[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

THE PREPARATION OF THYROXINE ANALOGS

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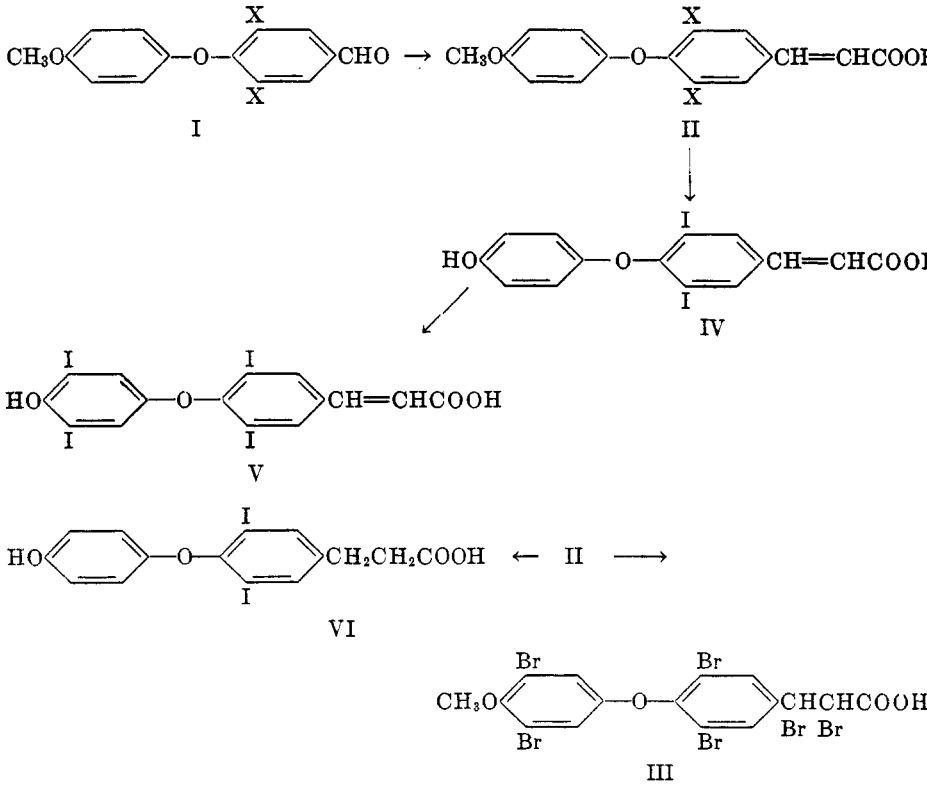
Variation of the side chain in tryptophan as exemplified by indoleacrylic acid produces a compound which interferes with the growth-stimulating action of tryptophan (1). In order to determine whether such a variation in structure among amino acids is general in producing antagonistic effects, β-substituted acrylic acids which have the same diphenyl ether nucleus as thyroxine have been synthesized for testing as possible antithyroid agents.

3,5-Diiodo-4-(4′-methoxyphenoxy)cinnamic acid (II, X = I) and 3,5-dibromo-4-(4′-methoxyphenoxy)cinnamic acid (II, X = Br) were prepared by condensing 3,5-diiodo-4-(4′-methoxyphenoxy)benzaldehyde (I, X = I) and 3,5-dibromo-4-(4′-methoxyphenoxy)benzaldehyde (I, X = Br) (2) with malonic acid in the presence of pyridine and piperidine.



I II IV V VI III

[1] Abstracted in part from the Ph.D. thesis (1949) of S. C. Wang and the M.S. thesis (1947) of Priscilla Lyons.

