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PREPARATIVE PURIFICATION OF 2-(2'-HYDROXYETHOXY)TEREPHTHALIC ACID WITH COUNTERCURRENT CHROMATOGRAPHY

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ABSTRACT

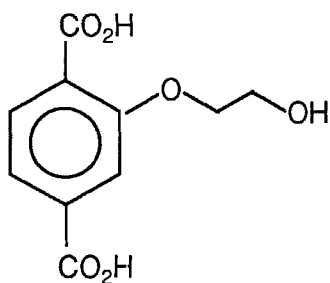
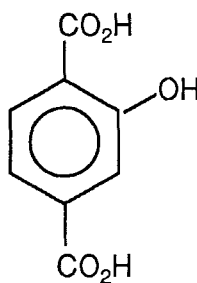
2-(2'-Hydroxyethoxy)terephthalic acid has been completely separated from its synthetic precursor, 2-hydroxyterephthalic acid using countercurrent chromatography on a preparative scale after more common separation techniques failed.

INTRODUCTION

An ongoing research project in our laboratory has involved the synthesis of certain electroactive organic materials. One of the required intermediates in this work was the title compound, 1, which was prepared by a relatively straightforward procedure. However, it

was always grossly contaminated with starting (2) and other materials and the usual purification methods (recrystallization, preparative thin-layer chromatography, and column chromatography) were not successful.

The present paper describes the successful purification of this synthetic organic intermediate by countercurrent chromatography on a gram scale with an Ito multi-layer coil countercurrent system.

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MATERIALS

2-(2'-Hydroxyethoxy)terephthalic acid (1) was prepared by stirring a solution of 2.0 g (11.0 mmol) of 2-hydroxyterephthalic acid (2) (1), 2.2 mL (2.66 g, 33.0 mmol) of 2-chloroethanol, 2.2 g (55.0 mmol) of NaOH, and 15 mL of water at room temperature for two days. The reaction mixture was filtered and the filtrate was acidified with 1.2 N HCl. A white precipitate was collected by filtration and dried (~2.9 g). Analytical TLC (Analtech Uniplates, silica gel HLF, EtOAc:HOAc, 97:3 by volume) of the product showed two zones, Rf's 0.16 and 0.41 (1 and 2, respectively). In EtOH:ether, 50:50, the Rf's were 0.19 and 0.59. The spot for 2 was characterized by a blue fluorescence under short-wave

ultraviolet light. It was this mixture that was separated by the procedure described in the present paper.

All solvents used in this work were either reagent or HPLC grade.

METHODS

The mixture of 1 and 2, prepared above, was slightly soluble in methanol at room temperature and insoluble in most other organic solvents. Purification of 1 was attempted using recrystallization (from methanol), preparative thin-layer chromatography (silica gel, 2 mm thick, EtOAc:HOAc, 97:3 by volume), absorption chromatography (silica gel, EtOAc:HOAc, 97:3 by volume), and reverse-phase chromatography (C-18 bonded silica gel, acetonitrile:water, 95:5 by volume). At best, these preparative methods gave only partial separation of 1 and 2 even though the corresponding analytical procedures showed adequate resolution. Conversion of the mixture to the acetate esters prior to separation attempts did not provide the esters of either 1 or 2 in pure form.

The partition coefficients of 1 and 2 were determined using analytical HPLC (C-18 silica gel, 10 μ , acetonitrile:water, 95:5 by volume) (2). The retention volume for the first peak (starting material, 2) was 3.2 mL and that of the second peak (product, 1) was 8.0 mL. K (upper phase) for a chloroform:methanol:water solvent system (37:37:26 by volume) was 0.74 for 2 and 1.60 for 1.

Countercurrent chromatography was performed with an Ito multi-layer coil separator-extractor (3). The upper layer of the above solvent system was the mobile phase. The inlet end (external or outer terminal of the coil) of the multi-layer coiled column of #14 PTFE tubing (1.6 mm I.D., 130 m long, 330 mL capacity) was connected to a Waters

Model 6000A pump and the column outlet (from the internal or inner terminal of the coil) was joined to an Isco UA-5 ultraviolet absorbance monitor (280/310 nm filter) and then to a fraction collector. One liter of the two-phase solvent system, chloroform:methanol:water (37:37:26), was thoroughly equilibrated and degassed in a separatory funnel at room temperature and the layers were separated before use. The column was first completely filled with the lower (stationary) layer. The mixture of 1 and 2 (2.36 g) was dissolved in 30 mL of the upper layer and warmed on a steam bath. This solution was clarified by filtration and the filtrate was injected into the column inlet. The multi-layer coiled column was rotated at 800 rpm while the upper (mobile) layer was pumped through it at the rate of 180 mL/h.

RESULTS AND DISCUSSION

Figure 1 illustrates the profile obtained from the countercurrent chromatographic separation of a mixture of 1 and 2. The mobile layer began to elute after about 10 minutes. The first component (1) eluted after 38 minutes and had a retention volume of 114-174 mL. Finally, the starting material (2) eluted after about 80 minutes and its retention volume was 240-310 mL. In some runs, a third and minor component, whose structure is unknown, eluted right after the first and one had to be careful to take several fractions near the end of the elution of the first component. The fractions, which contained only 1 by TLC, were pooled and the solvents were removed by distillation under reduced pressure. The residual crystalline white solid was homogeneous by TLC and weighed 1.59 g (67% of the mixture). Recrystallization from acetone-hexane afforded an analytical sample which melted at 223-224°C. Anal. Calcd. for $(C_{10}H_{10}O_6)_4 \cdot H_2O$: C, 52.05; H, 4.59. Found: C, 52.30; H, 4.41.

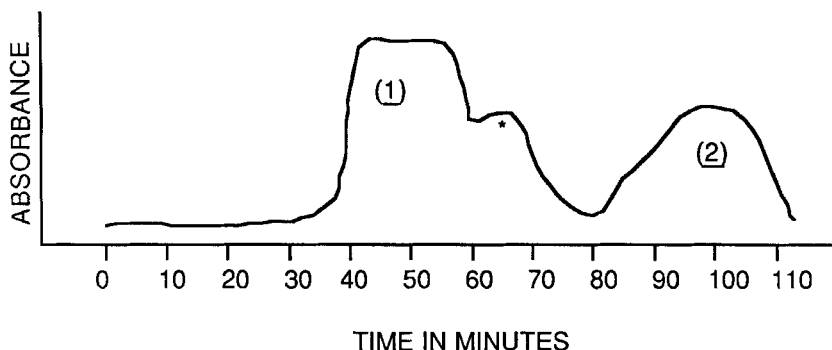


Figure 1. Plot of countercurrent chromatogram of 2-(2'-hydroxyethoxy)-terephthalic acid (1) and 2-hydroxyterephthalic acid (2). The shoulder at 65 minutes (*) was a minor impurity which was observed on occasion.

A similar workup of those fractions which contained the starting material, 2, yielded this component (approximately 30% of the mixture) in an essentially pure state.

The entire separation including column equilibration required only about 2 h. The wide baseline area between the two major components suggested that even greater sample loads may be possible, providing the third and minor component is absent.

In the present paper, countercurrent chromatography has been shown to be a mild, efficient, and rapid technique for the preparative separation of a synthetic organic reaction product, 2-(2'-hydroxyethoxy)terephthalic acid (1) from its precursor, 2-hydroxyterephthalic acid (2). The solvent system used provides 90% retention of the stationary phase in the coiled column and appears to be suitable for the separation of other organic synthesis products of intermediate polarity.

ACKNOWLEDGEMENTS

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