(20%), m.p. 158–159°. When mixed with the quinaldoin *N,N′*-dioxide obtained in the benzoin condensation, no depression in melting point was obtained.

A mixture of 0.1 g. of the quinaldoin, 20 ml. of pyridine and 5 ml. of water was allowed to stand for 10 days under an atmosphere of nitrogen. At the end of the period the dark solid which had formed was separated and washed with methanol and ether. The dry product, 0.015 g. (15%), when crystallized from pyridine under an atmosphere of nitrogen gave red needles of the enediol, m.p. 192–193° dec.

Potassium salt of 1,2-di-2-quinolyl-1,2-ethenediol N,N′-dioxide. To a mixture of 1.0 g. of quinaldehyde *N*-oxide in 10 ml. of pyridine was added, with stirring, 0.08 g. of potassium cyanide in 2 ml. of water. A white, glistening precipitate, which formed immediately, went into solution after the mixture was stirred for 30 min. at room temperature and refluxed for an equal length of time. Cooling in an ice bath gave a white solid which was crystallized twice from 95% ethanol by adding absolute ether and cooling to give 0.3 g. (24%) of the potassium salt, decomposing at 338–341°. Repeated crystallization from a solution in dimethylformamide by the addition of absolute ether and then from solution in absolute ethanol by the addition of absolute ether failed to give an analytical sample although the percentage of potassium, determined as ash, agreed reasonably well with the theory.

Quinaldoin N,N′-dioxide. Evaporation of the filtrate, from which the potassium salt was separated, to about 4 ml. and cooling gave brown crystals which, when crystallized from benzene using Norit A, yielded 0.43 g. (43%) of almost white needles, m.p. 157–158°.

Conversion of potassium salt to quinaldoin N,N′-dioxide. The salt, 2.0 g., in aqueous solution was acidified with hydrochloric acid and the mixture was extracted with ether in a continuous liquid-liquid extraction apparatus. The almost white solid, recovered from the ether and crystallized from benzene, weighed 1.8 g. (100%), m.p. 158–159°. There was no depression in melting point when mixed with an authentic sample.

Conversion of potassium salt to enediol. A mixture of 0.6 g. of the salt and 1.4 g. of benzoyl chloride (Eastman, white label) was boiled for 5 min. and, upon cooling, 80 ml. of ether and then 40 ml. of water were added. The red solid, which separated, was removed by filtration, washed with water, and dried. It weighed 0.37 g. (75%), melted at 190–191° dec. and gave the expected color tests. No depression in melting point was obtained when mixed with an authentic sample.

Copper derivative of quinaldoin N,N′-dioxide. The copper derivative was obtained in attempting to oxidize the quinaldoin to the quinaldil as follows: To a solution of 1 g. of copper sulfate in 50 ml. of water and 50 ml. of pyridine was added 1 g. of quinaldoin *N,N′*-dioxide. Heating overnight on a steam bath with air passing through the mixture gave 1.1 g. of a green solid, m.p. 306–307°, insoluble in water and most organic solvents. Final purification was accomplished by crystallization four times from a solution in dimethylformamide by the addition of absolute ether. The presence of water of crystallization in the chelate was indicated by strong infrared absorption at 3300 cm.$^{-1}$

Anal. Calcd. for $C_{40}H_{24}N_4O_8Cu_2.2H_2O$: C, 56.40; H, 3.31; N, 6.58; Cu, 14.9. Found: C, 56.16, 56.26; H, 3.89, 3.48; N, 6.57; Cu (ash) 15.2, 15.5.

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KNOXVILLE, TENN.

[CONTRIBUTION FROM THE WARNER-LAMBERT RESEARCH INSTITUTE]

β-[3-Iodo-4-(4′-hydroxyphenoxy)phenyl]propionic Acid and Iodinated Derivatives[1]

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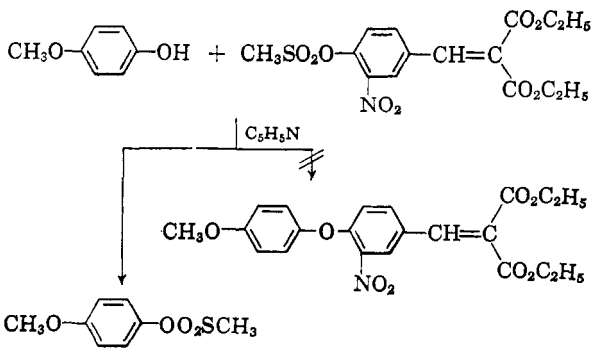
A number of alternate preparations of β-[3-iodo-4-(4′-hydroxyphenoxy)phenyl]propionic acid are presented. The iodination of this compound and the resulting products are described.