Halogenation of the two cinnamic acids to the corresponding tetrahalogenated compound could not be accomplished directly. Bromination of the bromocinnamic acid (II, X = Br) gave the hexabromo compound (III). Proof for this structure was the liberation of iodine from a solution of sodium iodide in acetone by III with the formation of sodium bromide. Iodination of the corresponding iodocinnamic acid (II, X = I) failed even under drastic conditions such as treatment with an excess of iodine in methanolic potassium hydroxide for 48 hours. Iodination could be accomplished, however, to the tetraiodo compound (V) if the demethylated product (IV) was used. Evidence for the *ortho* substitution of the iodine atoms is the intense red color produced by this compound (V) when warmed in alcohol with nitrous acid and then treated with ammonia. This color test is in general characteristic of *ortho*-diiodophenols (3).

The treatment with hydriodic acid apparently does not affect the double bond, since the presence of unsaturation in the tetraiodo compound (V) and also in the demethylated diiodocinnamic acid (IV) was demonstrated by absorption spectra measurements and polarographic studies. The substituted propionic acid (VI) necessary for this comparison was prepared from 3,5-diiodo-4-(4′-methoxyphenoxy)cinnamic acid (II, X = I) by treatment with hydriodic acid and red phosphorus in acetic anhydride.

All the compounds with the exception of 3,5-dibromo-4-(4′-methoxyphenxoy) cinnamic acid showed a thyroxine-like action. The results will be reported elsewhere.

EXPERIMENTAL[2]

3,5-Dibromo-4-(4′-methoxyphenoxy)benzaldehyde (I, X=Br). This aldehyde was prepared according to the directions of Schuegraf (2) with a slight modification. The intermediate nitrile was purified by distillation at reduced pressure; b.p. 205°/1 mm.

3,5-Dibromo-4-(4′-methoxyphenoxy)cinnamic acid (II, X = Br). A mixture of 3,5-dibromo-4-(4′-methoxyphenoxy)benzaldehyde (4.9 g.) and malonic acid (2.33 g.) in pyridine (8.1 ml.) containing three drops of piperidine was refluxed for three hours on the steam-bath. The resulting light tan solution was filtered into a mixture of conc'd hydrochloric acid (7.5 ml.) and 13 g. of ice with stirring. The white solid formed was filtered and washed, first with 10% hydrochloric acid, and then with water. The product (4 g., 87%) when recrystallized from ethyl acetate melted at 228–230°.

Anal. Calc'd for $C_{16}H_{13}Br_2O_4$: C, 44.89; H, 2.83.
Found: C, 45.25; H, 2.86.

β-[3,5-Dibromo-4-(4′-methoxyphenoxy)phenyl]-α,β-dibromopropionic acid (III). 3,5-Dibromo-4-(4′-methoxyphenoxy)cinnamic acid (II, X = Br) (2 g.) was kept in contact with bromine vapor in a desiccator until its weight increased by 1.5 g. (about 4–5 hours). The red color in the product was removed by dissolving the compound in alcohol and reprecipitating it by the addition of water. The product, recrystallized from benzene, melted at 210–215° with decomposition.

Anal. Calc'd for $C_{16}H_{10}Br_6O_4$: C, 25.77; H, 1.35.
Found: C, 26.00; H, 1.52.

Bromination of the dibromocinnamic acid (II, X = Br) in acetic acid gave a non-homogeneous product.

The hexabromo derivative when dissolved in acetone containing sodium iodide liberated iodine with the formation of sodium bromide. Upon pouring into water and filtering 3,5-

[2] Melting points are not corrected.

dibromo-4-(3′,5′-dibromo-4′-methoxyphenoxy)cinnamic acid was obtained. Recrystallization from ethanol or dilute acetone gave a crystalline product which melted at 273–275° d. (block)

Anal. Calc'd for $C_{16}H_{10}Br_4O_4$: C, 32.80; H, 1.72.

Found: 32.39; H, 1.91.

3,5-Diiodo-4-(4′-methoxyphenoxy)benzaldehyde (I, X = I). This aldehyde (I, X = I) was prepared according to the directions of Harington and Barger (3).

