A NOVEL SYNTHESIS OF MALEIC ANHYDRIDE-1- AND -2-^{13}C AND ITS SUBSEQUENT CONVERSION TO LABELED MALEIC HYDRAZIDE

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SUMMARY

Maleic anhydride-1- and 2-^{13}C were synthesized respectively from the available aspartic acid-4- and -3-^{13}C by way of the corresponding bromosuccinic acids and their anhydrides. The maleic anhydrides were converted into 1,2-dihydro-3,6-pyridazinedione-3- and -4-^{13}C on treatment with aqueous hydrazine sulfate. Nitrogen-15 labeled 1,2-dihydro-3,6-pyridazinedione was obtained from the latter reaction using hydrazine-^{15}N sulfate.

Key Words: Aspartic acid, bromosuccinic anhydride, maleic anhydride, maleic hydrazide

INTRODUCTION

An investigation of the pyrolytic behavior of the growth regulator, maleic hydrazide, II, (1,2-dihydro-3,6-pyridazinedione) involved a determination of the fate of particular atoms in the pyrogenetic processes involved. For this study, the 3 and 4 positions of maleic hydrazide were labeled with carbon 13 and the nitrogens were labeled with nitrogen 15.

The synthetic sequence reported herein was determined by the availability of the labeled precursors - hydrazine sulfate and aspartic acid. The usual method for the synthesis of maleic hydrazide involves the interaction of maleic anhydride with hydrazine or one of its salts in water(1), ethanol(2) or acetic acid(3). Of the variations tested, the reaction of maleic anhydride with hydrazine sulfate in water (1:1 mole ratio) was the simplest reaction to run and gave the purest product in high yield.

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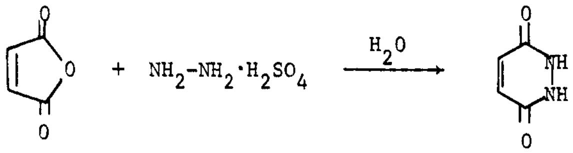
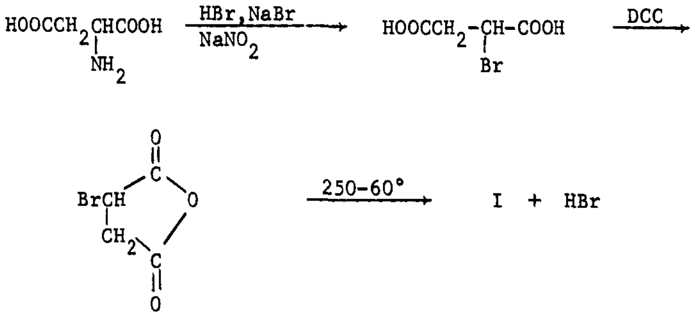


I II

The procedure utilized for the synthesis of maleic anhydride labeled at carbon 1 and carbon 2 from aspartic acid is outlined in Scheme 1.

DL-Bromosuccinic acid, obtained in high purity in over 90% yield by the diazotization of aspartic acid in an HBr-NaBr solution(4), was converted to the DL-bromosuccinic anhydride by treatment with N,N'-dicyclohexylcarbodiimide (DDC).

SCHEME 1



Pyrolytic dehydrobromination(5) of the crude anhydride (an oil) utilizing the controlled pyrolysis apparatus previously described(6) produced crystalline I of sufficient purity for the synthesis of maleic hydrazide. The overall yield of maleic hydrazide obtained from aspartic acid was ca. 55%.

The conversion of the bromosuccinic acid to the anhydride prior to the elimination of hydrogen bromide is essential because both the pyrolytic(7) and base-catalyzed(8) dehydrobrominations of bromosuccinic acid produce fumaric acid.

The report that fumaric acid can be transformed into maleic anhydride on heating$^{(9)}$ suggested that it might be possible to obtain I from bromosuccinic acid via fumaric acid in a single pyrolytic step. However, pyrolysis of bromosuccinic acid in the apparatus used above yielded only fumaric acid.

Preparation of maleic hydrazide-1,2-$^{15}N_2$ was achieved by treatment of maleic anhydride with hydrazine-$^{15}N_2$ sulfate. Benzalazine-$^{15}N_2$ was prepared from benzaldehyde and the labeled hydrazine sulfate as an additional means of determing isotopic content.

