The Biological Action of Substances Related to Thyroxine

2. FURTHER DERIVATIVES OF 3:5-DIODO-4-HYDROXYBENZOIC ACID

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In Part 1 of this series of communications (Sheahan, Wilkinson & MacLagan, 1951) it was shown that 3:5-diiodo-4-hydroxybenzoic acid exerted a slight antithyroxine activity when tested in mice by the oxygen-consumption method (MacLagan & Sheahan, 1950). Esterification produced a considerable enhancement of the activity, which was maximal when the *n*-butyl ester was used. The present paper describes the study of the effects produced by variation in molecular structure. All the derivatives tested were of the type

which has been shown to be important for antithyroxine potency. They include a number of ethers and acyl derivatives of the hydroxy acid, and, of these, Frieden & Winzler (1949) have reported that the benzyl ether exhibited a thyroxine-inhibitory action in tadpoles, an effect we also observed in mice (MacLagan, Sheahan & Wilkinson, 1949). In addition a number of branched-chain esters of the hydroxy acid were examined.

Wheeler & Liddle (1910) described the preparation of the methyl ester of 3:5-diiodo-4-methoxybenzoic acid by treatment of the hydroxy acid with methyl iodide and alkali, but in our experience poor yields were obtained. Similar results were obtained when 3:5-diiodo-4-hydroxybenzonitrile was methylated by this procedure. Recourse was therefore made to the method of Kalb, Schweizer, Zellner & Barthold (1926), who methylated 2:6-diiodo-4-nitrophenol with excess methyl sulphate in the presence of alkali. By this means the methoxy nitrile and the methyl ester of the methoxy acid were obtained in excellent yields from the hydroxy nitrile and hydroxy acid, respectively. The method was also applicable to the methylation of various alkyl 3:5-diiodo-4-hydroxybenzoates.

The *n*-propyl ether was obtained in moderate yield by treatment of 3:5-diiodo-4-hydroxybenzonitrile with *n*-propyl bromide and alkali, but in addition 3:5-diiodo-4-*n*-propoxybenzamide was obtained from the mother liquors.

Ethyl 3:5-diiodo-4-hydroxybenzoate reacted with benzyl chloride in the presence of alkali to give benzyl ether, but the *n*-propyl ester under similar conditions underwent de-iodination and *n*-propyl 3:5-dihydroxy-4-benzyloxybenzoate was isolated from the reaction mixture.

The branched-chain alkyl esters of 3:5-diiodo-4-hydroxybenzoic acid were prepared by methods similar to that described in our earlier paper (Sheahan *et al.* 1951).

EXPERIMENTAL

Chemical methods

Analyses by Drs Weiler and Strauss, Oxford, and by Herd and Mundy, London. Melting points are uncorrected.

3:5-Diiodo-4-methoxybenzonitrile. 3:5-Diiodo-4-hydroxybenzonitrile (Auwers & Reis, 1896) (18.5 g., 0.05 g.mol.) was dissolved in methanol (100 ml.) and treated with 10*N*-NaOH (10 ml.) and methyl iodide (28 g., 0.2 g.mol.). The mixture was heated under reflux for 90 min. While still hot, the precipitated NaI was removed by filtration, and the filtrate cooled and diluted with water (100 ml.). On standing the product (2.0 g.) separated as a white precipitate, which crystallized from methanol in colourless needles, m.p. 148°. (Found: C, 25.1; H, 1.7; I, 66.2. $C_8H_5ONI_2$ requires C, 24.9; H, 1.3; I, 66.0%.) No improvement in the yield was effected by varying the proportions of the reactants. The mother liquors yielded 16 g. of unreacted 3:5-diiodo-4-hydroxybenzonitrile, m.p. 202–204°, on acidification.

The methoxy nitrile was, however, obtained in 98% yield by the gradual addition, with vigorous shaking, of 20% NaOH to a hot solution of 3:5-diiodo-4-hydroxybenzonitrile (18.55 g.) in dimethyl sulphate (60 ml.) until the mixture was alkaline to phenolphthalein. The solid (18.7 g.) was then collected, washed with water and dried at 100°. After crystallization from methanol it had m.p. 148°, and proved to be identical with the 3:5-diiodo-4-methoxybenzonitrile described above.

