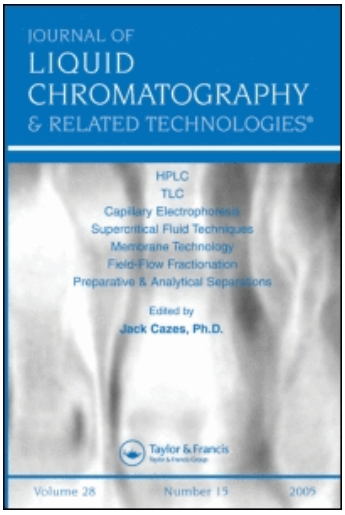

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Separation and Purification of the Isomers of Propylene Phenoxetol by Preparative High Performance Liquid Chromatography

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SEPARATION AND PURIFICATION OF THE ISOMERS OF PROPYLENE PHENOXETOL BY PREPARATIVE HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

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ABSTRACT

A simple, rapid separation in gram quantities of isomeric phenoxy-propanols present in a commercially available anti-microbial (propylene phenoxetol) is described. Use of the peak shaving-recycling technique gave products of >99% purity. The structural identity of each isomer was established by combined gas chromatography-mass spectrometry.

INTRODUCTION

In recent years, propylene phenoxetol has found increasing use as a broad spectrum anti-microbial agent in pharmaceutical, cosmetic and toiletry products. When this material is subjected to gas chromatography using stationery phases such as XE-60 or Carbowax 20M, a small impurity peak can be seen on the tail of the major component.

The importance of sample purity when evaluating biological activity has therefore, led us to examine this material more closely.

Complete resolution (α>1) of the two components can be achieved by using glass capillary open tubular columns coated with XE-60, details of which are described in the text. Analysis of a number of batches in this way has established that the ratio of major to minor component is fairly constant at approximately 9/1.

Similar resolution was also obtained on a silica column using normal phase HPLC under isocratic conditions. Consequently, the use of preparative HPLC as a means of isolating each compound was investigated. It was found that by a combination of peak shaving and recycling techniques, each compound could be rapidly separated in high purity.

Theoretical considerations based on the manufacturing process for this raw material suggested that these components were the isomers 1-phenoxy-2-propanol (I) and 2-phenoxy-1-propanol (II) with the latter as the minor component. Structural confirmation of this was obtained by subjecting each isolate to analysis by combined gas chromatography - mass spectrometry.

MATERIALS AND METHODS

Reagents

Ethyl acetate and n-hexane were HPLC grade (Rathburn Chemicals, Walkerburn, Scotland). Propan-2-ol was Analar grade

I II

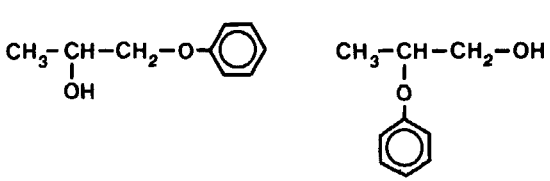

FIGURE 1 : I = 1-phenoxy-2-propanol
II = 2-phenoxy-1-propanol

(BDH Chemicals, Poole, England). Propylene phenoxetol was purchased from Nipa Laboratories, Treforest, Wales. Solvents were vacuum filtered through 0.5 μm, 47 mm diam. Fluoropore disc filters (Type FH LP 047 00, Millipore, Harrow, England).

Analytical HPLC Separation

A Waters Associates (Hartford, Cheshire, England) 6000A solvent delivery system was used to pump the mobile phase (n-hexane/ ethyl acetate, 85/15 v/v) at 2.0 ml/min. through a stainless steel column, 25 cm x 4.6 mm I.D. packed with Zorbax-Sil 850 (Du Pont, Stevenage, England).

Sample solutions (0.1% w/v in mobile phase) were injected automatically using a Du Pont 834 auto-sampler and pneumatically operated Valco valve fitted with a 20 μl fixed volume sample loop.

Column eluate was monitored at a sensitivity of 1 A.U.F.S. using a Waters Model 440 absorbance detector set at 280 nm. The detector output was displayed on a Hewlett Packard (Winnersh, England) 3380A integrator (attenuation 8).

Preparative HPLC Separation

A Waters Associates Prep LC/System 500 equipped with two PREP PACK-500/SILICA cartridges (30 cm x 5.7 cm) and a refractive index detector coupled to a chart recorder was used for the preparative separation. The mobile phase was n-hexane/propan-2-ol (98.5/1.5, v/v) with a flow rate of 250 ml/min (back pressure 5 atmospheres).

The crude sample was loaded in 10 ml aliquots as a 50% v/v solution in mobile phase using a gas-tight syringe. Collections of eluate were stripped of solvent using a rotary evaporator under reduced pressure and a steam bath.