3,5-Diiodo-4-(4′-methoxyphenoxy)cinnamic acid (II, X = I). 3,5-Diiodo-4-(4′-methoxyphenoxy)benzaldehyde (I, X = I) (4.8 g.) and malonic acid (2 g.) in pyridine (10 ml.) containing three drops of piperidine were treated in a similar fashion to that used with the corresponding dibromo compound. The product (5.2 g.), when recrystallized from benzene, melted at 250–251°.

Anal. Calc'd for $C_{16}H_{12}I_2O_4$: C, 36.81; H, 2.32.

Found: C, 37.31; H, 2.58.

The diiodocinnamic acid (II, X = I) was resistant to iodination with iodine in either ammonium hydroxide, alcoholic ammonium hydroxide, saturated sodium bicarbonate solution or benzene in the presence of mercuric oxide. No iodination was observed upon treating the compound in methanolic 2 *N* potassium hydroxide with ten times the theoretical amount of iodine for 48 hours with vigorous stirring.

3,5-Diiodo-4-(4′-hydroxyphenoxy)cinnamic acid (IV). 3,5-Diiodo-4-(4′-methoxyphenoxy) cinnamic acid (II, X = I) (0.5 g.) was refluxed with hydriodic acid (*d*, 1.70) (5 ml.) in glacial acetic acid (5 ml.) for one hour. The reaction mixture was poured into water and the crude solid (0.46 g.) was recrystallized from dilute alcohol, m.p. 262° with decomposition.

Anal. Calc'd for $C_{15}H_{10}I_2O_4$: C, 35.46; H, 1.28.

Found: C, 35.52; H, 2.31.

The *benzoate* of this compound prepared by treating the acid with benzoyl chloride in 10% sodium hydroxide, upon recrystallization from dilute ethanol, melted at 244–246°.

Anal. Calc'd for $C_{22}H_{14}I_2O_5$: C, 43.16; H, 2.30.

Found: C, 43.50; H, 2.22.

3,5-Diiodo-4-(3′,5′-diiodo-4′-hydroxyphenoxy)cinnamic acid(V).3,5-Diiodo-4-(4′-hydroxyphenoxy)cinnamic acid (IV, 0.4 g.) dissolved in *N* sodium hydroxide (40 ml.) was treated with stirring with 8 ml. of *N* potassium triiodide. After two hours the solution was saturated with sulfur dioxide and the gummy pink product, yield, 0.58 g., was purified by dissolving in 1% sodium hydroxide in 70% ethanol and reprecipitating with glacial acetic acid three times followed by recrystallization from a mixture of ethyl alcohol and acetic acid. The colorless powder obtained did not have a definite melting point. It started to darken at 180° and gradually turned into a dark viscous liquid above 200°.

Anal. Calc'd for $C_{15}H_{10}I_4O_4$: C, 23.71; H, 1.06.

Found: C, 24.35; H, 1.61.

This product gave an intense orange color when warmed in alcohol with nitrous acid and turned red when treated with ammonia (3).

β-[3,5-Diiodo-4-(4′-hydroxyphenoxy)phenyl]propionic acid (VI). A mixture of 3,5-diiodo-4-(4′-methoxyphenoxy)cinnamic acid (II, X = I) (0.33 g.), red phosphorus (0.24 g.), and hydriodic acid (*d*, 1.70) (2 ml.) in acetic anhydride (2 ml.) was refluxed for 75 minutes and filtered into 200 ml. of water. The solid (0.15 g.) was recrystallized from dilute alcohol; m.p. 235–238°. Additional product (0.1 g.) could be obtained by extracting the precipitate upon the filter with hot ethanol (10 ml.) and pouring into cold water (50 ml.).

Anal. Calc'd for $C_{15}H_{12}I_2O_4$: C, 35.32; H, 2.37.

Found: C, 35.29; H, 2.34.

The *benzoate* of this compound, prepared by treating the acid in 10% sodium hydroxide with benzoyl chloride, melted at 232–234° when recrystallized from dilute alcohol.

Anal. Calc'd for $C_{22}H_{16}I_2O_5$: C, 43.01; H, 2.63.

Found: C, 42.36; H, 2.90.

