SYNTHESIS OF MONO AND DI METHYL TARTRATES

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SUMMARY

Procedures were developed to synthesize as easily and cheaply as possible various optically active tartaric acid methyl esters for use in studies of enzymatic hydrolysis. The compounds prepared were d and l dimethyl tartrate and l monomethyl tartrate free from diester. Purity was checked by chromatographic and melting point tests.

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Pure samples of optically active tartaric acid esters were required for studies of enzymatic hydrolysis. The required syntheses demanded procedures that could obtain complete esterification of both acid groups of tartaric acid to give diesters and procedures that would block one acid group to allow synthesis of monoesters.

For the sake of simplicity methyl esters were chosen for the hydrolysis study. Several standard techniques were tried in an attempt to obtain pure diesters. The addition of thionyl chloride to iced methanol-tartaric acid solutions failed to give a good yield of diester product. Most of the product was retained in the water phase in a water-chloroform separation. Acidic esterification and the use of methyl azide were ruled out as impractical. The method finally used was esterification of a methanol solution of tartaric acid with dimethyl sulfite at reflux for five hours.

The finished diester reaction mixture was stripped of solvent at aspirator pressure and then vacuum distilled at a pressure of 0.5 mm of mercury. The diester product distilled at 125^{0}-135^{0} Centigrade. The distillate was an oil which crystallized slowly at 0^{0} C. to give transparent rod-shaped crystals with a melting point range of 35^{0}-40^{0} C. The yield was decreased by slow decomposition of the mixture in the distilling flask under continued heating. Approximately one gram of diester was obtained from five grams of acid. It was found that separation of a portion of the distillate with water-chloroform gave rapid crystallization from the chloroform phase. The yield of this separation was not good, however this technique was useful in producing seed crystals.

The technique used to prepare monoester was that specified by patent no. US 2,610,205. Equimolar quantities of tartaric acid and triethyl amine were mixed to form the mono quaternary amine salt which was then esterified with an equimolar quantity of thionyl chloride. To slow the reaction the thionyl chloride was first dissolved in anhydrous methanol before being added to the salt solution. The reaction solution was evaporated on a steam bath to

give a deliquescent crystalline product which was stored in a desicator. The composition of this product was analyzed by thin layer chromatography to verify that no diester had been formed. Since hydrolysis rates are determined by using a pH-stat the salt may be used as is without preparing free ester or removing the small residual amount of acid.

The samples prepared (d and l dimethyl tartrate and l monomethyl tartrate) were tested by thin layer chromatography. Samples were dissolved in methanol to give approximately 20% solutions, 1 µl of which was spotted on the silica plate. The plates were run in 25% acetone-75% heptane solution and were developed with permanganate. Undistilled, stripped diester product gave three spots: an acid spot at the origin, a diester spot near the top and a monoester streak in the middle. The distilled oil gave a diester spot with a faint monoester streak while the crystalline product showed only the diester spot. The dissolved monoester salt gave a monoester streak and a faint acid spot. It thus appears that the procedures used were successful in preparing monoester free from diester and diester free from monoester or acid.

As indicated by the chromatographic and melting point tests, the procedures used produce compounds of the required purity. Small test samples are available of all the required compounds so that large quantities may be prepared when desired.

EXPERIMENTAL

1. SYNTHESIS OF DIMETHYL TARTRATES-- 5.0 g. of d (or l) tartaric acid were placed in a 300 ml. three-necked flask fitted with dropping funnel, drying tube and stopper. 50 ml. of abs. methanol were added to dissolve the acid. The solution was cooled in an ice-salt bath and 8.2 g. of redistilled dimethyl sulfite was added at the rate of 20 drops per minute. After warming overnight the solution was refluxed for 5 hrs. The solvent was stripped off under aspirator pressure and the resulting oil was vacuum distilled at a pressure of 0.5 mm. of mercury. The diester distilled slowly at a temperature range of 125° to 135° C. Distillation was stopped when the high temperature began decomposing the material in the distilling flask. After 3 weeks at 0° C. the distillate crystallized to give about 1 g. of transparent crystals with a mp of 35°-40°.

2. SYNTHESIS OF MONOMETHYL TARTRATES-- 5.0 g. of l tartaric acid were placed in a 200 ml. flask. 3.8 g. of triethyl amine were added and then 25 ml. of abs. methanol was added to dissolve the acid. The flask was then placed in an ice bath and a solution of 4.0 g. of thionyl chloride in cold abs. methanol was added dropwise to the salt solution. After the solution had warmed overnight the solvent was removed on the steam bath. The resulting product was approximately 10 g. (wet weight) of white crystals. The crystals were washed once with $CHCl_3$ and placed in a vacuum desicator. Chromatographic tests did not detect any diester in the product.