On hydrolysis with NaOH the methoxy nitrile gave 3:5-diiodo-4-methoxybenzoic acid, m.p. 261–262°. Wheeler & Liddle (1910) report m.p. 265° for the acid obtained by hydrolysis of the methyl ester.

Methyl 3:5-diiodo-4-methoxybenzoate was obtained by the gradual addition with vigorous shaking of 20% NaOH to a suspension of 3:5-diiodo-4-hydroxybenzoic acid (10 g.) in dimethyl sulphate (60 ml.) previously heated to 70°. When alkaline to phenolphthalein the solid (9.77 g.) was filtered from the cooled mixture, washed with water and

dried at 20° over silica gel. After recrystallization from methanol it had m.p. 94–95°. Wheeler & Liddle (1910) report m.p. 95°.

Ethyl 3:5-diiodo-4-methoxybenzoate. 3:5-Diiodo-4-methoxybenzoic acid (1.24 g.) was heated under reflux with ethanol (25 ml.) containing H_2SO_4 (3 drops) for 3 hr. The solution was concentrated to about 10 ml. and the residue poured into a mixture of ice and 2N- Na_2CO_3 (20 ml.). The solid (1.03 g.) which separated was washed with water and dried over CaCl_2 . The *ethyl ester* crystallized from light petroleum (b.p. 60–80°) in colourless needles, m.p. 95–96°. (Found: C, 28.3; H, 2.6; I, 59.0. $\text{C}_{10}\text{H}_{10}\text{O}_3\text{I}_2$ requires C, 27.8; H, 2.6; I, 58.9%.)

n-Propyl 3:5-diiodo-4-methoxybenzoate was prepared by the method used for the methyl ester from *n*-propyl 3:5-diiodo-4-hydroxybenzoate (8.64 g.) and dimethyl sulphate (30 ml.). It separated as an oil (8.9 g.) which crystallized on storage. Recrystallization from light petroleum (b.p. 40–60°) gave the required *ester* as colourless needles, m.p. 58–59°. (Found: C, 29.8; H, 2.6; I, 56.8. $\text{C}_{11}\text{H}_{12}\text{O}_3\text{I}_2$ requires C, 29.6; H, 2.7; I, 57.0%.)

The *n-butyl ester* was prepared similarly from *n*-butyl 3:5-diiodo-4-hydroxybenzoate in almost theoretical yield. The oil which separated was induced to crystallize by cooling in ice. It crystallized from light petroleum (b.p. 40–60°) in large colourless prisms, m.p. 45°. (Found: C, 31.4; H, 2.8; I, 55.2. $\text{C}_{12}\text{H}_{14}\text{O}_3\text{I}_2$ requires C, 31.3; H, 3.05; I, 55.2%.)

Methyl 3:5-diiodo-4-ethoxybenzoate was prepared from 3:5-diiodo-4-ethoxybenzoic acid (Wilkinson, 1951) (1.5 g.), methanol (30 ml.) and H_2SO_4 (3 drops) by the method used for ethyl 3:5-diiodo-4-methoxybenzoate. The *product* crystallized from light petroleum (b.p. 80–100°) in colourless needles, m.p. 93°. (Found: C, 28.0; H, 2.2; I, 59.2. $\text{C}_{10}\text{H}_{10}\text{O}_3\text{I}_2$ requires C, 27.8; H, 2.3; I, 58.9%.)

The *ethyl ester*, prepared similarly, separated from light petroleum (b.p. 60–80°) in colourless needles, m.p. 71°. (Found: C, 30.3; H, 2.7; I, 57.0. $\text{C}_{11}\text{H}_{12}\text{O}_3\text{I}_2$ requires C, 29.6; H, 2.7; I, 57.1%.)

n-Propyl 3:5-diiodo-4-ethoxybenzoate. *n*-Propyl 3:5-diiodo-4-hydroxybenzoate (8.64 g.) was dissolved in ethyl sulphate (50 ml.) and heated on a steam bath. 20% NaOH (85 ml.) was added gradually to the heated mixture with vigorous shaking over 1.5 hr. The mixture was cooled and diluted with water. The oil, which separated, was induced to solidify on cooling with ice. The *ester* (9.1 g.) was collected, washed with water, and dried at 20° over CaCl_2 . It crystallized from light petroleum (b.p. 40–60°) in colourless prisms, m.p. 38°. (Found: C, 31.6; H, 3.3; I, 54.5. $\text{C}_{12}\text{H}_{14}\text{O}_3\text{I}_2$ requires C, 31.3; H, 3.05; I, 55.2%.)

