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

# THE PREPARATION OF IODOPHENOXYACETIC ACIDS

## S. WAWZONEK AND S. C. WANG<sup>1</sup>

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The ability of 2,4-diiodophenoxyacetic acid to function as an antithyroid agent (1) suggested the preparation of other iodophenoxyacetic acids for testing in the same manner. All but two of the compounds were prepared directly from the corresponding iodophenol by heating with ethyl bromoacetate and sodium butoxide in *n*-butanol. *m*-Iodophenoxyacetic acid was prepared from *m*-aminophenoxyacetic acid rather than from *m*-iodophenol because the latter was reported to lose iodine in boiling water (2).



A similar synthesis was used for 2,3-diiodophenoxyacetic acid since 2-iodo-3aminophenol was obtained only in very poor yields. The acids listed in Table I



are new compounds with the exception of 2,4-diiodophenoxyacetic acid.

Variations from the literature in the preparation of the iodophenols were made only with 2,4-diiodophenol and 2-iodo-3-nitrophenol. The yield of the former is low while the structure of the latter is not definite.

2,4-Diiodophenol was prepared by the mercuration of phenol followed by treatment of the resulting 2,4-diacetoxymercuriphenol with iodine. The over-all yield of the phenoxyacetic acid is 18% as compared with the 2% obtained from the direct iodination of phenol (3).

The preparation of 2-iodo-3-nitrophenol from 3-nitrophenol has been reported twice in the literature. The action of iodine and mercuric oxide on *m*-nitrophenol in acetic acid gave a compound melting at  $134^{\circ}$ . The 2,3-structure was assigned since *m*-nitrophenol on chlorination gives 2-chloro-3-nitrophenol (4). Iodination in ammonia was reported to give a compound melting at the same point (5). Repetition of the latter work by Brenans and Larivaille (6) demonstrated that the product was actually a mixture of 6-iodo-3-nitrophenol and a new 3-nitrotriiodophenol. The iodination in ammonia in this laboratory gave an amorphous solid melting between  $118^{\circ}$  and  $130^{\circ}$ .

<sup>1</sup> Abstracted in part from the Ph.D. thesis of S. C. Wang, 1949.

2-Iodo-3-nitrophenol was made by the mercuration of m-nitrophenol followed by replacement of the acetoxymercuri group with iodine.



The orientation was demonstrated by synthesis of 2-iodo-3-nitrophenol by the Sandmeyer reaction from 2-amino-3-nitrophenol whose structure has already been established (7). Further proof for this structure was the fact that the 2,3-diiodophenoxyacetic acid derived from it gave a marked depression in melting point when mixed with each of the other isomeric diiodophenoxyacetic acids.

The results as antithyroid agents will be presented elsewhere.

	vield, %	м.р., °С.	FORMULA	ANALYSIS			
PHENOXYACETIC ACID				Calc'd		Found	
		,		С	H	С	н
2,3-Diiodo	96.74	172-174	$C_{3}H_{6}I_{2}O_{3}$	23.78	1.47	23.43	1.29
2,4-Diiodo	99.0	165 - 167	$C_8H_6I_2O_3$				
2,5-Diiodo	91.6	175-177	$C_8H_6I_2O_8$	23.78	1.47	23.81	1.47
2,6-Diiodo	92.3	167-168	$C_8H_6I_2O_3$	23.78	1.47	23.99	1.49
3,4-Diiodo	78.9	179-181	$C_{8}H_{6}I_{2}O_{3}$	23.78	1.47	23.52	1.67
3,5-Diiodo	88.0	193 - 195	$C_8H_6I_2O_3$	23.78	1.47	23.95	1.54
2,4-Diiodo-6-methyl	90.1	205	$C_9H_8I_2O_3$	25.86	1.93	26.12	1.99
2,6-Diiodo-4-methyl	95.9	168 - 169	$C_9H_8I_2O_3$	25.86	1.93	25.79	1.92
2,4,6-Triiodo-3-methoxy	69.7	229-230	$C_9H_7I_3O_4$	19.30	1.26	19.83	1.33
2-Iodo-3-nitro	79.0ª	182184	$C_8H_6INO_5$	29.74	1.87	29.84	1.88
2-Iodo-3-amino	61.4ª	164 d.	$C_8H_8INO_8$	32.79	2.75	32.28	2.71

TABLE I IODOPHENOXYACETIC ACIDS

<sup>a</sup> Method of preparation is described in the experimental.

#### EXPERIMENTAL<sup>2</sup>

Iodophenols. 2,5-Diiodo- (8), 3,4-diiodo- (9), 3,5-diiodo- (10), 2,6-diiodo- (11), 2,4,6-triiodo- (12), 2,6-diiodo-4-methyl- (5), 2,4-diiodo-6-methyl- (5), and 2,4,6-triiodo-3-methoxy-phenol (13) were made by methods described in the literature.

2,4-Diiodophenol. To a suspension of 2,4-diacetoxymercuriphenol (14) (20 g.) in 10% potassium iodide was added a solution of iodine (33 g.) and potassium iodide (33 g.) in water (300 ml.); the resulting mixture was stirred vigorously for 30 minutes. The product was filtered, washed with 10% potassium iodide and then dissolved in ethanol (100 ml.). The ethanol solution was filtered into ice-water (1 kg.). The 2,4-diiodophenol separated as colorless needles, m.p. 68-70°, which could be used directly in the preparation of the phenoxyacetic acid; yield, 10.4 g.