2-Phenyl-4-[3,5-diiodo-4-(4′-methoxyphenoxy)benzal]-5-oxazolone. This azalactone was prepared according to the directions of Harington and Barger (3).

Absorption spectra. All spectra were determined with a Beckman Quartz Spectropho-

tometer Model DU in silica cells with a path length of 1 cm. The solutions used were prepared with a concentration of 10 mg. of the sample in a liter of 95% ethanol. Measurements of the optical densities were made regularly at 2 mμ intervals within the range 220–300 mμ and at 5 mμ intervals above 300 mμ except in the neighborhood of maxima where the interval was reduced to 1 mμ.

The spectra obtained for these compounds are given in Figures 1 and 2; the wave-length and molar extinction coefficients for the maxima in the spectrum of each compound are listed in Table I.

An examination of Table I indicates that in general these compounds exhibit two maxima. Similar to other benzene derivatives with unsaturated side chains the fine structure is absent. This apparent simplicity in the absorption band structure indicates that in all three substituted cinnamic acids the whole molecule acts as a single resonator. The maximum in the 275 mμ region is characteristic of the halogenated cinnamic acids and occurs at

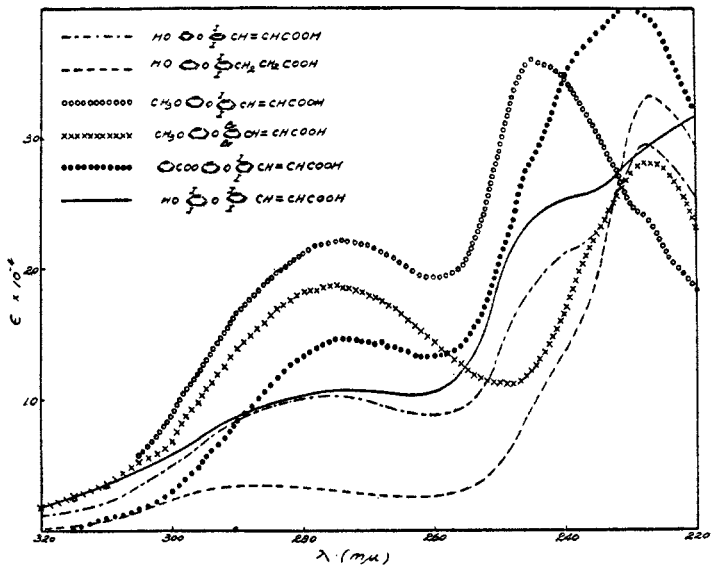


FIG. 1. ABSORPTION SPECTRA OF HALOGENATED 4-PHENOXYCINNAMIC ACIDS AND β-[3,5 DIIODO-4-(4′-HYDROXYPHENOXY)PHENYL]PROPIONIC ACID IN ETHANOL

a slightly greater wave length than that of cinnamic acid (4). The absence of this band for β-[3,5-diiodo-4-(4′-hydroxyphenoxy)phenyl]propionic acid verifies the structure of this compound.

Polarographic behavior. The polarographic measurements were made with a Sargent Model XII Polarograph at 25°. The electrolysis cell consisted of a cylindrical vessel provided with side-arms for the admission of nitrogen and for connection to the mercury pool.

The compounds were studied in a 0.001 *M* concentration in a 75% dioxane-water mixture with 0.175 *M* tetrabutylammonium iodide as a supporting electrolyte and 0.001% Methyl Red as a maximum suppressor. To eliminate the hydrogen wave one ml. of 0.0416 *N* tetramethylammonium hydroxide was included in each 25 ml. of solution for compounds with a carboxyl group and 2 ml. of the base for compounds with a free phenolic group and a carboxyl group.

The anode potential, measured against a saturated calomel electrode with a sintered-glass salt bridge of the type described by Laitinen (5), was −0.4534 volts.

The dropping-mercury electrode had the following characteristics. At a pressure of 65.6 cm. of mercury the drop time in the solution used was 3.87 seconds (open current).