3:5-Diiodo-4-n-propoxybenzonitrile. 3:5-Diiodo-4-hydroxybenzonitrile (9.3 g., 0.025 g.mol.) was dissolved in *n*-propanol (50 ml.) and 10N-NaOH (5 ml.). *n*-Propyl bromide (12.3 g., 0.1 g.mol.) was added and the mixture heated under reflux for 2 hr. After concentration to about 25 ml., the mixture was filtered and diluted with water (10 ml.). The solid (2.07 g.) which separated crystallized from 95% methanol in colourless prisms, m.p. 115°, and proved to consist of the required *nitrile*. (Found: C, 29.1; H, 2.4; I, 62.5. $\text{C}_{10}\text{H}_8\text{ON}_2\text{I}_2$ requires C, 29.1; H, 2.2; I, 61.5%.) Further addition of water precipitated a solid (1.3 g.), m.p. 165–167°, which crystallized from methanol in colourless needles, m.p. 170–171°, identified as 3:5-diiodo-4-*n*-propoxybenzamide. (Found: C, 28.2; H, 2.3; N, 3.2; I, 59.0. $\text{C}_{10}\text{H}_{11}\text{O}_2\text{N}_2\text{I}_2$ requires C, 27.9; H, 2.5; N, 3.25; I, 59.0%.) Acidification of

the mother liquors regenerated unreacted hydroxybenzonitrile (5.4 g.), m.p. 202–205°.

Improved yields of the *n*-propoxyamide were obtained by using twice the above amounts of 10N-NaOH and *n*-propyl bromide, and prolonging the period of heating to 2.5 hr. By this means the yield of amide was increased to 5.4 g. (50%) and 4.56 g. of unreacted starting material were recovered.

3:5-Diiodo-4-n-propoxybenzoic acid. The nitrile (2.5 g.) dissolved in hot ethanol (10 ml.) was heated under reflux with 5N-NaOH (25 ml.) for 2 hr. The solution was diluted with water (10 ml.) and filtered. The filtrate was acidified with HCl to precipitate the *acid* (2.32 g.), which crystallized from benzene in colourless needles, m.p. 191°. (Found: C, 28.1; H, 2.4; I, 58.7. $\text{C}_{10}\text{H}_{10}\text{O}_3\text{I}_2$ requires C, 27.8; H, 2.3; I, 58.9%.) The acid was also obtained in good yield by similar treatment of the amide.

The *methyl ester* crystallized from light petroleum (b.p. 40–60°) in colourless needles, m.p. 55°. (Found: C, 29.9; H, 2.65; I, 56.7. $\text{C}_{11}\text{H}_{12}\text{O}_3\text{I}_2$ requires C, 29.6; H, 2.7; I, 57.0%.)

The *ethyl ester* separated from the same solvent in colourless plates, m.p. 44–45°. (Found: C, 31.6; H, 3.0; I, 55.3. $\text{C}_{12}\text{H}_{14}\text{O}_3\text{I}_2$ requires C, 31.3; H, 3.0; I, 55.2%.)

Methyl 3:5-diiodo-4-benzoyloxybenzoate, prepared by esterification of 3:5-diiodo-4-benzoyloxybenzoic acid (Frieden & Winzler, 1949), crystallized from methanol in colourless needles, m.p. 123°. (Found: C, 36.5; H, 2.2; I, 51.6. $\text{C}_{18}\text{H}_{12}\text{O}_4\text{I}_2$ requires C, 36.5; H, 2.4; I, 51.4%.)

Ethyl 3:5-diiodo-4-benzoyloxybenzoate. Ethyl 3:5-diiodo-4-hydroxybenzoate (Part 1) (4.18 g.) in ethanol (15 ml.) was treated with 2N-NaOH (5 ml.) and benzyl chloride (1.3 g.), and the mixture heated under reflux for 15 min., during which time an oil separated. After cooling, water (10 ml.) was added to complete the separation of the oily product. On refrigeration this was obtained as a solid (1.84 g.). The *ester* was obtained as colourless needles, m.p. 72°, from ethanol. (Found: C, 37.8; H, 2.7; I, 50.2. $\text{C}_{18}\text{H}_{14}\text{O}_4\text{I}_2$ requires C, 37.8; H, 2.75; I, 50.0%.)