In pursuance of an interest in analogs of thyroxine, β-[3-iodo-4-(3′-iodo-4′-hydroxyphenoxy)-phenyl]propionic acid and its 3,3′,5′-triiodo analog were required. The method of synthesis employed in the preparation of 3,5-diiodo analogs[2] was not applicable because the syntheses depend on the activation of a methanesulfonyloxy group by two nitro groups. It was hoped that the methanesulfonyloxy group in the position *para* to a bis(carbethoxy)vinyl group might prove to be sufficiently activated by even one *ortho* nitro group. This proved not to be the case. Transesterification took place to the exclusion of etherification.[3]



(1) Presented before the Division of Medicinal Chemistry at the 132nd meeting of the American Chemical Society, New York, N. Y., September 1957.

(2) R. I. Meltzer, D. L. Lustgarten, and A. Fischman, *J. Org. Chem.*, 22, 1577 (1957) and references therein.

To avoid transesterification, a chloro group was tried in place of the methanesulfonyloxy group. Reaction of ethyl 4-chloro-3-nitrocinnamate (III) with *p*-methoxyphenol in the presence of pyridine failed, however, until the *p*-methoxyphenol was first converted to its potassium salt. The ethyl 4-chloro-3-nitrocinnamate (III) was prepared by the condensation of 4-chloro-3-nitrobenzaldehyde (II) with refluxing diethyl malonate in the presence of piperidine. This procedure gave unreproducible yields. When acetic acid was used as the solvent for reaction, the product was diethyl 4-chloro-3-nitrobenzalmalonate (IV). Etherification of this compound, however, proceeded with vigorous evolution of carbon dioxide and the formation of only low yields of 3-nitro-4-(4′-methoxyphenoxy)cinnamic acid (XIII) and its ester, VII. Ethyl 4-chloro-3-nitrocinnamate was, therefore, again resorted to as starting material but was now prepared from 4-chloro-3-nitrobenzaldehyde *via* a Perkin reaction and esterification.

Ethyl 3-nitro-4-(4′-methoxyphenoxy)cinnamate (VII), was catalytically reduced to ethyl β-[3-amino-4-(4′-methoxyphenoxy)phenyl]propionate (VIII). This could be isolated and purified or diazotized in the impure unisolated state. Treatment of the diazotized product with potassium triiodide gave ethyl β-[3-iodo-4-(4′-methoxyphenoxy)phenyl]propionate (IX). This could not be obtained pure and was hydrolyzed to give the corresponding acid, X, which could be readily crystallized and purified. Demethylation proved difficult. In the past,[2] demethylation of compounds containing 3,5-diiodo substituents had not presented any problem. In the present case, however, with only a 3-iodo substituent, demethylation with hydriodic acid was accompanied by loss of iodine to result in XII. Block and Powell[4] had reported the use of a mixture of hydriodic acid, hydrobromic acid and phosphorus with a compound containing a labile iodine. By a variation of their procedure, it was possible to obtain very poor yields of the desired product XI. The product was practically free of deiodinated materials as determined by paper partition chromatography.

Because of the extremely poor yields, it was decided to remove the methyl ether before the introduction of the iodine. Accordingly, ethyl β-[3-amino-4-(4′-methoxyphenoxy)phenyl]propionate (VIII) was treated with hydriodic acid to give β-[3-amino-4-(4′-hydroxyphenoxy)phenyl]propionic acid (XV). Diazotization and treatment with potassium triiodide resulted in satisfactory yields of XI, free of contamination by any deiodinated material.

The etherification of ethyl 4-chloro-3-nitrocinnamate with *p*-methoxyphenol frequently resulted in the formation of small amounts of 3-nitro-4-(4′-methoxyphenoxy)cinnamic acid (XIII) along with the ester, VII. By increasing the amount of alkali used in the etherification, the reaction resulted in the formation of the acid, XIII, to exclusion of any ester, VII. This simplified the purification procedure and the acid could be reduced and demethylated in a manner analogous to that used with the ester. A further simplification consisted of the treatment of the acid, XIII, or its ester, VII, with hydriodic acid, red phosphorus and acetic anhydride. This resulted in the one step conversion to β-[3-amino-4(4′-hydroxyphenoxy)phenyl]propionic acid (XV).

This acid was also prepared by two other modifications. Thus, 4-chloro-3-nitrobenzaldehyde (II) was coupled with *p*-methoxyphenol to give 3-nitro-4-(4′-methoxyphenoxy)benzaldehyde (XVI). This aldehyde was condensed with either acetic anhydride *via* a Perkin reaction or was condensed with diethyl malonate. The product in the one case was 3-nitro-4-(4′-methoxyphenoxy)cinnamic acid (XIII) and in the other case was presumably XVII. Both XIII and XVII were then converted by hydriodic acid, acetic anhydride and phosphorus to β-[3-amino-4-(4′-hydroxyphenoxy)-phenyl]propionic acid (XV). The reaction *via* XVII was not developed and was, therefore, carried out in only very poor yield.

Iodination of β-[3-iodo-4-(4′-hydroxyphenoxy)-phenyl]propionic acid (XI) was carried out to give both 3,3′-diiodo compound, XVIII, and the 3,3′,5′-triiodo compound, XIX.

