

SYNTHESIS OF 2,3-DIHYDROXYBENZOIC ACID - (CARBOXYL-¹⁴C)

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SUMMARY

2,3-Dihydroxybenzoic acid-(carboxyl-¹⁴C) can be synthesized in high overall yield from commercially-available 2,3-dimethoxybenzoic acid. The synthetic route features the application of a Curtius rearrangement, the thermal decomposition of a carboxylic acid azide to an isocyanate. The method is suitable for the preparation of the title compound on both micro and semimicro scales.

Key Words: 2,3-Dihydroxybenzoic Acid, Carbon-14

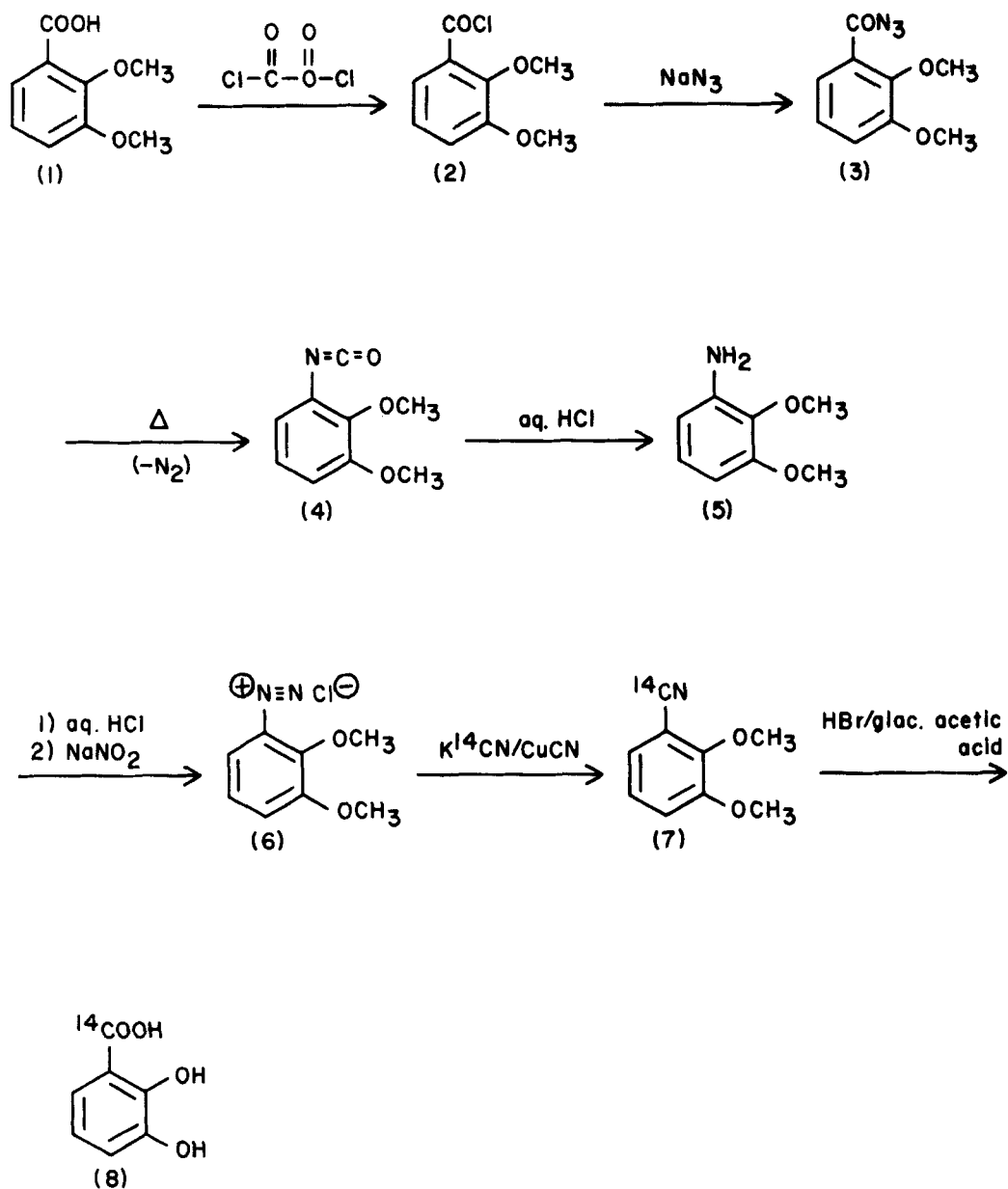
INTRODUCTION

2,3-Dihydroxybenzoic acid is an orally-effective and specific iron-chelating agent, with which the quantity of iron that is excreted is a function both dose and time^(1,2). In this communication, the synthesis, in good yield, of 2,3-dihydroxybenzoic acid (carboxyl-¹⁴C), a ¹⁴C-labelled analog that should be of value in metabolic studies of the mechanisms of iron excretion, is described.

DISCUSSION

The synthetic route to 2,3-dihydroxybenzoic acid-(carboxyl ^{14}C) is shown in Scheme 1.

SCHEME 1.



The starting material, 2,3-dimethoxybenzoic acid (1) is commercially available. Conversion of the starting material to the corresponding isocyanate (4) was effected, in high yield, by Curtius rearrangement⁽³⁾ of the intermediate azide (3). The azide (3) was readily prepared by treatment of the acid chloride (2) with aqueous sodium azide. The isocyanate (4) was converted to 2,3-dimethoxyaniline (5) by acid-catalyzed hydrolysis. Diazotization of the aniline (5) and subsequent treatment of the resulting diazonium salt (6) with cuprous cyanide/potassium cyanide- ^{14}C yielded the labelled benzonitrile (7)⁽⁴⁾. Simultaneous hydrolysis of the nitrile group and demethylation of the methoxy groups with hydrobromic acid/glacial acetic acid afforded ^{14}C -labelled 2,3-dihydroxybenzoic acid (8) in good overall yield.

EXPERIMENTAL