Attempted preparation of n-propyl 3:5-diiodo-4-benzoyloxybenzoate. *n*-Propyl 3:5-diiodo-4-hydroxybenzoate (4.32 g.) in *n*-propanol (15 ml.) was treated as described for the ethyl ester. After removal of the solvent, water was added to precipitate the product, which crystallized from light petroleum (b.p. 60–80°) in colourless clusters, m.p. 98–100°, which did not contain iodine. They appeared to consist of *n*-propyl 3:5-diiodo-4-benzoyloxybenzoate. (Found: C, 67.6; H, 6.8. $\text{C}_{17}\text{H}_{18}\text{O}_4$ requires C, 67.6; H, 6.0%.)

The following acyl derivatives of *n*-butyl 3:5-diiodo-4-hydroxybenzoate were prepared by dissolving the ester (2 g.) in pyridine (2 ml.) and adding the acid anhydride or chloride (0.5–1 g.). After standing at room temperature for 30 min., the mixture was heated to 60° for a further 10 min. The cooled mixture was poured into water (20 ml.) and when the gum which separated had solidified it was collected by filtration and washed with water.

Acetate. Highly refractive colourless hexagonal plates, m.p. 80°, from methanol. (Found: C, 32.5; H, 2.9; I, 51.8. $\text{C}_{18}\text{H}_{14}\text{O}_4\text{I}_2$ requires C, 32.0; H, 2.9; I, 52.1%.)

Propionate. Large colourless prisms, m.p. 84–85°, from light petroleum (b.p. 40–60°). (Found: C, 34.0; H, 3.15; I, 51.6. $\text{C}_{19}\text{H}_{16}\text{O}_4\text{I}_2$ requires C, 34.2; H, 3.3; I, 51.7%.)

Benzoate. Colourless irregular clusters, m.p. 74°, from light petroleum (b.p. 40–60°). (Found: C, 39.5; H, 3.2; I, 45.7. $\text{C}_{18}\text{H}_{16}\text{O}_4\text{I}_2$ requires C, 39.3; H, 2.9; I, 46.2%.)

Carbethoxy derivative. Prepared similarly, using ethyl chloroformate (1 ml.). Colourless plates, m.p. 79°, from methanol. (Found: C, 32.5; H, 3.1; I, 48.9. $C_{14}H_{14}O_5I_2$ requires C, 32.5; H, 3.1; I, 49.1%.)

Methyl 3:5-diiodo-4-acetoxybenzoate was prepared in a similar manner from methyl 3:5-diiodo-4-hydroxybenzoate. It crystallized from methanol in colourless plates, m.p. 121°. (Found: C, 27.1; H, 1.9; I, 57.0. $C_{10}H_8O_4I_2$ requires C, 26.9; H, 1.8; I, 57.0%.)

2-Ethylbutyl p-hydroxybenzoate. p-Hydroxybenzoic acid (27.6 g.) was heated under reflux with 2-ethylbutanol (100 ml.), benzene (100 ml.) and H_2SO_4 (4 g.) for 3 hr., a McIntyre stillhead being employed to separate the water liberated during the reaction. The cooled mixture was neutralized with NaOH, and acidified with acetic acid. The solvents were removed by steam distillation and the residue extracted with ether. The extract was dried (Na_2SO_4), the solvent removed, and the product (26.5 g.) distilled. It was obtained as a pale-yellow oil, b.p. 141–142°/0.3 mm. (Found: C, 69.8; H, 8.2. $C_{13}H_{18}O_2$ requires C, 70.2; H, 8.1%.)