The purity of the compounds was best determined by the use of circular papergrams and *t*-amyl alcohol saturated with 6*N* ammonia as solvent. The spots were visualized[5] by spraying with a 2% solution of 4-aminoantipyrene in 2% sodium carbonate followed by spraying with a 2% potassium ferricyanide solution. The colors obtained and the R_f values were: 3-iodo, peach, 0.6; 3,3′-diiodo, brown-red, 0.45; and 3,3′,5′-triiodo, magenta, 0.3.

EXPERIMENTAL[6]

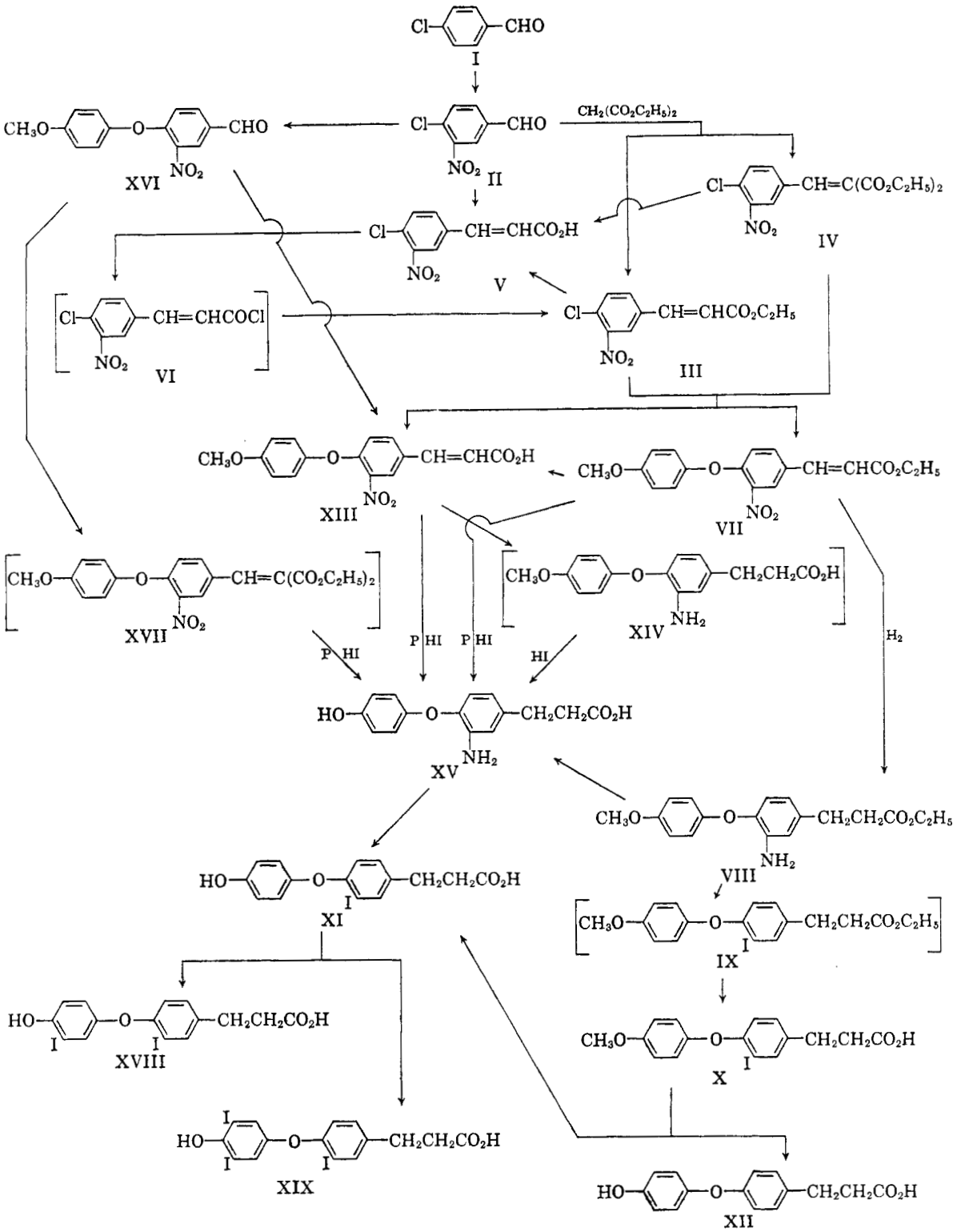
4-Chloro-3-nitrobenzaldehyde (II). To 600 ml. of stirred, ice-cooled sulfuric acid was added 108 g. (1.27 moles) of sodium nitrate. After 10 min. of stirring, there was slowly

(3) J. A. McRae, R. Y. Moir, J. J. Ursprung, and H. H. Gibbs, *J. Org. Chem.*, **19**, 1500 (1954) reported that 2-nitro-4-carbomethoxyphenol could be etherified with another phenol by the use of *p*-toluenesulfonyl chloride and pyridine. This would indicate either that *p*-toluenesulfonyl chloride was a more satisfactory agent than methanesulfonyl chloride or, more likely, that a *p*-carbomethoxy group was more activating than a *p*-bis(carbethoxy)vinyl group.

