were poured into a mixture of ice and 20% hydrochloric acid. After the ice had melted, the fluorescent organic layer was washed with 10% sodium bicarbonate solution, then with water, and dried over magnesium sulfate. The ether was distilled, and the residue was recrystallized twice from absolute ethanol to give intensely yellow crystals, m.p. 118–119°. The yield was 2.94 g. (43%). The infrared spectrum[6] of this material shows no bands for carbonyl or hydroxyl groups. The only significant band, besides those usually ascribed to a methyl group or a substituted benzene ring, appears at 1150 cm.$^{-1}$, and may be assigned to an ether linkage.[7]

Anal.[8] Calcd. for $C_{24}H_{22}O$: C, 88.31; H, 6.79. Found: C, 88.19; H, 6.73.

Treatment of o-duroylphenylphenylcarbinol with acid. A solution of 600 mg. (1.7 mmoles) of *o*-duroylphenylphenylcarbinol in 100 ml. of ether was shaken in a separatory funnel with an equal volume of 40% hydrochloric acid. The ether layer was washed with sodium bicarbonate solution, then with water, and dried over magnesium sulfate; the ether was removed on the concentrator. The yellow residue was recrystallized twice from absolute ethanol with Darco decolorization to give 450 mg. (83%) of 1-duryl-3-phenylisobenzofuran, m.p. 118–119°.

1-Duryl-3-(2-methoxyphenyl)isobenzofuran. To a solution of *o*-duroylphenyllithium in ether at −30° to −35°, prepared from 2.54 g. (0.008 mole) of *o*-duroylbromobenzene and 9.20 ml. of 0.87*N* *n*-butyllithium solution, was added all at once a solution of 1.09 g. (0.008 mole) of *o*-methoxybenzaldehyde in 15 ml. of dry ether. The resultant yellow-green reaction mixture was subsequently treated as in the procedure involving benzaldehyde. The yield was 0.86 g. (30%); the analytical sample melted at 127–128°. The infrared spectrum of this material is almost identical with that of 1-duryl-3-phenylisobenzofuran.

Anal. Calcd. for $C_{25}H_{24}O_2$: C, 84.23; H, 6.78. Found: C, 84.12; H, 6.69.

1-Duryl-3-(4-methoxyphenyl)isobenzofuran. By the method described in the preceding example, 1.09 g. (0.008 mole) of *p*-methoxybenzaldehyde was condensed with *o*-duroylphenyllithium; the lithium reagent was prepared from 2.54 g. (0.008 mole) of *o*-duroylbromobenzene and 9.41 ml. of 0.85*N* *n*-butyllithium solution, yield 1.05 g. (33%), m.p. 123–124°. The infrared spectrum was almost superimposable on that of 1-duryl-3-(2-methoxyphenyl)isobenzofuran.

Anal. Calcd. for $C_{25}H_{24}O_2$: C, 84.23; H, 6.78. Found: C, 84.10; H, 6.70.

1-Duryl-3-(2-chlorophenyl)isobenzofuran. A solution of 1.12 g. (0.008 mole) of *o*-chlorobenzaldehyde in 10 ml. of dry ether was added to an ethereal solution of *o*-duroylphenyllithium at −30° to −35°, prepared from 2.54 g. (0.008 mole) of *o*-duroylbromobenzene and 10.4 ml. of 0.75*N* *n*-butyllithium solution. The reaction mixture was treated as in the preceding example, yield 1.15 g. (40%); the pure compound melted at 131–132°. The spectral data are similar to those of the preceding examples.

Anal. Calcd. for $C_{24}H_{21}OCl$: C, 79.86; H, 5.88. Found: C, 80.01; H, 5.80.