Branched-chain alkyl 3:5-diiodo-4-hydroxybenzoates. The alkyl p-hydroxybenzoates were treated with iodine (2 g. mol.) and potassium iodate ($\frac{1}{2}$ g. mol.) in aqueous ethanol as described by Sheahan *et al.* (1951). By this means the following esters were prepared:

isoButyl 3:5-diiodo-4-hydroxybenzoate, which crystallized from ethanol in colourless needles, m.p. 149°. (Found: C, 29.3; H, 2.7; I, 56.3. $C_{11}H_{12}O_4I_2$ requires C, 29.6; H, 2.7; I, 57.0%.)

sec.-Butyl 3:5-diiodo-4-hydroxybenzoate. Colourless plates

from 90% ethanol, m.p. 111°. (Found: C, 29.0; H, 2.8; I, 56.2. $C_{11}H_{12}O_4I_2$ requires C, 29.6; H, 2.7; I, 57.0%.)

isoAmyl 3:5-diiodo-4-hydroxybenzoate. Colourless needles from aqueous methanol, m.p. 98–100°. (Found: C, 30.6; H, 3.1; I, 55.2. $C_{13}H_{14}O_4I_2$ requires C, 31.3; H, 3.1; I, 55.2%.)

2-Ethylbutyl 3:5-diiodo-4-hydroxybenzoate. Colourless plates, m.p. 69–70°, from light petroleum (b.p. 60–80°). (Found: C, 33.0; H, 3.5; I, 52.5. $C_{13}H_{18}O_4I_2$ requires C, 32.9; H, 3.5; I, 53.6%.)

3:5-Diiodo-4-phenoxybenzoic acid and its methyl and n-butyl esters were provided through the courtesy of Glaxo Laboratories Ltd.

Methods of testing

The compounds were tested for antithyroxine activity in mice by the oxygen-consumption method of MacLagan & Sheahan (1950) with the improvements described by Sheahan *et al.* (1951).

RESULTS

The effects of ether formation on the antithyroxine properties of 3:5-diiodo-4-hydroxybenzoic acid are shown in Fig. 1. The methyl, ethyl and n-propyl ethers were slightly more active than the hydroxy acid and equalled the activity of the benzyl ether. The phenyl ether, however, proved the most active of the series, producing a significant reduction of the thyroxine effect at a total dose of 100 mg./kg.

Table 1. *The antithyroxine effects of esters of 3:5-diiodo-4-alkoxybenzoic acids*

Compound	Total dosage (mg./kg.) which produced	
	Significant response*	No response
$CH_3O-C_6H_2(I)_2-COOR,$	R = H CH ₃ C ₂ H ₅ n-C ₃ H ₇ n-C ₄ H ₉	400 (69%) — 100 (48%) — — 200 400 50 400 400
$C_2H_5O-C_6H_2(I)_2-COOR,$	R = H CH ₃ C ₂ H ₅ n-C ₃ H ₇	400 (77%) 400 (25%) 50 (32%) — 200 200 25 400
$n-C_3H_7O-C_6H_2(I)_2-COOR,$	R = H CH ₃ C ₂ H ₅	400 (53%) 1000 (32%) — 200 400 1000
$Ph-CH_2O-C_6H_2(I)_2-COOR,$	R = H CH ₃ C ₂ H ₅	400 (45%) 1000 (64%) 1000 (68%) 200 400 400
$Ph-O-C_6H_2(I)_2-COOR,$	R = H CH ₃ n-C ₄ H ₉	100 (26%) — — 50 400 400

* The figures in brackets indicate the percentage inhibition of the thyroxine effect at the stated dose. The figures were subjected to statistical analysis by 'Student's' *t* test.

Table 1 shows the results obtained when esters of the alkoxy acids were tested. They suggest that the optimal length of hydrocarbon chain associated with

Fig. 1. Antithyroxine effect of a series of ethers of 3:5-diiodo-4-hydroxybenzoic acid.

3:5-diiodo-4-hydroxybenzoic acid is from three to five carbon atoms, which may be in one chain as in the *n*-butyl ester, or in more than one, as in ethyl 3:5-diiodo-4-ethoxybenzoate. This suggests that in this series, a partition effect is involved in the mechanism of the antithyroxine action, but we have not yet completed this aspect of our study. In the case of the methoxy and ethoxy acids, a maximum antithyroxine effect was observed with the ethyl ester, but the esters of the *n*-propoxy, phenoxy and benzyloxy acids were less active than the free acids.

It is noteworthy that in no case was the activity of the alkoxy esters comparable with that of the hydroxy benzoates. It would therefore appear that, assuming some competitive antagonism is exerted against thyroxine, the group

is more effective than

Some acyl derivatives of the active alkyl diiodo-4-hydroxybenzoates were also tested. A number of *O*-acyl substituents in the *n*-butyl ester caused a marked diminution in activity (Fig. 2) whilst the *O*-acetyl derivative of the methyl ester was quite inactive at 400 mg./kg.

