SYNTHESIS OF GALLIC ACID (-^{14}COOH)

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SUMMARY

A series of reactions was elaborated for the transformation of 1,2,3-trimethoxybenzene into gallic acid-$^{14}CO_2H$. The intermediate 1-bromo-3,4,5-trimethoxybenzene was prepared by nitration, reduction, diazotization, and decomposition of the diazonium salt in the presence of cuprous bromide. The halide-exchange reaction of the aryl bromide with butyl lithium, decomposition of the intermediate lithio derivative with $^{14}CO_2$, and demethylation, led to gallic acid-$^{14}CO_2H$.

Key Words: Gallic acid-^{14}COOH; semimicorsynthesis.

INTRODUCTION

In order to study the metabolism and distribution of various tannin-like compounds it was necessary to prepare selectively labelled gallic acid. With respect to the requirements for maintaining chemical and biological properties, it was possible to consider labelling with either ^{3}H or ^{14}C atoms. A method was devised for the synthesis of 3,4,5-trihydroxybenzoic acid -^{14}COOH, because labelling with tritium usually leads to non-specifically labeled products. The devised chemical sequence minimizes the number of reaction steps with radioactive material and incorporates readily available starting materials.

The intermediate 1-bromo-3,4,5-trimethoxybenzene cannot be

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prepared chemically pure (TLC and GLC) and in good yield, via the bromination of 1,2,3-trimethoxybenzene, 1,2,3-trihydroxybenzene or 1,3-dimethoxy-2-hydroxybenzene followed by selective debromination of the resulting polybromo derivatives to mono-bromo compounds, although these reactions are described in the literature (1,2). Bromination with pyridinium bromide perbromide or dioxane dibromide did not yield the desired product. The degradation of the silver salt of the acid according to the methods of Hunsdiecker (3) did not prove to be feasible.

Methods for the conversion of 3,4,5-trimethoxyaniline (4,5) into 1-halo or 1-cyano- 3,4,5-trimethoxybenzenes were found to be suitable procedures. Accordingly, diazotization of the aniline followed by cuprous halide (or cyanide) mediated decompositions of the intermediate diazonium salt provided high product yields. The reaction of 1-iodo-3,4,5-trimethoxybenzene with cuprous cyanide in dimethylformamide gave the nitrile in 80% yield. Galloylgallic acid can result by the reaction of imide ion with hydroxyl groups generated during demethylation, thus the nitrile was hydrolyzed in alkali medium and then the protecting methyl groups were removed with hydrogen iodide. A butyl lithium procedure was used for the synthesis of the labelled gallic acid because the preparation of $Cu^{14}CN$ results in a loss of activity at this stage.

The 1-bromo-3,4,5-trimethoxybenzene does not easily react with magnesium to form the Grignard compound. Halogen reduction and demethylation are observed when using highly active magnesium prepared by potassium metal reduction of magnesium salts. The halide-exchange reaction of the aryl bromide with butyl lithium in ether resulted in an intermediate lithio derivative. Subsequent reaction with $^{14}CO_2$, generated from $Ba^{14}CO_3$, provided the labelled gallic acid derivative.

Acidic demethylation reactions were complicated by the ready decarboxylation of the resulting gallic acid. Aluminium bromide, boron trifluoride, pyridinium hydrochloride, or an aqueous solution of hydrogen iodide were found to be unsuitable demethylation reagents. An 80% yield of demethylated product was obtained with 45% hydrogen iodide in acetic acid at the optimum thermal conditions.

EXPERIMENTAL

Preparation of non-radioactive compounds

1,2.3-Trimethoxybenzene II. Compound II was prepared by the reaction of pyrogallol (I) with dimethyl sulfate in alkaline medium (6). A 66% yield of product melting at 47°C was realized.

1-Nitro-3,4,5-methoxybenzene III. Compound III was obtained in accordance with the literature (4,7) by the nitration of II. Three recrystallizations from acetic acid provided a 42% yield of material melting at 100°C.

3,4,5-Trimethoxyaniline IV. A mixture of 10 g of III in 200 mL of acetic acid containing 2.5 g of 10% palladium on charcoal was hydrogenated at ambient tempreature and pressure. The theoretical absorption of hydrogen took place after 6 hrs. The catalyst was removed by filtration under an inert atmosphere and the solution was concentrated to a volume of 50 mL. After acidification with hydrochloric acid and dilution with 250 mL of diethyl ether, the crude product was collected. The weight of the hydrochloride of IV was 8,8 g (87%).