Materials--2,3-Dimethoxybenzoic acid, unlabelled 2,3-dihydroxybenzoic acid, and various organic solvents were purchased from Aldrich Chemical Company, Inc., Milwaukee, Wisconsin. Potassium cyanide- ^{14}C was a product of Rosechem, Los Angeles, California. Other inorganic compounds were obtained either from the Alfa Division of Ventron Corporation, Danvers, Massachusetts, or J. T. Baker Chemical Company, Phillipsburg, New Jersey. Radioactivity disintegrations were measured with a Unilux III liquid scintillation system manufactured by Nuclear Chicago, Chicago, Illinois. Thin layer radiochromatograms were generated with a Berthold radioscaner Model LB2723, purchased from Varian Aerograph, Walnut Creek, California. Thin layer plates, etc. were all products of the Applied Science Division, Laboratory Group, Milton Roy Company.

2,3-Dimethoxybenzoisocyanate (4) -- 2,3-Dimethoxybenzoic acid (1) (1.82 g, 10 mmol) was dissolved in dry benzene (10 ml). To this solution was slowly added, with stirring in an atmosphere of dry nitrogen, oxalyl chloride (1.51 g, 12 mmol). The mixture was then heated to boiling and was boiled under reflux for 1 hr. The solvent was evaporated (rotary evaporator, water aspiration vacuum) from the cooled reaction mixture to yield 2 g (100% yield) of crude 2,3-dimethoxybenzoyl chloride (2). A solution of crude 2,3-dimethoxybenzoyl chloride (2.0 g, 10 mmol) and acetone (10 ml) was then added to a cold (ice-water bath) stirred solution of sodium azide (780 mg, 12 mmol) and distilled water (10 ml). The addition was made at such a rate that the temperature of the reaction mixture remained between 10 and 15°C. When addition was complete, the mixture was allowed to come to room temperature, and was stirred for an additional 1 hr. The mixture was then extracted 3 x 10 ml benzene. The combined benzene extracts were heated at 60°C until evolution of a gas, presumably nitrogen, ceased, indicating conversion of the azide (3) to the corresponding isocyanate (4). The cooled reaction mixture was filtered, and the solvent was removed from the filtrate by distillation. The oily residue, 1.44 g, represented an 80% yield, based on 2,3-dimethoxybenzoic acid (1), of crude 2,3-dimethoxybenzoisocyanate (4).