Gas Chromatography

A Hewlett-Packard 5880A gas chromatograph equipped with flame ionisation detectors and capillary injection system was used for purity evaluation of propylene phenoxetol samples.

Chromatography was performed on a WCOT glass capillary column, 25 metres x 0.25 mm (I.D.) containing XE-60 as stationary phase (Phase Separations, England). Column temperature was 105°C and both detector and injection port were set at 250°C.

Injections (1µl) of samples diluted in ethyl acetate were made using a Hewlett-Packard 7672A autosampler with the injection system in the split mode. Nitrogen was used both as carrier gas and make-up gas. Column flow was 2.5 ml/min with a split ratio of 144/1.

Mass Spectrometry

A Finnigan (Hemel Hempstead, England) 3200GC-MS/6100 data system was employed to confirm the structures of the two isomers. Gas chromatography was carried out using a 20 metre x 0.3 mm glass column coated with Carbowax 20M and linear temperature programmed from 60-210°C at 6°C/minute, with a helium flow rate of 2 ml/minute. The mass spectrometer was operated with a 300 µA filament emission current and 70 eV ionisation energy. The data system attached to the instrument allowed continuous scanning and recording every 1 second for m/e 40 to 250. Ions below m/e 40 were not collected because of the relatively high levels of m/e 32 unavoidably present in the system from air when operating under GC-MS conditions.

RESULTS

Preparative Liquid Chromatography Procedure

The injection of a diluted sample of commercial grade 1-phenoxy-2-propanol onto the analytical column gave complete resolution of the two isomers as can be seen in Fig. 2. However, complete resolution is not an absolute requirement in preparative work, and the mobile phase was therefore modified to reduce k' values and hence reduce the volume of mobile phase required. The

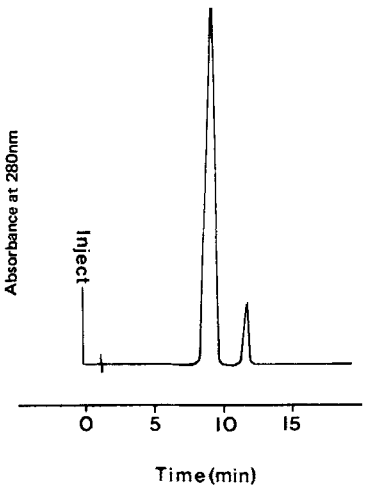

FIGURE 2 : Analytical HPLC separation of phenoxy-propanol isomers.

preparative separation was found to be extremely reproducible, each injection having the same elution profile.

Eight 10 ml samples of a 50:50 v/v dilution of commercial 1-phenoxy-2-propanol with mobile phase were injected onto the preparative silica columns. Following each injection, the column eluate was fed to waste until the first upward inflection was seen on the chart recorder. The discarding of the early eluates allowed removal of minor impurities including trace levels of phenol that may be present.

The column eluate was fractioned as shown in Fig. 3(a). Fractions 1-3 from each injection representing crude major isomer were bulked and evaporated to low volume (approx. 50 ml) with the aid of a steam bath and a rotary evaporator operated under reduced pressure. Analysis of this concentrated sample was carried out using the analytical column and an area percentage calculation indicated the sample to be > 98% pure.

The concentrate was re-chromatographed as 2 x 25 ml injections and the fraction collected in each case is shown by the unshaded

