from a large volume of ethanol, fine needles, m.p. 263° dec.

Anal. Calcd. for $C_{15}H_9I_5O_4$: C, 19.84; H, 0.99; I, 69.90. Found: C, 20.95; H, 1.37; I, 70.29.

Acknowledgment.—The authors are indebted to Dr. H. J. Cahnmann of the National Institutes of Health for helpful discussions and also to Professor T. Kubota for his interest in this work.

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(16) F. Tiemann and R. Ludwig, *Ber.*, **15**, 2050 (1882).