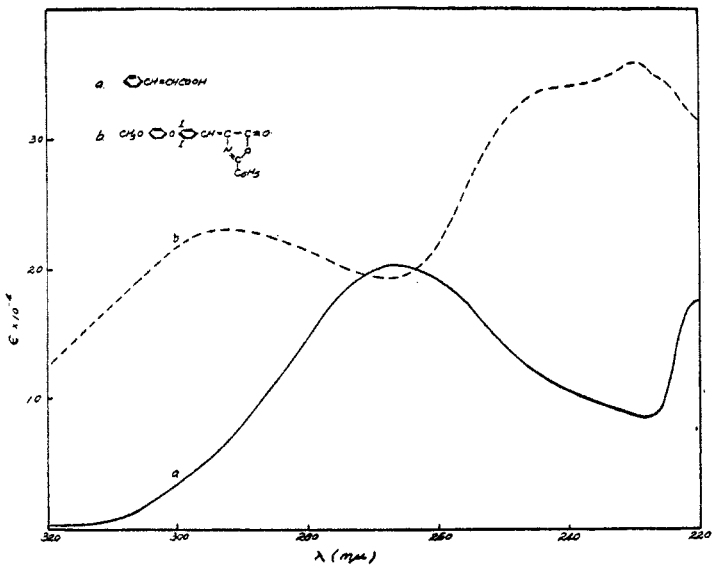


FIG. 2. ABSORPTION SPECTRA OF CINNAMIC ACID AND 2-PHENYL-4-[3,5-DIIODO-4-(4′-METHOXYPHENOXY)BENZAL]-5-OXAZOLONE IN ETHANOL

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA FOR HALOGENATED CINNAMIC ACIDS AND RELATED COMPOUNDS IN ETHANOL

COMPOUND	MAXIMA		MAXIMA	
	mμ	ε × 10⁻⁴	mμ	ε × 10⁻⁴
Cinnamic acid	220	1.75	267	2.02
3,5-Dibromo-4-(4′-methoxyphenoxy)cinnamic acid (II)	227	2.80	275	1.87
3,5-Diiodo-4-(4′-methoxyphenoxy)cinnamic acid (II)	245	3.60	274	2.22
3,5-Diiodo-4-(4′-hydroxyphenoxy)cinnamic acid (IV)	227	2.94	276	1.02
3,5-Diiodo-4-(4′-benzoyloxyphenoxy)cinnamic acid	229	4.06	274	1.46
3,5-Diiodo-4-(4′-hydroxy-3′,5′-diiodophenoxy) cinnamic acid (V)	220	3.12	273	1.07
β-[3,5-Diiodo-4-(4′-hydroxyphenoxy)phenyl]propionic acid (VI)	227	3.32	289	0.35
2-Phenyl-4-[3,5-diiodo-4-(4′-methoxyphenoxy) benzal]-5-oxazolone	230	3.60	292	2.31

The value of m was 1.44 mg. sec.$^{-1}$ with a calculated value of $m^{2/3} t^{1/6}$ of 1.598 mg.$^{2/3}$ sec$^{-1/2}$.

The half-wave potentials and diffusion current constants are given in Table II. Three polarograms corrected for residual current are shown in Figure 3.

An examination of the half-wave potentials in Table II indicates that all the compounds with the exception of β-[3,5-diiodo-4-(4′-hydroxyphenoxy)phenyl]propionic acid give a wave at −2.05 volts. This value therefore represents reduction of the α,β-double bond.