(4) Paul Block and G. Powell, *J. Am. Chem. Soc.*, **64**, 1070 (1942).

(5) W. C. Ellenbogen described this procedure before the Physical Chemistry Committee at the American Drug Manufacturers Assoc., Research and Development Section Meeting, Edgewater Park, Miss., November 1956. The procedure is based on E. Emerson, *J. Org. Chem.*, **8**, 417 (1943).

(6) Melting points, taken on a Fisher-John's block, are uncorrected.



added to this mixture, 168 g. (1.2 moles) of *p*-chlorobenzaldehyde while keeping the temperature below 15°. The reaction mixture was then allowed to reach room temperature and then was heated by a water bath to 60–70° and maintained at that temperature for 1 hr. Stirring was continued throughout. The yellow suspension was poured into ice, filtered, washed with water, and taken up in chloroform. The chloroform solution was washed with water, sodium bicarbonate solution and water. The dried solution was concentrated to about 400 ml. and then diluted with petroleum ether (b.p. 60–71°) until just cloudy. On standing, 183 g. (82%) of crystalline material, m.p. 65–66°, resulted; reported[7] m.p. 64.5°. Instead of precipitating the product by the addition of petroleum ether, complete evaporation of the chloroform would result in an almost quantitative yield of product

(7) H. H. Hogdson and H. G. Beard, *J. Chem. Soc.*, 20 (1927).

satisfactory for further use and melting only 3° or 4° lower than the purified product.

Ethyl 4-chloro-3-nitrocinnamate (III). (a) Crude noncrystalline 4-chloro-3-nitrobenzaldehyde (52 g., 0.28 mole) obtained by evaporation of the chloroform solution from a nitration of 42 g. (0.3 mole) of *p*-chlorobenzaldehyde, was combined with 48.5 g. (0.3 mole) of diethyl malonate and 7.5 ml. of piperidine. An exothermic reaction ensued. This solution was maintained with external heating at reflux for 20 min., cooled, and taken up in hot ethanol. Cooling gave 6 g. (8%) of slowly crystallizing material, m.p. 126–128°. Recrystallization raised the melting point to 130.5–131.5°. The melting point deteriorated on standing and the pale yellow crystals darkened.

Anal. Calcd. for $C_{11}H_{10}O_4NCl$: C, 51.67; H, 3.94; Cl, 13.87; N, 4.28. Found: C, 51.95; H, 3.59; Cl, 14.31; N, 4.63.

(b) A mixture of 60.5 g. (0.24 mole) of 4-chloro-3-nitrocinnamic acid, 98 g. (0.84 mole) of thionyl chloride and 200 ml. of benzene was maintained at reflux for 1 hr. The solution was then evaporated to dryness, 650 ml. of absolute ethanol was added, and refluxing was maintained for 1 hr. At no time was the reaction free of solid. Cooling and filtration gave the product, III, m.p. 124–125°, in 85% yield.

4-Chloro-3-nitrocinnamic acid (V). A reaction mixture of 84 g. (0.45 mole) of 4-chloro-3-nitrobenzaldehyde, 84 g. of fused sodium acetate and 630 ml. of acetic anhydride was kept at reflux for 7 hr., whereafter the reaction mixture was poured into ice water. The decomposed reaction mixture was filtered after about 1 hr. The precipitate was extracted with dilute ammonia. The extract on acidification gave a solid which, after recrystallization from aqueous alcohol, melted at 195–197°, and weighed 45.5 g. (45%); (capillary m.p. 182–184°).

The same compound, as shown by mixed melting point, was obtained on hydrolysis of both reaction products of diethyl malonate and 4-chloro-3-nitrobenzaldehyde, III and IV. The ethyl 4-chloro-3-nitrocinnamate (III) or the diethyl 4-chloro-3-nitrobenzalmalonate (IV) was dissolved in about twenty times its volume of refluxing 1:1 acetic acid, 4*N* hydrochloric acid. After a couple of hours at reflux, cooling gave a yellow precipitate which was recrystallized as above. The capillary melting point was 182–184°; (reported[8] m.p. 184–5°).

Diethyl 4-chloro-3-nitrobenzalmalonate (IV). A solution of of 36 g. each of 4-chloro-3-nitrobenzaldehyde (193 mmoles) and diethyl malonate (225 mmoles) in 200 ml. of acetic acid and 4 ml. of piperidine was maintained at reflux for 5 hr. under a helices-packed column while distilling at a rate to maintain reflux head temperature at 113–115°. Removal of the solvent under vacuum gave an oil which solidified on addition of alcohol. Recrystallization from ethanol gave 35 g. (55%) of white product m.p. 67–69°.

Anal. Calcd. for $C_{14}H_{14}O_6NCl$: C, 51.31; H, 4.31; N, 4.27; Cl, 10.82. Found: C, 51.55; H, 4.43; N, 4.72; Cl, 11.00.