1-Duryl-3-(4-chlorophenyl)isobenzofuran. A solution of *o*-duroylphenyllithium at −30° to −35° was prepared from 2.54 g. (0.008 mole) of *o*-duroylbromobenzene and 10.3 ml. of 0.78*N* *n*-butyllithium solution. The lithium reagent was condensed with *p*-chlorobenzaldehyde by the method described for *o*-chlorobenzaldehyde, yield 1.19 g. (41%); m.p. 129–130°. The infrared spectrum is almost superimposable on that of 1-duryl-3-(2-chlorophenyl)isobenzofuran.

Anal. Calcd. for $C_{24}H_{21}OCl$: C, 79.86; H, 5.88. Found: C, 79.71; H, 5.81.

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(6) The infrared spectra were determined by Mr. James Brader, Mr. Paul McMahan, Mrs. Mary Verkade, and Miss Charlene Leubke.

(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1958.

(8) The microanalyses were performed by Mr. Josef Nemeth, Miss Claire Higham, and Miss Jane Liu.

3-(*p*-Methoxyphenoxy)-2,6-dinitrobenzaldehyde and Two of Its Derivatives

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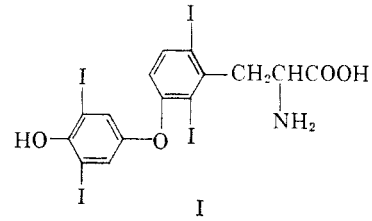
The present work was started for the purpose of testing the feasibility of the synthesis of the thyroxine analog (I) by starting with commercially available *m*-hydroxybenzaldehyde. The project will not be completed, but several intermediate nitro compounds have been prepared and it seems possible that the entire synthesis could be accomplished.



Two isomeric 3-hydroxydinitrobenzaldehydes, *viz.* 3-hydroxy-2,6-dinitrobenzaldehyde and 3-hydroxy-4,6-dinitrobenzaldehyde were prepared according to Hodgson and Beard[1] by nitration of 3-hydroxy-6-nitrobenzaldehyde.[2] It was advantageous to separate these two isomers by chromatography on Magnesol[3] rather than by fractional crystallization.

The reaction of *p*-toluenesulfonyl chloride with 3-hydroxy-2,6-dinitrobenzaldehyde yielded 3-(*p*-toluenesulfonyloxy)-2,6-dinitrobenzaldehyde which reacted with *p*-methoxyphenol in pyridine[4] to produce 3-(*p*-methoxyphenoxy)-2,6-dinitrobenzaldehyde. Reduction with aluminum isopropoxide gave 3-(*p*-methoxyphenoxy)-2,6-dinitrobenzyl alcohol. An attempt to prepare this compound by reaction of 3-(*p*-toluenesulfonyloxy)-2,6-dinitrobenzyl alcohol with *p*-methoxyphenol in pyridine was unsuccessful. Phosphorus pentachloride con-

* Deceased.

(1) H. H. Hodgson and H. G. Beard, *J. Chem. Soc.*, 2375 (1927).

(2) R. Pschorr, *Ber.*, **34**, 4000 (1901); P. Friedlaender and O. Schench, *Ber.*, **47**, 3043 (1914).

(3) J. C. Colbert, D. W. Fox, and C. Matuszak, *J. Am. Chem. Soc.*, **77**, 2447 (1955).

(4) *Cf.* E. T. Burrows, J. C. Clayton, B. A. Hems, and A. G. Long, *J. Chem. Soc.*, S190 (1949).

verted the 3-(*p*-methoxyphenoxy)-2,6-dinitrobenzyl alcohol to 3-(*p*-methoxyphenoxy)-2,6-dinitrobenzyl chloride. Reaction with sodium ethyl acetamidomalonate, followed by treatment with acid, would be expected to produce β-(3-*p*-methoxyphenoxy-2,6-dinitrophenyl)-DL-alanine.[5] Reduction of the nitro groups of this amino acid to amino groups might result in the formation of a hydrocarbostyril[6] derivative, but substitution of iodine atoms for the two nitro groups probably could be accomplished by starting with the hydantoin[7] derived from β-(3-*p*-methoxyphenoxy-2,6-dinitrophenyl)-DL-alanine. In this connection some tests were started with the related compound, β-(3-hydroxy - 4,6 - dinitrophenyl) - DL - alanine which readily yielded 5-(3-hydroxy-4,6-dinitrobenzyl)hydantoin by successive treatment with potassium cyanate and hydrochloric acid.

