33% ethylamine was added rapidly at below 5°, 10.4 ml. of $1N$ 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 $1N$ iodine in potassium iodide solution. After an additional 15 min. of stirring, the reaction mixture was acidified with $4N$ 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.

MORRIS PLAINS, N. J.

[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.

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(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).

EXPERIMENTAL[3]

4-Chloro-3-nitrophenylacetamide. To a stirred mixture of 59.6 g. of sodium nitrate (0.7 mole) in 400 ml. of concd. sulfuric acid at 0–5°, was added dropwise over a period of 45 min. to 1 hr., 100 g. (0.664 mole) of *p*-chlorobenzyl cyanide. Stirring was continued in the cold for 0.5 hr. after complete addition. The reaction mixture was then heated and maintained for 1 hr. at 60–70°. The cooled reaction mixture was poured onto ice. The product separated as a light yellow solid and was filtered and washed with water. Two recrystallizations from 50% aqueous ethanol yielded 127.5 g. (90%) of the desired material which had a melting point of 128–130°.

Anal. Calcd. for $C_8H_7N_2O_3Cl$: C, 44.77; H, 3.29; Cl, 16.52. Found: C, 44.91; H, 3.36; Cl, 16.60, 16.32.

Oxidation of 4-chloro-3-nitrophenylacetamide. Chromic acid oxidation[4] gave a product, m.p. 185–186°. This did not depress the melting point of an authentic sample of 4-chloro-3-nitrobenzoic acid prepared from *p*-chlorobenzaldehyde.

4-(4'-Methoxyphenoxy)-3-nitrophenylacetamide. (a) A mixture of 34.6 g. (279 mmoles) of *p*-methoxyphenol, 12.7 g. of potassium hydroxide, and 75 ml. of pyridine was heated with an open flame until all the potassium hydroxide had dissolved. To this solution, cooled slightly (90–100°), was added 30 g. (140 mmoles) of the 4-chloro-3-nitrophenylacetamide in one portion. The resultant dark brown solution was heated to reflux with an open flame and allowed to react without additional heat. When the boiling had subsided, the mixture again was brought up to reflux, and the flame removed. This refluxing procedure was repeated twice more. The reaction mixture was then poured into ice and the aqueous solution extracted with chloroform. The combined chloroform extracts were washed with water, with 4*N* hydrochloric acid and with water. The dried chloroform extracts were evaporated to dryness. The crude residual oil was recrystallized twice from acetonitrile to give 14.0 g. (33%) of the desired product which melted at 131–132°.

Anal. Calcd. for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27; amide N, 4.65. Found: C, 59.54; H, 4.69; N, 9.13; amide N, 4.51.

(b) A mixture of 2.63 g. (47 mmoles) of potassium hydroxide and 8.7 g. (70.2 mmoles) of *p*-methoxyphenol was heated slowly with an open flame until all the potassium hydroxide had dissolved. To the liquid melt was added 5.0 g. (23.4 mmoles) of 4-chloro-3-nitrophenylacetamide and the mixture was heated to 130° and kept at this temperature for about 5 min. A slightly exothermic reaction occurred on addition of the chloro compound. The reaction mixture was allowed to cool to 50° and then chloroform and water were added. The aqueous layer was separated from the organic layer and extracted with chloroform. The combined chloroform extracts were washed with water with 4*N* hydrochloric acid, and with water. The dried chloroform solution was evaporated to dryness and the residue was recrystallized from benzene to give 4.0 g. (57%) of product melting at 124–126°. Further purification raised the melting point to 131–132°.

4-(4'-Hydroxyphenoxy)-3-aminophenylacetic acid. A suspension of 7.0 g. (23.2 mmoles) of 4-(4'-methoxyphenoxy)-3-nitrophenylacetamide and 0.7 g. of 10% palladium on charcoal in 150 ml. of acetic acid was reduced in a Parr shaker. The reduced solution was treated with 75 ml. of hydriodic acid (57%) and filtered. The filtrate was kept at reflux for 2.25 hr. and then concentrated to dryness. The residue was dissolved in 25 ml. of water and neutralized with concentrated ammonia. The resultant precipitate, 6.0 g. of product (theory 6.02 g.), was twice recrystallized from aqueous ethanol and then from ethanol to melt at 195–196.5°. The unrecrystallized product was satisfactory for the next step.

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 64.86; H, 5.05; N, 5.41. Found: C, 64.72; H, 5.11; N, 5.44, 5.72.