Ethyl 3-nitro-4-(4'-methoxyphenoxy)cinnamate (VII). (a) To a fusion of 0.7 g. (12.5 mmoles) of potassium hydroxide, 3 drops of water, and 3.3 g. (26.5 mmoles) of *p*-methoxyphenol was added 2.85 g. (11.2 mmoles) of ethyl 4-chloro-3-nitrocinnamate. An exothermic reaction ensued. After addition of 0.3 g. of copper dust, the temperature was slowly raised to 150°, maintained there for an hour and then raised to 180° and maintained there for 15 min. The reaction mixture was poured onto ice and extracted with chloroform. The chloroform extract was washed with 2*N* sodium hydroxide and water, dried, and concentrated under vacuum. The resulting dark tar taken up in hot ethanol gave 0.9 g. (23%) of crystals melting at 119–120° on cooling. Recrystallization from alcohol gave a pale yellow product, VII, m.p. 126.5–7°.

Anal. Calcd. for $C_{18}H_{17}O_6N$: C, 62.97; H, 4.99; N, 4.08. Found: C, 63.17; H, 4.99; N, 3.96.

(8) J. van der Lee, *Rec. trav. chim.*, **45**, 674 (1926).

(b) To a fusion of 2.5 g. (20 mmoles) of *p*-methoxyphenol, 0.9 g. (16 mmoles) of potassium hydroxide, and 3 ml. of pyridine, was added 3.16 g. (12.3 mmoles) of ethyl 4-chloro-3-nitrocinnamate. The reaction mixture was maintained at reflux for 2 hr. and then poured onto ice and extracted with chloroform. The chloroform extract was washed with 4*N* hydrochloric acid and water and then dried. Evaporation of the chloroform left orange crystals, which were recrystallized from ethanol to give 2.1 g. (50%) of product, VII, m.p. 122–123°. Further recrystallization raised the melting point to 126.5–127°. When all the aqueous layers of this reaction work-up were combined, the resulting acidic solution deposited a yellow solid. Recrystallization of this from aqueous acetic acid gave a product which by melting point and mixed melting point proved itself to be XIII obtained previously by acid hydrolysis of VII.

(c) Under the same reaction conditions using diethyl 4-chloro-3-nitrobenzalmalonate in place of ethyl 4-chloro-3-nitrocinnamate, the exothermic reaction obtained was accompanied by vigorous evolution of carbon dioxide and resulted in low yields of ester, VII, (about 10%) and very small amounts of acid, XIII. When the whole reaction mixture was worked up to convert all esters present to acids, only small amounts of XIII were obtained.

3-Nitro-4-(4'-methoxyphenoxy)cinnamic acid (XIII). (a) Ethyl 3-nitro-4-(4'-methoxyphenoxy)cinnamate (2 g., 58 mmoles), was dissolved in 15 ml. of acetic acid and 15 ml. of 4*N* hydrochloric acid. After 4 hr. at reflux, the cooled solution deposited yellow solid which on recrystallization from aqueous acetic acid or aqueous alcohol melted at 211–213°.

Anal. Calcd. for $C_{16}H_{13}NO_6$: C, 60.95; H, 4.16; N, 4.44; neut. equiv. 315. Found: C, 61.04; H, 4.02; N, 4.60; neut. equiv. 315.

(b) To a fusion of 25 g. (200 mmoles) of *p*-methoxyphenol, 9 g. (160 mmoles) of potassium hydroxide, and 30 ml. of pyridine, was added 15.8 g. (62 mmoles) of ethyl 4-chloro-3-nitrocinnamate. After 1 hr. at reflux, this was poured into water, acidified, and filtered. The precipitate was washed with dilute hydrochloric acid and water. Recrystallization from aqueous alcohol gave 14.9 g. (75%) of product XIII m.p. 208–211° after drying under vacuum. The melting point drops on exposure to air to about 182–184° but rises again on drying under vacuum.

(c) A mixture of 2 g. (73 mmoles) of crude uncrystallized 3-nitro-4-(4'-methoxyphenoxy)benzaldehyde, 2 g. of fused sodium acetate, and 15 ml. of acetic anhydride was maintained at reflux for 6 hr. After being poured into water, the decomposed reaction mixture was extracted with chloroform. The chloroform extract was extracted with dilute ammonia and water. The combined aqueous extracts were acidified and filtered. The resulting product, 1.1 g. (47%), did not depress the melting point of the material prepared above.

3-Nitro-4-(4'-methoxyphenoxy)benzaldehyde (XVI). To a fusion of 14.9 g. (0.12 mole) of *p*-methoxyphenol, 5.4 g. (0.9 mole) of potassium hydroxide and 25 ml. of pyridine at 40–45°, was added 11.6 g. (0.06 mole) of 4-chloro-3-nitrobenzaldehyde portionwise. The temperature rose to 70–75° After 0.5 hr. the reaction mixture was poured into water and extracted with chloroform. The chloroform extracts were washed with 4*N* hydrochloric acid and with water, dried over magnesium sulfate, filtered and evaporated to dryness. The oil was usually used as such. It could be induced to crystallize by cooling and scratching whereafter it was washed with *n*-propyl alcohol and then recrystallized from isopropyl alcohol. Because of its tendency to oil out even when apparently pure, recrystallization was not usually carried out. The product melted at 57.5–58°; reported[9] m.p. 64°.