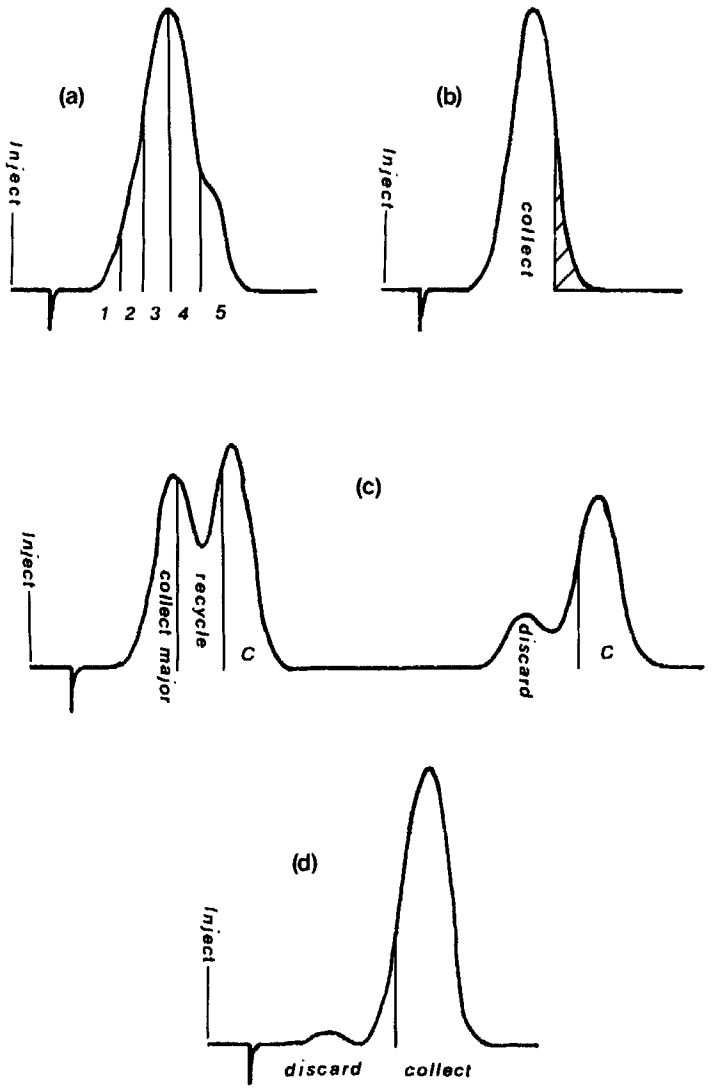

FIGURE 3 : (a) Fractionation of phenoxy-propanol

(b) Purification of major isomer

(c) Separation of minor isomer using the recycle technique

(d) Final purification of minor isomer

section in Fig.3(b). Evaporation of the combined fractions yielded 15g of a clear oily liquid which chromatographed as a single peak of 99.9% purity on the analytical column. The purity was confirmed by capillary GC because of the non-universal response of the UV detector employed with the analytical column. Fractions 4 were discarded but fractions 5 from the eight injections were bulked and evaporated as before. An injection of this concentrated sample onto the analytical column indicated that it was an approximately 50:50 mixture of the two isomers. The concentrate was then injected in two portions onto the preparative column and fractionated as shown in Fig.3(c) using the recycling technique.

The bulk fractions C were concentrated as before and found to be 98.6% pure minor isomer. The sample was therefore re-chromatographed on the preparative column using a single injection and the eluate containing the minute amount of major isomer discarded (Fig.3(d)). Complete removal of the solvent from the minor isomer fraction collected then yielded 2.2g of a clear oily liquid. When this was injected onto the analytical column, the purity had increased to 99.7% which was confirmed by capillary column GC.

Structural Confirmation

Fig. 4 shows the total ion current (T.I.C.) trace obtained from the examination of a standard solution of commercial 1-phenoxy-2-propanol and two major discrete components are apparent. Figs.5(a) and (b) show the full mass spectra of the 2 discrete components present in the commercial sample. The major component (RT 2.5 min) has a molecular ion at m/e 152 and prominent ions at m/e 108, 94 (100%), 78, 77, 59 and 45, (Fig.6(a)). The spectrum is consistent with the structure of 1-phenoxy-2-propanol (I) and is identical to that obtained from the major isomer prepared by HPLC (Fig.7(a)).

The spectrum is also identical to that of a standard given in the Eight Peak Index of Mass Spectra compiled by the Mass Spectrometry Data Centre (Spectrum No. D1554).

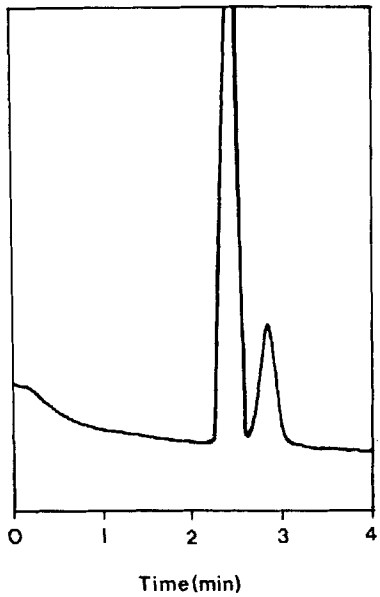

FIGURE 4 : Total ion current of GC-MS.

The mass spectrum (Fig.5(b)) of the minor component in the mixture (RT 2.8 min) and the pure minor component itself (Fig.7(b)) both show a molecular ion at m/e 152 and prominent ions at m/e 121, 94 (100%), 77, 66 and 51. The molecular ion and base peak rearrangement ion (Fig.6(b)) indicate the component to be an isomer of 1-phenoxy-2-propanol and the presence of an abundant ion at m/e 121 suggests the component to be 2-phenoxy-1-propanol (II). The spectrum is also consistent with that of authentic 2-phenoxy-1-propanol given in the Eight Peak Index.