If the reaction mixture was allowed to stand two days before the isolation of the product, practically pure 2,4,6-triiodophenol was obtained, m.p. 157–158°.

2-Acetoxymercuri-3-nitrophenol. To a solution of 3-nitrophenol (48.5 g.) and sodium hydroxide (10.4 g.) in water (600 ml.) was added a solution of mercuric acetate (108 g.) in water (600 ml.) containing acetic acid (10 ml.). The resulting mixture was heated at 100°

<sup>&</sup>lt;sup>2</sup> Melting points are not corrected.

for 30 minutes with vigorous stirring and filtered; yield, 125.4 g. This product was identical in its properties with the 2-acetoxymercuri-3-nitrophenol prepared by mercurating 3-nitrophenol in ethanol (15).

#### 2-10do-3-Nitrophenol

(A) From 2-acetoxymercuri-3-nitrophenol. A suspension of 2-acetoxymercuri-3-nitrophenol (40 g.) in 10% potassium iodide (250 g.) was treated with 10% potassium triiodide (250 g.). After 30 minutes of stirring in the cold the 2-iodo-3-nitrophenol (24.5 g.) was filtered. Recrystallization from water gave long yellow needles, m.p. 122-123°.

(B) From 2-amino-3-nitrophenol. A solution of 2-amino-3-nitrophenol (7) (1.35 g.) in concentrated sulfuric acid (15 ml.) was treated with powdered sodium nitrite (1.5 g.) with stirring while the temperature was kept below 5°. After two hours of stirring the mixture was poured onto ice and the resulting clear diazonium salt solution was added to 9 g. of potassium iodide in water (20 ml.). The resulting mixture contained a red precipitate and was heated at 100° for 30 minutes. Removal of the iodine with sodium bisulfite followed by cooling gave a solid which was purified by dissolving in alkali and reprecipitating with acid. Crystallization from water gave a product melting at 123–124°; yield, 1.4 g. This product did not depress the melting point of the sample prepared by method A.

Anal. Calc'd for C<sub>6</sub>H<sub>4</sub>INO<sub>3</sub>: C, 27.20; H, 1.52.

Found: C, 27.16; H, 1.62.

*Phenoxyacetic acids.* The following general procedure was used for preparing the phenoxyacetic acids, and is a modification of that used for 2,4,6-triiodophenoxyacetic acid (16). The results for the individual compounds are listed in Table I.

The phenol (0.01 mole) was treated in *n*-butyl alcohol (40 ml.) containing sodium *n*-butoxide (0.019 mole) with ethyl bromoacetate (3.1 ml.) and the solution refluxed for three hours. After standing overnight the ethyl ester of the phenoxyacetic acid was saponified by refluxing for one hour with 30% sodium hydroxide (13.5 ml.), the resulting solution poured into 200 ml. of water, and the *n*-butyl alcohol removed by steam-distillation. The product was precipitated by acid and recrystallized from benzene.

2,4,6-Triiodophenoxyacetic acid (16) and 2,4,6-triiodo-3-methoxyphenoxyacetic acid were recrystallized from ethanol and dilute ethanol respectively.

3-Iodophenoxyacetic acid. 3-Aminophenoxyacetic acid (4.4 g.) (17) was converted into 3iodophenoxyacetic acid (4.1 g.) by using directions similar to those given for the preparation of 2-iodo-3-nitrophenol. The solid, after one crystallization from benzene, melted at 115-116°. Koelsch (18) reports 114-115.5°.

2-Iodo-3-nitrophenoxyacetic acid. A solution of 2-iodo-3-nitrophenol (26.5 g.) and sodium hydroxide (18 g.) in water (75 ml.) was refluxed with monochloroacetic acid (18.9 g.) for four hours. After cooling, the phenoxyacetic acid was precipitated by acid and purified by dissolving in 6 N ammonium hydroxide and reprecipitating. Recrystallization from a mixture of benzene and ethyl acetate gave crystals melting at 182-184°; yield 25.5 g.

2-Iodo-3-aminophenoxyacetic acid. A solution of 2-iodo-3-nitrophenoxyacetic acid (0.7 g.) in 6 N ammonium hydroxide (10 ml.) was added, with stirring, to a boiling solution of ferrous sulfate (5 g.) in water (6 ml.). The solution was made alkaline with concentrated ammonia (3-4 ml.), refluxed for ten minutes, and filtered into 1 ml. of glacial acetic acid. Upon cooling 0.39 g. of 2-iodo-3-aminophenoxyacetic acid was obtained, m.p. 164° d.

2,3-Diiodophenoxyacetic acid. 2-Iodo-3-aminophenoxyacetic acid (1.3 g.) was converted to 2,3-diiodophenoxyacetic acid (1.73 g.) by the procedure used for 2-iodo-3-nitrophenol. Crystallization from benzene gave m.p.  $172-174^{\circ}$  which was depressed more than  $30^{\circ}$  by the addition of any one of the other five diiodophenoxyacetic acids.

#### SUMMARY

The preparation of various iodophenoxyacetic acids for testing as antithyroid agents is described.

IOWA CITY, IOWA

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