4-(4'-Hydroxyphenoxy)-3-iodophenylacetic acid. To a cold (0–5°) stirred solution of 10.6 g. (41 mmoles) of 4-(4'-hydroxyphenoxy)-3-aminophenylacetic acid in 200 ml. of acetic acid, 15 ml. of sulfuric acid and 50 ml. of water was added, in one portion, 16.5 ml. of a 2.5 mmoles/ml. solution of sodium nitrite (theory, 16.4 ml.). The reaction mixture was stirred in the cold for 1 hr. This cold solution was poured into a cold (0–5°), rapidly stirred mixture consisting of 200 ml. of water, 200 ml. of chloroform, 28.8 g. of sodium iodide, 17.3 g. of iodine, and 5.7 g. of urea. Stirring was continued in the cold for an additional 15 min. The solution was then maintained at reflux for 15 min., cooled, and the layers separated. The aqueous layer was extracted with chloroform. The combined chloroform extracts were washed with water, with sodium bisulfite solution, and again with water. The dried chloroform solution was evaporated to dryness and the yellow residue was recrystallized from aqueous acetic acid thrice to give 11.0 g. (78%) of product melting at 166–168°, reported[2] m.p. 109°.

Anal. Calcd. for $C_{14}H_{11}O_4I$: C, 45.44; H, 3.00; I, 34.30. Found: C, 45.50; H, 2.95; I, 34.20.

4-(4'-Hydroxyphenoxy)phenylacetic acid. (a) A mixture of 1 g. (2.7 mmoles) of 4-(4'-hydroxyphenoxy)-3-iodophenylacetic acid, 25 ml. of acetic acid, and 25 ml. of 57% hydriodic acid was maintained at reflux for 3.5 hr. The reaction mixture on standing over night deposited a crystalline material. The solid was filtered, washed with water, and recrystallized from aqueous ethanol. The product melted at 199–200° simultaneously with a sample of 4-(4'-hydroxyphenoxy)-phenylacetic acid prepared below. The identity of the material was further established by circular paper partition chromatography using *t*-amyl alcohol-6*N*-ammonia.

(b) A mixture of 5 g. (8 mmoles) of 4-(4'-hydroxy-3'-iodophenoxy)-3,5-diiodophenylacetic acid,[5] 200 ml. of 1*N* sodium hydroxide and 2 g. of 5% palladium-calcium carbonate was subjected to reduction in a Parr shaker. Hydrogen uptake was theoretical. The filtered reaction mixture was treated with 50 ml. of 4*N* hydrochloric acid and extracted with about 250 ml. of ethyl ether in small portions. The combined ether extracts were washed with water containing a small amount of sulfurous acid. The dried ether layer was evaporated to dryness to give 1.7 g. (89%) of the completely deiodinated compound, m.p. 195–198°. The product, after two recrystallizations from aqueous ethanol, gave the analytical sample, m.p. 197–198.5°.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 69.06; H, 5.19.

4-(4'-Hydroxy-3'-iodophenoxy)-3-iodophenylacetic acid. 4-(4'-Hydroxyphenoxy)-3-iodophenylacetic acid (1.0 g., 2.7 mmoles) was dissolved in 20 ml. of 33% aqueous ethylamine and 5.4 ml. of 1*N* iodine in potassium iodide solution was added as rapidly as possible at 0° with vigorous stirring. After 1 hr. at room temperature, the *p*H of the reaction mixture was adjusted with glacial acetic acid to 9.6. The supernatant solution was decanted after 10 min. and diluted with 40 ml. of water. From this solution, upon further acidification with glacial acetic acid, a crystalline material precipitated. After two recrystallizations from ethanol and one from 50% aqueous acetic acid, the product melted at 147–150°, reported[2] m.p. 113°.

Anal. Calcd. for $C_{14}H_{10}O_4I_2$: C, 33.90; H, 2.03; I, 51.17. Found: C, 33.83; H, 2.01; I, 50.75.

4-(4'-Hydroxy-3',5'-diiodophenoxy)-3-iodophenylacetic acid. 4-(4'-Hydroxyphenoxy)-3-iodophenylacetic acid (1.0 g., 2.7

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[3] Melting points were taken on a Fisher Johns melting point block and are uncorrected.

[4] R. L. Shriner and R. C. Fuson, *Systematic Identification of Organic Compounds*, Wiley, 1935, p. 139.

[5] Obtained in a previous study by iodination of 4-(4'-hydroxyphenoxy)-3,5-diiodophenylacetic acid.[1]

mmoles) was dissolved in 20 ml. of 33% aqueous ethylamine and 10.8 ml. (5.4 mmoles) of a 1*N* iodine in potassium iodide solution was added dropwise with stirring in an ice bath. After an hour at room temperature, the reaction mixture was acidified at 0° with 20% aqeous acetic acid. The supernatant solution was decanted and the residual oil was crystallized from acetic acid. It melted at 184–186° after recrystallization from acetic acid, reported[2] m.p. 220°.

Anal. Calcd. for $C_{14}H_9O_4I_3$: C, 27.03; H, 1.46; I, 61.22. Found: C, 27.51; H, 1.46; I, 61.04.

MORRIS PLAINS, N. J.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF LEPETIT S.P.A.]