EXPERIMENTAL

3-Hydroxy-2,6-dinitrobenzaldehyde. 3-Hydroxy-6-nitrobenzaldehyde (15 g., 0.09 mole) was nitrated according to Hodgson and Beard[1] to produce a mixture (13.5 g.) of 3-hydroxy-2,6-dinitrobenzaldehyde and 3-hydroxy-4,6-dinitrobenzaldehyde along with some unchanged 3-hydroxy-6-nitrobenzaldehyde. The mixture was, for the most part, dissolved in 290 ml. of boiling benzene and the solution was left overnight at 25° to deposit 2.4 g. of crystalline 3-hydroxy-6-nitrobenzaldehyde. The filtrate was passed, with gentle suction, through a Magnesol-Hyflo Super-Cel column (20 × 3 cm.) prepared from a suspension of 32 g. of Magnesol[8] and 6.5 g. of Hyflo Super-Cel[9] in benzene. The column was eluted first with 800 ml. of benzene and then with 900 ml. of a 1% acetic acid solution in benzene. The first eluate was combined with the original benzene solution which had passed through the column. This solution was treated with a little acetic acid to liberate the phenolic compounds from any salts[3] that might be present, and the solvent was evaporated *in vacuo*; some benzene was added and evaporated *in vacuo* to remove acetic acid. The residual crystals (4.7 g.) appeared to be a mixture, as they could not be recrystallized readily from aqueous ethanol. The aqueous ethanol was removed and the substance was rechromatographed as described below. The second eluate was treated with a little acetic acid and the solvent was evaporated *in vacuo*; some benzene was added and evaporated *in vacuo*. The crystalline residue (6.05 g.) upon recrystallization from aqueous ethanol afforded in two crops 3.8 g. of needles melting at 90–92°, not depressed when mixed with crystals of 3-hydroxy-2,6-dinitrobenzaldehyde (m.p. 94–95°) which had been purified by fractional recrystallization of the mixed nitration products from water and from aqueous ethanol. The mother liquor from the recrystallization of the 6.05 g. was evaporated *in vacuo* and the residue was combined with the above 4.7 g. of crystals for rechromatography.

A solution of the substance in 100 ml. of benzene was passed through a Magnesol-Hyflo Super-Cel column prepared with 20 g. of Magnesol and 4 g. of Hyflo Super-Cel. The column was eluted first with 500 ml. of benzene. This eluate was combined with the original benzene solution which had passed through the column; a little acetic acid was added and the solvent was evaporated *in vacuo*. The crystalline residue has not yet been identified, but presumably consists largely of 3-hydroxy-4,6-dinitrobenzaldehyde. The column was then eluted with 500 ml. of a 1% acetic acid solution in benzene. This eluate was treated with a little acetic acid and the solvent was evaporated *in vacuo*; some benzene was added and evaporated *in vacuo*. The residue upon recrystallization from aqueous ethanol yielded in two crops 1.5 g. of 3-hydroxy-2,6-dinitrobenzaldehyde melting at 88–91°, making the yield of this compound 5.3 g. or 33% calculated on the 3-hydroxy-6-nitrobenzaldehyde that reacted.

In the course of the separation of the isomers of 3-hydroxydinitrobenzaldehyde by fractional recrystallization of the mixed products of nitration of 3-hydroxy-6-nitrobenzaldehyde from water and from aqueous ethanol, crystals of 3-hydroxy-2,6-dinitrobenzaldehyde melting at 110–111° (corr.) were isolated on one occasion. A final recrystallization from water and drying in an evacuated desiccator over calcium chloride did not change the melting point.