(9) J. Roche, R. Michel, J. Nunez, and C. Jacquemin, *Compt. rend.*, **244**, 1507 (1957).

Anal. Calcd. for $C_{14}H_{11}O_5N$: C, 61.54; H, 4.06; Found: C, 61.28; H, 4.06;

Ethyl β-[3-amino-4-(4'-methoxyphenoxy)phenyl]propionate (VIII). A solution of 6.86 g. (20 mmoles) of ethyl 3-nitro-4-(4'-methoxyphenoxy)cinnamate in 200 ml. of acetic acid was shaken in an atmosphere of hydrogen in the presence of 10% palladium on charcoal. Uptake of hydrogen ceased in less than an hour when the theoretical amount of hydrogen had been consumed. Evaporation of the filtered reaction mixture under vacuum resulted in a solid which melted at 44–45° after recrystallization from aqueous alcohol.

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.35; H, 6.72; N, 4.58.

β-[3-Iodo-4-(4'-methoxyphenoxy)phenyl]propionic acid (X). To a solution of 20 mmoles of ethyl 3-amino-4-(4'-methoxyphenoxy)phenylpropionate in 200 ml. of acetic acid (obtained by reduction of 6.86 g. (20 mmoles) of the corresponding nitro compound) there was added 6 ml. of sulfuric acid in 10 ml. of acetic acid and 25 ml. of water. To the resulting solution at 0–5° was added dropwise, about five times the theoretical amount of 10% sodium nitrite solution, without obtaining a positive test for nitrous acid with starch-iodide paper. (In another run, the starch-iodide paper test did appear to operate successfully. In still another run using purified amine, the starch-iodide paper test failed but excess nitrous acid could be detected by addition of a drop of reaction mixture to freshly prepared samples of potassium iodide-starch solution.) After stirring for about 1 hr., the reaction mixture was poured into a stirred mixture of 10 g. of sodium iodide, 6 g. of iodine, 7.5 g. of urea, 100 ml. of water and 100 ml. of chloroform at room temperature. Stirring was continued for 1 hr. at room temperature and 1 hr. in a bath at 60°. The chloroform layer was separated, washed with sodium metabisulfite solution and with water, dried, and concentrated under vacuum. The residue was taken up in 40 ml. of acetic acid and 20 ml. of 4*N* hydrochloric acid. This solution was maintained at reflux for 2 hr., diluted with 20 ml. of water and cooled. Recrystallization from aqueous acetic acid using Norit gave 4.7 g. (59%) of product m.p. 118–119°. Further purification raised the melting point to 120.5–121.5°.

Anal. Calcd. for $C_{15}H_{15}O_4I$: C, 48.26; H, 3.80; I, 31.87. Found: C, 48.20; H, 3.82; I, 31.53.

β-[4-(4'-Hydroxyphenoxy)phenyl]propionic acid (XII). A mixture of 3.3 g. (8.3 mmoles) of 3-iodo-4-(4'-methoxyphenoxy)phenylpropionic acid, 30 ml. of acetic acid and 30 ml. of hydriodic acid (sp. g. 1.7) was maintained at reflux for 1.5 hr. and evaporated to dryness. The residue was washed with sodium metabisulfite and water before recrystallization from aqueous acetic acid. There was obtained a product, m.p. 175°, which contained no iodine and gave a ferric chloride test for a phenol. Analysis was consistent with the structure XII. The yield was 1.3 g. (61%) after two recrystallizations; reported[10] m.p. 161°.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 70.19, 70.39; H, 5.62, 5.75.

When the reaction was carried out using 120 ml. of acetic acid and 60 ml. of hydrobromic acid (48%) at reflux for 2.5 hr., there was obtained deiodinated product contaminated with what may have been starting material which had not been demethylated.

β-[3-Amino-4-(4'-hydroxyphenoxy)phenyl]propionic acid (XV). (a) A solution of 14.9 g. (43.5 mmoles) of ethyl 3-nitro-4-(4'-methoxyphenoxy)cinnamate (VII) in 250 ml. of acetic acid was shaken in an atmosphere of hydrogen at about 45 to 30 lbs. of pressure in the presence of 10% palladium on charcoal. The theoretical uptake of hydrogen for the reduction of the nitro group and the double bond took less than 1 hr. The reaction solution was filtered after the addition of 120 ml. of hydriodic acid (sp. g. 1.7). The filtrate was kept at reflux for 2 to 3 hr. and then concentrated to dryness under vacuum. The residue was taken up in 4*N* hydrochloric acid, decolorized with sodium bisulfite, made just basic with dilute ammonia and then just acid with acetic acid. The cooled reaction product when filtered gave 12.8 g. (99%) of product. Recrystallization from 10% acetic acid in water gave 11 g. (85%) of material, m.p. 178.5–180°.