TABLE II

HALF-WAVE POTENTIALS AND DIFFUSION CURRENT CONSTANT OF SUBSTITUTED CINNAMIC ACIDS AND RELATED COMPOUNDS IN 0.175 *M* TETRABUTYLAMMONIUM IODIDE-75% DIOXANE SOLUTION

COMPOUND	$E_{1/2}$ *vs* S.C.E. volts	$I_d/Cm^{2/3}t^{1/6}$
Cinnamic Acid	−2.03	1.99
3,5-Dibromo-4-(4′-methoxyphenoxy)cinnamic acid (II)	−1.66	1.25
	−1.91	1.09
	−2.06	0.99
3,5-Diiodo-4-(4′-methoxyphenoxy)cinnamic acid (II)	−1.22	1.58
	−1.53	1.40
	−2.07	1.34
3,5-Diiodo-4-(4′-hydroxyphenoxy)cinnamic acid (IV)	−1.34	1.53
	−1.68	1.12
	−2.05	0.87
3,5-Diiodo-4-(4′-hydroxy-3′,5-diiodophenoxy)cinnamic acid (V)	−1.26	1.71
	−1.58	0.87
	−1.84	1.15
	−2.03	0.81
β-[3,5-Diiodo-4-(4′-hydroxyphenoxy)phenyl]propionic acid (VI)	−1.36	1.43
	−1.72	1.18
2-Phenyl-4-[3,5-diiodo-4-(4′-methoxyphenoxy)benzal]-5-oxazolone	−0.93	0.81
	−1.37	1.99
	−1.67	0.93
	−2.08	0.44

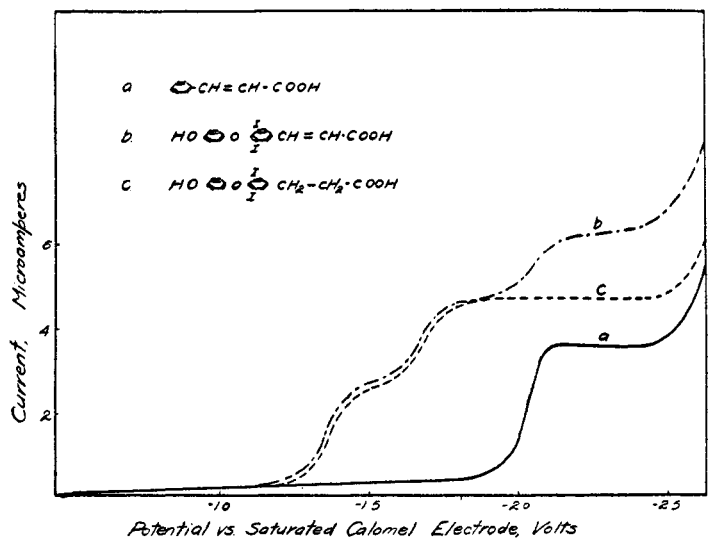


FIG. 3. POLAROGRAMS OF CINNAMIC ACID, 3,5-DIIODO-4-(4′-HYDROXYPHENOXY)CINNAMIC ACID AND β-[3,5-DIIODO-4-(4′-HYDROXYPHENOXY)PHENYL]PROPIONIC ACID IN 0.175 *M* TETRABUTYLAMMONIUM IODIDE, 75% DIOXANE

(Corrected for residual current)

Comparison of the diffusion current constant for cinnamic acid with that of the ψ-methyl ester of phthalaldehyde acid (6) points to a two-electron reduction and the formation of dihydrocinnamic acid. A similar behavior must take place with the halogenated derivatives.

The earlier waves represent the reduction of the halogens on the aromatic ring since the values for the iodo compounds are more positive than those for the bromo compounds. The half-wave potentials at −1.26 v., −1.58 v., and −1.84 v. observed for 3,5-diiodo-4-(4′-hydroxy-3′,5′-diiodophenoxy)cinnamic acid are more negative than the three waves reported for thyroxine at −1.20 v., −1.42 v., and −1.70 v. (7) due to the presence of the cinnamic acid derivative as the phenoxide ion.

SUMMARY

1. 3,5-Diiodo-4-[4′-hydroxy-3′,5′-diiodophenoxy]cinnamic acid and related compounds have been prepared for testing as possible antithyroid agents.

2. Ultraviolet absorption data and polarographic data are presented as proof for the unsaturation in this compound.

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