Anal. Calcd. for $C_7H_4N_2O_6$: C, 39.63; H, 1.90; N, 13.21. Found (dried at 57° *in vacuo*): C, 39.50; H, 1.99; N, 13.37.

The *p*-nitrophenylhydrazone prepared from the crystals melting at 110–111° was recrystallized by dissolving it in hot glacial acetic acid, cooling the solution to 25° and adding water to turbidity. The air-dried, red crystals exploded at 247–248°. The *p*-nitrophenylhydrazone prepared from crystals of 3-hydroxy-2,6-dinitrobenzaldehyde melting at 94–95° exploded at 248°. Hodgson and Beard[1] reported a melting point of 94° for 3-hydroxy-2,6-dinitrobenzaldehyde and an explosion point of 240–242° for its *p*-nitrophenylhydrazone.

Anal. Calcd. for $C_{13}H_9N_5O_7$: N, 20.17. Found (dried at 80° *in vacuo*): N, 19.85.

3-(p-Toluenesulfonyloxy)-2,6-dinitrobenzaldehyde. A mixture of 1.5 g. (7.1 mmoles) of 3-hydroxy-2,6-dinitrobenzaldehyde and 1.47 g. (7.7 mmoles) of *p*-toluenesulfonyl chloride was dissolved in 45 ml. of acetone. The solution was treated with 1.8 ml. of 1.92*N* sodium hydroxide, refluxed for 30 min., then treated with 1.8 ml. of 1.92*N* sodium hydroxide and again refluxed for 30 min. The solution was decanted from some crystals of sodium chloride and the solvent was evaporated at 25° *in vacuo*. A solution of the residue in ethyl acetate was extracted once with 10% sodium carbonate solution, then washed with water and dried over anhydrous sodium sulfate. After filtration the solvent was evaporated *in vacuo* to deposit crystals, which were purified from a mixture of benzene and *n*-hexane; yield 1.85 g. or 71%; m.p. 125–127° (corr.).

Anal. Calcd. for $C_{14}H_{10}N_2O_8S$: C, 45.90; H, 2.75; N, 7.65. Found (dried at 55° *in vacuo*): C, 46.15; H, 2.90; N, 7.72.

3-(p-Methoxyphenoxy)-2,6-dinitrobenzaldehyde. To a mixture of 1.85 g. (5 mmoles) of 3-(*p*-toluenesulfonyloxy)-2,6-dinitrobenzaldehyde and 2.5 g. (20 mmoles) of *p*-methoxyphenol was added 10 ml. of anhydrous pyridine. The crystals dissolved when the mixture was shaken for a few minutes at room temperature and the solution then was shaken on a machine at 26–28° for 22 hr. The solution was diluted with 125 ml. of chloroform, then washed twice with 75 ml. portions of 5% hydrochloric acid, once with 45 ml. of *N* sodium hydroxide, then with 15 ml. of 5% hydrochloric acid, and finally with 25 ml. of water. After being dried over anhydrous sodium sulfate, the chloroform solution was treated with Norit and the solvent was evaporated *in vacuo* (bath 40–45°). The residual sirup crystallized from its concentrated solution in absolute ethanol, 0.384 g. or 24% of yellow crystals melting at 126–129° being obtained as the first

(5) *Cf.* E. L. Jackson, *J. Am. Chem. Soc.*, **79**, 2912 (1957).

(6) E. L. Jackson, *J. Am. Chem. Soc.*, **77**, 4860 (1955).

(7) *Cf.* E. T. Borrows, J. C. Clayton, and B. A. Hems, *J. Chem. Soc.*, S199 (1949); J. R. Chalmers, G. T. Dickson, J. Elks, and B. A. Hems, *J. Chem. Soc.*, 3424 (1949).