Bis(4-hydroxyphenyl)acetic Acid Derivatives

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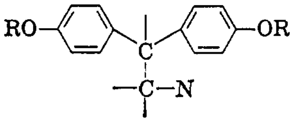
Bis(4-hydroxyphenyl)acetic acid was obtained by a new synthesis from 4-hydroxy-4'methoxydiphenylacetic acid. Some new derivatives of bis(4-acetoxyphenyl)- and bis(4-hydroxyphenyl)acetic acid are described.

A recent publication by M. H. Hubacher[1] on the synthesis of bis(4-hydroxyphenyl)acetic acid prompted us to publish the results of some work we carried out in this field and particularly the preparation of the above acid and of some derivatives of the same.[2] The purpose of our research was to obtain some amides of bis(4-hydroxyphenyl)-acetic acid containing the structure



which, according to Schmidt and Seeger's observations[3] is common to several substances having a particularly interesting laxative action.

Bis(4-hydroxyphenyl)acetic acid was obtained by Hubacher by direct condensation of glyoxylic acid with phenol and sulfuric acid and by demethylation with pyridinium chloride of bis(4-anisyl)-acetic acid. In our new procedure, in which glyoxylic acid is not used, 4-hydroxy-4'-methoxydiphenylacetic acid[4] is demethylated with 48% hydrobromic acid and glacial acetic acid by known methods[5] to bis(4-hydroxyphenyl)acetic acid, the characteristics of which correspond to those described by Hubacher. 4-Hydroxy-4-methoxydiphenylacetic acid was prepared by condensing the cyanohydrin of anisaldehyde with phenol and sulfuric acid by a modification of a method described in the literature,[6] and by subsequent alkaline saponification of the 4-hydroxy-4'-methoxydiphenylacetonitrile obtained.

An attempt to condense the cyanohydrin of 4-hydroxybenzaldehyde with phenol, in order to avoid the subsequent demethylation, was unsuccessful as under the necessary reaction conditions sulfuric acid decomposes the cyanohydrin before it reacts with phenol. Bis(4-hydroxyphenyl) acetic acid was converted into the diacetyl ester and this latter into the acyl chloride from which, by reaction with different amines, the corresponding amides were prepared. The bis(4-acetoxyphenyl)-acetamides were easily hydrolyzed to bis(4-hydroxyphenyl)acetamides. Bis(4-hydroxyphenyl)-acetanilide and bis(4-hydroxyphenyl)acetomorpholide were converted also into bisphenylglyceryl ethers by reaction with glycerine α-chlorohydrin.

The substances listed in Table 1 were assayed for their laxative action, but found to be inactive.

EXPERIMENTAL

4-Hydroxy-4'-methoxydiphenylacetonitrile. The product, obtained according to Bistrzycki, *et al.*,[6] after repeated experiments was always admixed with traces of colored impurities.[7] We have found that by modifying as follows the reaction conditions, colorless 4-hydroxy-4'-methoxydiphenylacetonitrile is obtained in good yields.

In 720 g. of phenol heated to 50–60°, 450 g. of cyanohydrin of anisaldehyde[4] was dissolved, the clear colorless solution was poured under strong stirring in 1860 ml. of 73% sulfuric acid at a temperature of 70–75°. The solution was then stirred for 10 min. at 100°. The reaction mixture, which during the addition became orange-red, after some minutes produced white-pink 4-hydroxy-4'-methoxydiphenylacetonitrile; it was cooled at about 40° and poured into 16 l. of water and ice. The white solid was collected on a Buchner, washed with water, and suspended in 5000 ml. of 2% sodium bicarbonate. After washing and filtering to neutral reaction with water the white product was crystallized from 75% acetic acid; yield 485 g. (73%) of 4-hydroxy-4'-methoxydiphenylacetonitrile, needles, m.p. 175–176°.

Bis(4-hydroxyphenyl)acetic acid. Four hundred and five grams of 4-hydroxy-4'-methoxydiphenylacetic acid obtained by alkaline hydrolysis of 4-hydroxy-4'-methoxy-

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[1] M. H. Hubacher, *J. Org. Chem.*, 24, 1949 (1959).

[2] The pharmacological properties of diethylaminoethyl-ester of bis-(4-hydroxyphenyl)acetic acid were described by S. S. Libermann, *Farmakol. i. Toksikol.*, 19(6), 10 (1956); *Chem. Abstr.*, 51, 7587c (1957), but no reference was made to the synthesis of the compound.

[3] L. Schmidt and E. Seeger, *Arzeneimittel-Forsch.*, 6, 22 (1956).

[4] O. E. Schultz and J. Schnekenburger, *Arch. Pharm.*, 291/63, 362 (1958).

[5] R. Stoermer, *Ber. deut. chem. Ges.*, 41, 323 (1908).

[6] A. Bistrzycki, J. Paulus, and R. Perrin, *Ber. deut. chem. Ges.*, 44, 2596 (1911).

[7] R. Stoermer, *Ber. deut. chem. Ges.*, 44, 1863 (1911).