2,3-Dimethoxyaniline (5) -- To crude 2,3-dimethoxybenzoisocyanate (4) (1.44 g, 8 mmol) was added 20% (wt/vol) hydrochloric acid (10 ml). The mixture was heated to boiling and was boiled under reflux for 3 hr. The cooled reaction mixture was then neutralized by the careful addition of 20% (wt/vol) aqueous sodium hydrogen carbonate. The neutralized solution was extracted 3 x 10 ml diethyl ether. The ether extract was dried over anhydrous sodium sulfate. Evaporation of the solvent from the dried extract gave 1.05 g (70% yield based on 2,3-dimethoxybenzoisocyanate) of crude 2,3-dimethoxyaniline (5).

2,3-Dimethoxybenzonitrile-(nitrile-¹⁴C) (7) -- Crude 2,3-dimethoxyaniline (5) (1.83 mg, 1.2 mmol) was dissolved in 20% (wt/vol) hydrochloric acid (5 ml). The resulting solution of 2,3-dimethoxyaniline hydrochloride was cooled to 10°C (ice-water bath), and a solution of sodium nitrile (105 mg, 1.5 mmol) and distilled water (3 ml) was slowly added. Thirty minutes after addition was completed, solid potassium carbonate was slowly added until the solution was neutral ($p^H \approx 7$) to pHydron[®] test paper. The solution of 2,3-dimethoxybenzene-diazonium hydrochloride (6) was then filtered to remove suspended solids. To the filtrate were added, successively, a solution of potassium cyanide-¹⁴C (65 mg, 1.0 mmol, 5 mCi/mmol) and distilled water (2 ml), and a solution of cuprous cyanide (136 mg, 0.4 mmol) and distilled water (2 ml). The mixture was allowed to warm to room temperature, then was heated at 40°C for 1 hr. The cooled reaction mixture was extracted 3 x 10 ml diethyl ether. The combined ether extracts were washed 3 x 5 ml distilled water and were then dried over anhydrous sodium sulfate. Evaporation of the solvent gave 114 mg (3.5 mmol at 5 mCi/mmol, 70% yield) of crude 2,3-dimethoxybenzonitrile-(nitrile-¹⁴C) (7).

2,3 Dihydroxybenzoic Acid-(carboxyl-¹⁴C) (8) -- A mixture of crude 2,3-dimethoxybenzonitrile-(nitrile-¹⁴C) (7) (114 mg), glacial acetic acid (3 ml) and constant-boiling hydrobromic acid (8 ml) was heated to boiling and was boiled under reflux for 5 hr. The reaction mixture was then allowed to cool to room temperature. The solvent was evaporated under reduced pressure. Distilled water (10 ml) was added to the residue, and the resulting mixture was extracted 4 x 10 ml diethyl ether. The combined ether extracts were washed 3 x 5 ml distilled water and were then dried over anhydrous sodium sulfate. Isolation and purification of 2,3-dihydroxybenzoic acid-(carboxyl-¹⁴C) (8) was effected by silicic gel column chromatography of the ether solution (30 g of 70/230 mesh

silica gel G in a 25 cm x 2.5 mm i.d. glass column; with petroleum ether 30°C-60°C b.p. was used for preparation of the column. Elution with 2 x 100 ml petroleum ether: diethyl ether 50:50 pulled the compound out of the column. Evaporation of solvent from the eluate gave 61.6 mg (2 mmol at 5 mCi/mmol, 40% yield based on potassium cyanide-¹⁴C) of 2,3-dihydroxybenzoic acid-(carboxyl-¹⁴C) (8). The material displayed chromatographic behavior identical to that of authentic unlabelled 2,3-dihydroxybenzoic acid. Thin layer radiochromatography showed no detectable radioactive impurities.

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