Anal. Calcd. for $C_{15}H_{15}O_4N$: C, 65.92; H, 5.53; N, 5.12. Found: C, 65.86; H, 5.41; N, 5.17.

(b) The preparation starting with 3-nitro-4-(4'-methoxyphenoxy)cinnamic acid (XIII) in place of the ester was exactly the same *via* catalytic reduction.

(c) A mixture of 3.15 g. (10 mmoles) of 3-nitro-4-(4'-methoxyphenoxy)cinnamic acid (XIII) 65 ml. of hydriodic acid (sp. g. 1.7) and 3 g. of red phosphorus to which was cautiously added 65 ml. of acetic anhydride, was maintained at reflux for 3 hr. Concentration under vacuum left a residue which was taken up in water, made just basic with dilute ammonia and then just acid with acetic acid. The filtered product, XV, (85% yield), did not depress the melting point of the above material.

(d) A solution of 2.7 g. (10 mmoles) of crude uncrystallized 3-nitro-4-(4'-methoxyphenoxy)benzaldehyde, 1.6 g. (10 mmoles) of diethyl malonate, 25 ml. of acetic acid and 0.5 ml. of piperidine was maintained at reflux, for 4 hr. under an efficient fractionating column. The temperature of the reflux was maintained at 115° by the very slow removal of distillate whenever the temperature dropped. The reaction mixture was concentrated under vacuum and the residual oil taken up in 65 ml. of hydriodic acid (sp. g. 1.7). After the addition 3 g. of red phosphorus, 65 ml. of acetic anhydride was added cautiously. The resulting reaction was maintained at reflux for 3 hr., filtered, stripped of solvent, taken up in water, made just alkaline with ammonia, and filtered. Recrystallization from 10% acetic acid gave about 15% of product which did not depress the melting point of authentic XV.

β-[3-Iodo-4-(4'-hydroxyphenoxy)phenyl]propionic acid (XI). (a) To a mixture of 17.7 g. (65 mmoles) of 3-amino-4-(4'-hydroxyphenoxy)phenylpropionic acid and 600 ml. of acetic acid was added with stirring and cooling, 30 ml. of sulfuric acid in 300 ml. of water. Keeping the temperature below 5°, a 17% solution of sodium nitrite was added until a positive starch-iodide test was obtained. This required 29 ml. (70 mmoles) of sodium nitrite solution. The reaction solution was then poured into a rapidly stirred ice-cooled mixture of 30 g. (175 mmoles) of sodium iodide, 18 g. (70 mmoles) of iodine, 6 g. (100 mmoles) of urea, 500 ml. of water and 500 ml. of chloroform. The resulting mixture, with stirring, was allowed to reach room temperature and after 30 min. of stirring was brought to reflux for 15 min. The separated aqueous layer was extracted with chloroform and the chloroform layers were combined and washed with water, with 5% sodium metabisulfite, and with water. Concentration of the dried chloroform solution under vacuum left a residue, which was recrystallized from aqueous acetic acid to give 20 g. (80%) of product, XI, m.p. 154–156°. On paper partition chromatography, only one spot was visible. Further recrystallization can raise the melting point to 159–160°.

Anal. Calcd. for $C_{15}H_{13}O_4I$: C, 46.89; H, 3.41; I, 33.04. Found: C, 47.18; H, 3.50; I, 32.06.

(b) A mixture of 1.2 g. (3 mmoles) of 3-iodo-4-(4'-methoxyphenoxy)phenylpropionic acid, 1.5 g. red phosphorus, 0.7 ml. of hydriodic acid (sp. g. 1.7), 3.75 ml. of hydrobromic acid (47%) and 22.5 ml. of acetic acid was maintained at reflux for 1 hr., whereafter it was filtered. Evaporation of the filtrate to dryness and repeated recrystallization gave a small amount (*ca.* 10%) of product, XI, melting at 157–159° and containing only the faintest trace of deiodinated material.

β-[3-Iodo-4-(4'-hydroxy-3'-iodophenoxy)phenyl]propionic acid (XVIII). To a solution of 2 g. (5.2 mmoles) of 3-iodo-4-(4'-hydroxyphenoxy)phenylpropionic acid in 40 ml. of

(10) J. Walker, *J. Chem. Soc.*, 347 (1942).

33% ethylamine was added rapidly at below 5°, 10.4 ml. of 1*N* iodine in potassium iodide solution. The resulting solution was then acidified by the dropwise addition of acetic acid to a *p*H of 8.3. The crystalline precipitate was filtered off and recrystallized from aqueous alcohol. The product weighed 1 g. (*ca.* 38%) and melted at about 90° when dried under vacuum at room temperature. The product contained nitrogen. To remove traces of the 3,3′5′-triiodo compound, additional recrystallizations from absolute ethanol were required. Recrystallization from ethanol without water was possible only after the compound was at most only slightly contaminated with triiodo compound. Drying under 1 mm. pressure at 100° for several hours resulted in a loss of iodine. Drying under 1 mm. pressure at 56° for 8 hr. resulted in an oil free of nitrogen and which had a proper analysis. This oil solidified on standing to a product with a poor melting point. The same product, free of nitrogen, could be obtained by precipitation of the oil from a hot acetic acid solution, by addition of water and cooling.