A number of branched-chain esters of 3:5-diiodo-4-hydroxybenzoic acid, related to the highly active *n*-butyl ester, were also examined, but their activities were much lower than the isomeric straight-chain compounds (Fig. 3).

Fig. 2. Antithyroxine effect of acyl derivatives of *n*-butyl 3:5-diiodo-4-hydroxybenzoate.

Fig. 3. Antithyroxine effect of branched-chain esters of 3:5-diiodo-4-hydroxybenzoic acid.

3:5-Diiodo-4-methoxybenzonitrile produced a significant reduction of the thyroxine effect at a total dose of 1000 mg./kg., but was inactive at 400 mg./kg. 3:5-Diiodo-4-*n*-propoxybenzonitrile and the corresponding benzamide, however, were inactive at 1000 and 400 mg./kg. respectively.

SUMMARY

1. A series of fifteen 3:5-diiodo-4-alkoxybenzoic acids and their esters has been tested for antithyroxine activity by the oxygen consumption method in mice, but all were markedly inferior to *n*-butyl 3:5-diiodo-4-hydroxybenzoate.

2. Four branched-chain alkyl esters of 3:5-diiodo-4-hydroxybenzoic acid were found to be much less active than the straight-chain esters.

3. 3:5-Diiodo-4-methoxybenzonitrile exerted slight antithyroxine activity, but 3:5-diiodo-4-*n*-propoxybenzonitrile and the corresponding benzamide were inactive.

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The Biological Action of Substances Related to Thyroxine

3. SUBSTANCES DERIVED FROM 3:5-DIODO-4-HYDROXYBENZALDEHYDE AND RELATED COMPOUNDS

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The dimethylacetal of 3:5-diiodoanisaldehyde (Wilkinson, 1949) was shown by MacLagan, Sheahan & Wilkinson (1949) to exhibit an antithyroxine action when tested in mice by the oxygen-consumption method (MacLagan & Sheahan, 1950). This effect was only produced at a total dosage of 1000 mg./kg. and it was the object of the work described in the present communication to survey a series of related compounds in the hope of finding more effective substances. Frieden & Winzler (1949) have shown that 3:5-diiodo-4-benzyloxybenzoic acid was active by the amphibian-metamorphosis test, a result we have confirmed in mice by the oxygen-consumption test (Wilkinson, Sheahan & MacLagan, 1951). Accordingly, we decided to examine the benzyl ether of 3:5-diiodo-4-hydroxybenzaldehyde and its dimethylacetal, but as frequently occurs when two supposedly active groups are combined in one compound, the products had no pharmacological action. We therefore turned our attention to a more systematic study of derivatives of a series of ethers of 3:5-diiodo-4-hydroxybenzaldehyde and related substances.

The ethyl and benzyl ethers of the hydroxy aldehyde were obtained by the methods used for the preparation of the corresponding ethers of the diiodohydroxybenzoates (Wilkinson *et al.* 1951). The ethyl ether was characterized as its oxime and

dimethyl acetal, and the benzyl derivative was converted into its dimethyl acetal by the usual procedure. By similar means 3:5-diiodo-2-methoxybenzaldehyde and its dimethyl acetal were prepared from 3:5-diiodosalicylaldehyde. Some esters of 3:5-diiodo-4-hydroxybenzaldehyde were obtained by standard methods and some of these were readily converted into the corresponding acetals.

In order to determine whether mono-iodo substituted compounds were likely to be of any interest we prepared 5-iodovanillin and 5-iodoveratraldehyde. The latter was obtained by the methylation of the former by the method of Kalb, Schweizer, Zellner & Barthold (1926) using a large excess of methyl sulphate. Less drastic conditions failed to produce more than a trace of the required veratraldehyde.

EXPERIMENTAL

Chemical methods

Micro-analyses were by Drs Weiler and Strauss, Oxford. All melting points are uncorrected.

The following new derivatives of 3:5-diiodoanisaldehyde are reported:

Oxime. Colourless needles, m.p. 153°, from benzene. Highly soluble in most organic solvents, except light petroleum. (Found: C, 24.0; H, 1.7; I, 62.8. $C_9H_7O_2NI_2$ requires C, 23.8; H, 1.8; I, 63.1%.)