(8) A synthetic magnesium silicate obtained from the Westvaco Chlor-alkali Division of the Food Machinery and Chemical Corporation, South Charleston, W. Va. The "industrial regular" grade was used.

(9) A diatomaceous filter aid obtained from Johns-Manville, Baltimore, Md.

crop. A second crop (67 mg., 4%) melting at 115–118° was isolated from the filtrate. The analytical sample was purified from absolute ethanol and dried in an evacuated desiccator over calcium chloride; m.p. 130–131° (corr.).

Anal. Calcd. for $C_{14}H_{10}N_2O_7$: C, 52.83; H, 3.17; N, 8.80. Found: C, 53.04; H, 3.27; N, 8.45.

Crystals of a pyridinium salt sometimes separated during the reaction of 3-(*p*-toluenesulfonyloxy)-2,6-dinitrobenzaldehyde and *p*-methoxyphenol in dry pyridine, but upon continuation of the shaking or stirring the crystals dissolved slowly to produce 3-(*p*-methoxyphenoxy)-2,6-dinitrobenzaldehyde. The pyridinium salt was prepared readily from 3-(*p*-toluenesulfonyloxy)-2,6-dinitrobenzaldehyde and pyridine. A solution of 64 mg. (0.17 mmole) of 3-(*p*-toluenesulfonyloxy)-2,6-dinitrobenzaldehyde in 0.1 ml. of dry pyridine was stirred by hand at room temperature. After a few minutes a mass of crystals separated and after 25 min., 1.5 ml. of chloroform was added. The crystals were collected, washed with chloroform and dried in an evacuated desiccator over calcium chloride; yield 56 mg. or 72% m.p. 221–223° dec. (uncorr.).

Anal. Calcd. for $C_{19}H_{15}N_3O_8S$: N, 9.44. Found: N, 9.30.

3-(p-Methoxyphenoxy)-2,6-dinitrobenzyl alcohol. To a solution of 0.36 g. (1.1 mmoles) of 3-(*p*-methoxyphenoxy)-2,6-dinitrobenzaldehyde in 7.5 ml. of warm anhydrous toluene was added 0.42 ml. of an approximately 1.4*M* solution of aluminum isopropoxide in anhydrous 2-propanol. The procedure for reduction of the aldehyde was then the same as described[5] previously for the reduction of 3-methoxy-2,6-dinitrobenzaldehyde. After evaporation of residual solvent *in vacuo*, the residue was mixed with 25 ml. of 2% hydrochloric acid which produced a sirup. The mixture was extracted thrice with benzene and then thrice with ethyl acetate. The solutions were dried over anhydrous sodium sulfate, combined, and the solvents were evaporated *in vacuo*. The residual sirup was taken up in 2-propanol, the solution was concentrated at room temperature to a thin sirup and seeded with crystals of 3-(*p*-methoxyphenoxy)-2,6-dinitrobenzyl alcohol.[10] Well-formed prisms separated slowly, 183 mg. melting at 83–86° being obtained in the first crop. The filtrate was evaporated to dryness at 25°, some benzene was added and evaporated. A solution of the residual sirup in 5 ml. of benzene was passed through a column (7 × 1 cm.) of activated alumina which was then washed with 5 ml. of benzene. The column was eluted first with 25 ml. of ethyl ether, then with 35 ml. of chloroform (containing 0.8% ethanol), and finally with 15 ml. of acetone. The benzene solution, which had passed through the column, was combined with the ether and acetone eluates and the solvents were evaporated. A solution of the residual sirup in 5 ml. of benzene was passed through a short, activated alumina column which was washed first with 3 ml. of benzene and then with 4 ml. of ether. The column then was eluated with 30 ml. of chloroform and this solution was combined with the chloroform eluate from the first chromatography. Evaporation of the chloroform left a sirup which, upon crystallization from 2-propanol, gave 72 mg. melting at 84–86° (uncorr.), making the total yield 70%. The analytical sample was dried in an evacuated desiccator over calcium chloride.