Anal. Calcd. for $C_{15}H_{12}O_4I_2$: C, 35.32; H, 2.37; I, 49.76. Found for sample dried at room temperature: C, 34.70; H 2.91; I, 47.37. Found for sample dried at 56°: C, 35.21; H, 2.81; I, 49.37. Found for sample dried at 100°: I, 41.51.

β-[3-Iodo-4-(4′-hydroxy-3′,5′-diiodophenoxy)phenyl]propionic acid (XIX). To a solution of 1.5 g. (3.93 mmoles) of 3-iodo-4-(4′-hydroxyphenoxy)phenylpropionic acid in 40 ml. of 33% ethylamine at 0–5° was added dropwise with stirring, 16 ml. of 1*N* iodine in potassium iodide solution. After an additional 15 min. of stirring, the reaction mixture was acidified with 4*N* hydrochloric acid while maintaining the temperature below 5°. Filtration gave the product which weighed 1.4 g. (56%) after one recrystallization from acetic acid and melted at 116–117° when dried at room temperature. An additional recrystallization gave 1 g. (40%) of pure product m.p. 131–132° after drying at 100° at 1 mm. pressure.

Anal. Calcd. for $C_{15}H_{11}O_4I_3$: C, 28.33; H, 1.74; I, 59.87. Found: C, 28.51; H, 1.77; I, 60.46.

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[CONTRIBUTION FROM THE WARNER-LAMBERT RESEARCH INSTITUTE]

4-(4′-Hydroxyphenoxy)-3-iodophenylacetic Acid and Iodinated Derivatives

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A synthesis for the preparation of 4-(4′-hydroxyphenoxy)-3-iodophenylacetic acid and its iodinated products is presented. The procedure is simpler than that previously reported in the literature. The constants obtained are not in agreement with the published report.

In pursuance of our interest in thyroxine analogues[1a] we had occasion to prepare 4-(4′-hydroxyphenoxy)-3-iodophenylacetic acid and its iodinated derivatives. These products had previously been prepared by Roche *et al.*[2] by a more involved synthesis. The published melting points are not in agreement with the presently reported work and the published analytical data were not as satisfactory. The infrared absorption spectra of the products reported herein are in agreement with the assigned structures.

Nitration of 4-chlorophenylacetonitrile introduced a nitro group and simultaneously hydrolyzed the nitrile to the amide. The position of the nitro group *ortho* to the chlorine was apparent from the reactivity of the chlorine and by the oxidation of the nitration product to 3-chloro-4-nitrobenzoic acid. Coupling of the 4-chloro-3-nitrophenylacetamide with *p*-methoxyphenol was the poorest step in the sequence. Reaction of the potassium salt of the phenol in pyridine was carried out but was not easily duplicated. It was found preferable, therefore, to use excess *p*-methoxyphenol as solvent at 130°. As expected, these conditions of ether formation were very much more vigorous than those required when in place of a *p*-carboxamidomethyl group, a carbethoxyvinyl group[1b] was present. Catalytic reduction of the nitro group gave an amine which could best be handled by direct treatment with hydriodic acid to remove both the amide group and the methyl ether. The quantitatively formed 4-(4′-hydroxyphenoxy)-3-aminophenylacetic acid could be used without purification in a diazotization reaction for replacement of the amine by iodide. The removal of the methyl ether before the introduction of the iodine not only greatly improved the yield, but more importantly eliminated the need for careful and tedious removal of 4-(4′-hydroxyphenoxy)phenylacetic acid. Iodination of 4-(4′-hydroxyphenoxy)-3-iodophenylacetic acid could be carried out to give either the 3,3′-diiodo compound or the 3,3′,5′-triiodo compound. In both cases, it was necessary to recrystallize, at least in a final recrystallization, from an acidic solvent to eliminate any ethylamine salt from the product.

As expected,[1b] removal of the iodine from 4-(4′-hydroxyphenoxy)-3-iodophenylacetic acid could be carried out by refluxing hydriodic acid to give 4-(4′-hydroxyphenoxy)phenylacetic acid. This was identical with material obtained by catalytic hydrogenation of 4-(4′-hydroxy-3′-iodophenoxy)-3,5-diiodophenylacetic acid.

(1) (a) R. I. Meltzer, David M. Lustgarten, and Alex Fischman, *J. Org. Chem.*, **22**, 1577 (1957). (b) R. I. Meltzer, S. Farber, E. Merrill, and A. Caro, *J. Org. Chem.*, in press.

(2) J. Roche, R. Michel, J. Nunez, and C. Jacquemin, *Compt. rend.*, **245**, 77 (1957).