1-Bromo-3,4,5-trimethoxybenzene V. A suspension of 8,8 g of IV in 300 mL water and 100 mL 57% hydrobromic acid were heated on a water bath to 70°C. After cooling to -5°C with stirring, a solution of 20,7 g of sodium nitrite in 100 mL water was added. The mixture was stirred at -5°C for 15 min., excess nitrous acid was decomposed by the addition of urea until a negative test with potassium iodide-starch paper was observed. A cooled (0°C) freshly prepared solution of cuprous bromide (86.5 g in 250 mL of 57% hydrobromic acid) was added to the reaction mixture. Decomposition of the diazonium salt was carried out at 60 - 70°C until the evolution of nitrogen gas ceased. The reaction mixture was extracted with chloroform, washed with 10% sodium hydroxide, and dried over calcium chloride. Fractional distillation (147.5 - 149°C at 11 torr) and TLC of the distilate provided X g (74%) of material melting at 79 - 80°C.

A melting point of 78°C is recorded (1) for the product obtained via the methylation of 1,3-dimethoxy-2-hydroxy-5-bromobenzene.

Preparation of labelled derivatives

Trimethylgallic acid - ^{14}C VI. To a cooled (-5°C) and stirred solution of 1.00 g (4.04 mmol) of V in 30 mL of anhydrous ether, under a blanket of argon, was added 5 mL of 0.85 N butyl lithium in benzene (4.25 mmol). The resulting mixture was stirred at -5°C for 15 min and then the mixture was cooled to -75°C in a dry-ice ethanol bath. The reaction vessel was flushed with argon and evacuated. A mixture of 4 mL of concentrated sulfuric acid and 1.32 g (6.70 mmol) of powdered barium carbonate - ^{14}C (200 mCi, specific activity 30 mCi/mmol) in a 25 mL flask was heated to 120°C. The evolved gaseous carbon dioxide - ^{14}C was passed into the flask containing the stirred etheral solution of lithio compound. The cooling bath was removed and the reaction mixture was allowed to warm to ambient temperature over a time period of about one hour. The unreacted gaseous carbon dioxide - ^{14}C was bubbled through 50 mL of 30% barium hydroxide solution. The reaction mixture was treated with 30 mL of 10% NaOH solution. The aqueous layer was separated, acidified with sulfuric acid to pH 2.0, and the product was extracted with two 30 mL portions of ether. The combined etheral extracts were washed with water and dried over anhydrous magnesium sulfate. Evaporation under reduced pressure provided 0.41 g (1.94 mmol, 47.3 mCi) of crystalline, light yellow colored product melting at 167-9°C, for a 48% weight yield and a 23.6% activity yield. The specific activity of the crude material was 24.38 mCi/mmol. The purity of the trimethyl gallic acid - ^{14}C was checked by means of TLC (Silufol UV 254) by developing with benzene/methyl alcohol (95:5). Visualization of the TLC plate under ultraviolet light gave an R_f for the product VI of 0.7 and this spot contained 96.0% of the total activity in the chromatogram.

Gallic acid - ^{14}C VII. A mixture of 0.41 g (1.94 mmol, 47.3 mCi) of VI in 7 mL of glacial acetic acid (analytical grade) containing 7 mL of 57% hydrogen iodide solution (Merck, redistilled) was heated under reflux for 4 hrs. The reaction mixture was evaporated to dryness at 40°C under reduced pressure. The resulting brownish-black crystalline residue was triturated in 20 mL of water, the solids were filtered, and the water was evaporated under reduced pressure. This procedure was repeated two more times. The product had a light brown color and TLC showed only one spot after the third evaporation. The gallic acid prepared in this manner contained traces of iodine which made synthetic reactions impossible until further purification. The gallic acid - ^{14}C was recrystallized twice from 2 mL of water treating with charcoal, thus giving a yield of 0.080 g (0.47 mmol) of white colored product which had a ^{14}C activity of 11.5 mCi.

CONCLUSION

A method was elaborated for the semimicro synthesis of labelled gallic acid, - $^{14}CO_2H$. The purity of the final product was sufficient for biological testing as well as for continued synthetic elaboration. The labelled gallic acid was prepared in about 25% isotopic yield. The mass yield of the pure product was about 15% and the specific activity corresponded to the specific activity of the initial barium carbonate.

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