Anal. Calcd. for $C_{14}H_{12}N_2O_7$: C, 52.50; H, 3.78; N, 8.75. Found: C, 52.80; H, 3.80; N, 8.09.

3-(p-Toluenesulfonyloxy)-2,6-dinitrobenzyl alcohol. The reduction of 0.5 g. (1.4 mmoles) of 3-(*p*-toluenesulfonyloxy)-2,6-dinitrobenzaldehyde was carried out essentially as described for the reduction of 3-(*p*-methoxyphenoxy)-2,6-dinitrobenzaldehyde, using 8 ml. of anhydrous toluene and 0.46 ml. of 1.4*M* solution of aluminum isopropoxide in anhydrous 2-propanol. The solvent then was evaporated *in vacuo*. The residue was mixed with 12 ml. of 5% hydrochloric acid, the suspended solid was collected, washed with water, and purified from absolute ethanol; m.p. 154–156° (corr.); yield 367 mg. or 73%.

Anal. Calcd. for $C_{14}H_{12}N_2O_8S$: C, 45.65; H, 3.29; N, 7.61. Found (dried at 79° *in vacuo*): C, 45.69; H, 3.50; N, 7.32.

3-(p-Methoxyphenoxy)-2,6-dinitrobenzyl chloride. A solution of 60 mg. (0.19 mmole) of 3-(*p*-methoxyphenoxy)-2,6-dinitrobenzyl alcohol in 1 ml. of dry, alcohol-free chloroform was cooled in ice-water and treated with 49 mg. (0.24 mmole) of phosphorus pentachloride. After the cold mixture had been shaken until all solid had dissolved, the solution was kept at room temperature for 2 hr. It was then diluted with 2 ml. of chloroform, washed once with water, four times with 5% sodium bicarbonate solution, and finally with water. After the solution had been dried over calcium chloride and filtered, the solvent was evaporated *in vacuo* (bath 40°). The residual sirup crystallized, after dissolution in benzene and removal of the solvent *in vacuo*. Recrystallization from a mixture of benzene and *n*-hexane gave as a first crop 37 mg. or 58% of yellow prisms melting at 115–117°. Another recrystallization from benzene raised the melting point to 120–121° (corr.). Although analytical data are not available, the method of preparation[5] of the compound would be expected to produce 3-(*p*-methoxyphenoxy)-2,6-dinitrobenzyl chloride.

5-(3-Hydroxy-4,6-dinitrobenzyl)hydantoin. To a suspension of 75 mg. (0.28 mmole) of β-(3-hydroxy-4,6-dinitrophenyl)-D,L-alanine in 0.8 ml. of water was added 60 mg. of potassium cyanate. After the mixture had been boiled under reflux for 15 min., 50 mg. of potassium cyanate was added; the red solution was refluxed for 15 min., then treated with 50 mg. of potassium cyanate and refluxed for an additional 15 min. To the solution, at room temperature, was added dropwise 0.5 ml. of 37% hydrochloric acid which precipitated some solid. The mixture was refluxed for 1 hr. and then cooled in ice water for 20 min. The brown solid was collected, washed with a little water, and air-dried; yield 72 mg. (88%) melting at 245° dec. The compound can be recrystallized from much water as small, short needles. The analytical sample was obtained by extracting the crude product repeatedly with a boiling mixture of 2-propanol and ethanol, and finally concentrating the filtered solution to a small volume. The yellow crystals melted at 253° dec. (corr.; bath preheated to 225°).

Anal. Calcd. for $C_{10}H_8N_4O_7$: C, 40.55; H, 2.72. Found: 40.41; H, 2.84.

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(10) The first crystals of this compound were obtained previously by passing a benzene solution of the crude sirup through a short column of activated alumina, eluting as described below and crystallizing the sirup from aqueous ethanol.

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