EXPERIMENTAL

DL-Bromosuccinic acid-4-^{13}C. The procedure is similar to that of Holmberg$^{(4)}$. To a stirred, ice-cooled solution of 1.01 g (7.52 mmol) _DL_-aspartic acid-4-^{13}C (90%-4-^{13}C, KOR Isotopes*) and 3.33 g sodium bromide in 7 ml 2N HBr, 0.93 g of pulverized sodium nitrite was added portionwise over a period of 1.75 hr. The mixture was stirred for an additional 15 min, 1.4 ml of 40% H_2SO_4 was added, and stirring and cooling continued for an additional 15 min. The resulting suspension was extracted with five 8-ml portions of ether and the combined reddish-brown extracts were dried ($MgSO_4$). Filtration and solvent removal yielded 1.40 g. (6.75 mmol, 94.1%) _DL_-bromosuccinic acid-4-^{13}C, mp 164-165°. The mp of an authentic sample was 163-165°.

Maleic Anhydride-1-^{13}C. To 686 mg (3.48 mmol) of _DL_-bromosuccinic acid-4-^{13}C dissolved in 8 ml of acetonitrile, a solution of 728 mg (3.53 mmol) of dicyclohexylcarbodiimide in 8 ml of acetonitrile was added. A white precipitate began to form almost immediately. After standing for 1 hr, the precipitate was removed by filtration and the solvent evaporated from the filtrate _in vacuo_. (Minor amounts of solvent remaining do not diminish the yield or quality of the final product). The resulting brownish oil was placed in a small tube which in turn was placed in the 168 x 1.1 cm (0.9 cm i.d.) quartz tube positioned horizontally in the pyrolysis apparatus$^{(6)}$. The movable oven, 5-cm long, surrounds a section

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of the tube and is driven along the pyrolysis tube by a variable speed pulley system. The oil was pyrolyzed at 250° using a He flow of 35 ml/min. (N_2 may be substituted for He), and furnace speed of 11-12 mm/min over a distance of 160 cm. The liquid which traveled to the end of the tube with the furnace solidified on cooling and, on removal, melted at 49-52° (mp of commercial maleic anhydride, 52-54°), and weighed 279 mg (2.84 mmol, 81.8%).

The product is usually white but occasinally contains brown-colored impurities. These may be removed by resubjecting the material to pyrolysis in a clean tube with almost complete recovery.

1,2-Dihydro-3,6-pyridazinedione-3-^{13}C. A mixture of 1.147 g (11.70 mmol) of maleic anhydride-1-^{13}C, 1.522 g (11.70 mmol) of hydrazine sulfate, and 11.8 ml of water was stirred and heated under reflux for 4 hr. After cooling in ice, filtering and washing successively with cold water (15 ml), absolute ethanol (3 ml) and ether (3 ml), there was obtained 1.027 g (9.17 mmol, 78.4%) of white crystalline product, mp 306-307°. In some experiments the product gives a positive test for hydrazine(10). Removal is readily accomplished by recrystallization from water.

A mass spectrum indicated that 90.7% of the product contained a ^{13}C label. Observation was made at the 112, 113 and 114 (P, P+1, P+2) peaks.

1,2-Dihydro-3,6-pyridazinedione-4-^{13}C. From 3.048 g (22.91 mmol) aspartic acid-3-^{13}C (90% 3-^{13}C, KOR Isotopes*) there was obtained 1.261 g (11.26 mmol, 49.1%) of product, mp 312-314°. A mass spectrum indicated that 90.9% of the product contained a ^{13}C label.

1,2-Dihydro-3,6-pyridazinedione-1,2-$^{15}N_2$. From 361 mg (3.68 mmol) maleic anhydride and 461 mg (3.54 mmol) hydrazine sulfate (97% $^{15}N_2$, Merck, Sharp and Dohme) there was obtained 341 mg (5.04 mmol, 85.8%) of product. Analysis of the mass spectrum in the parent peak region indicated that 92.6% of the molecules bore a $^{15}N_2$ label and 7.4% bore a ^{15}N label. This corresponds to the values obtained from the mass spectrum of benzalazine-$^{15}N_2$ prepared from benzaldehyde and hydrazine sulfate $^{15}N_2$. Analysis was made at the 131, 132, 133 and 134 $[Ph-CH=N-N=CH]^{+}$(11) peaks.

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