DISCUSSION

Several papers and patents (1-5) have reported the synthesis of 1-phenoxy-2-propanol. Of these methods the reaction of phenol

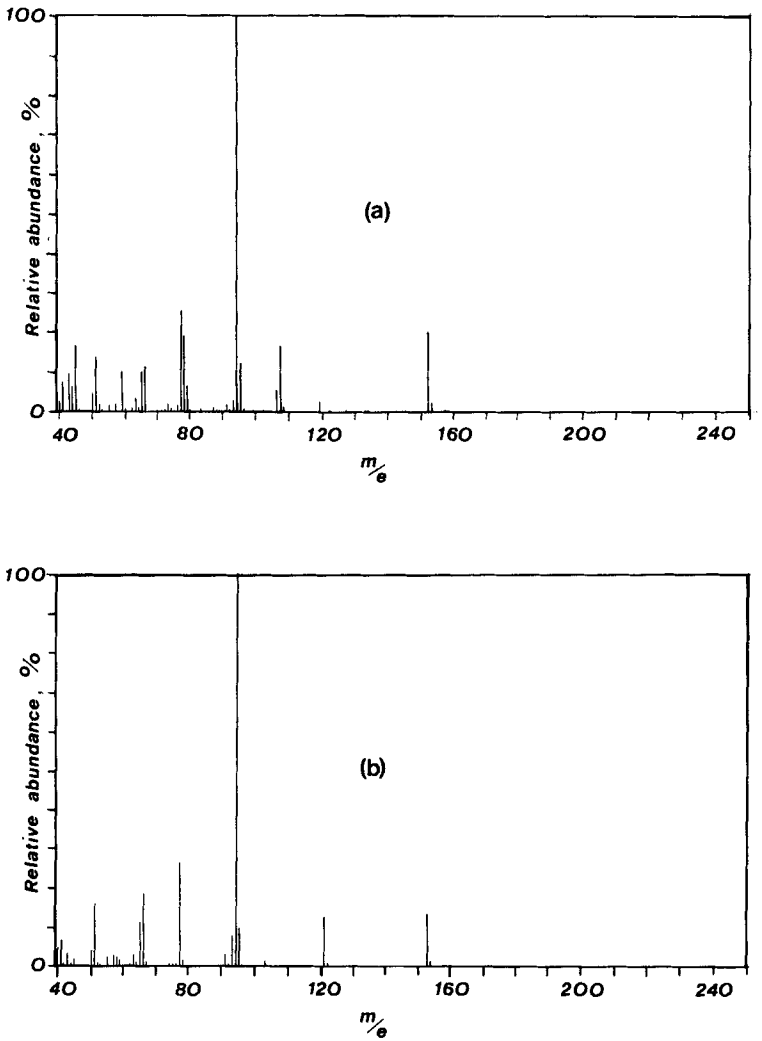

FIGURE 5 : (a) Mass spectrum of phenoxy-propanol component (RT 2.5 min.)

(b) Mass spectrum of phenoxy-propanol component (RT 2.8 min.).

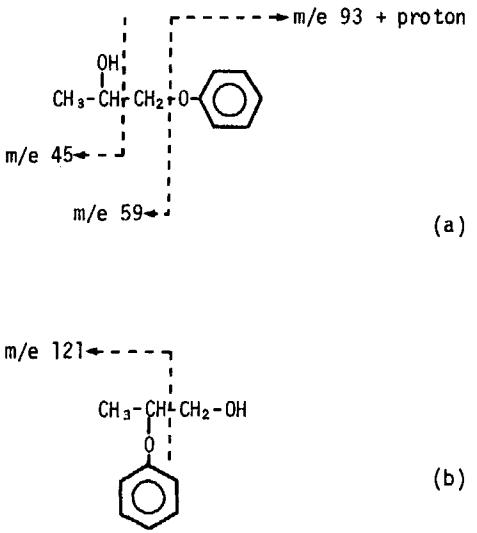

FIGURE 6 : Fragmentation pathways for (a) 1-phenoxy-2-propanol and (b) 2-phenoxy-1-propanol.

with propylene oxide under basic conditions, is the simplest and most efficient and forms the basis of the manufacturing process. The reaction probably involves attack by phenoxide ion at the primary carbon atom of the epoxide ring by an S_N2 mechanism thereby leading to the formation of I (Fig.8). Substitution at the secondary carbon atom would, of course, lead to II and indeed a by-product is formed in nearly all these reactions which Okawara (4) indirectly identified as II by the formation of 2-phenoxy-propionic acid upon oxidation.

1-Phenoxy-2-propanol may be prepared free from II in reduced yield but the method is tedious (1). Clearly the preparation of pure I by the foregoing methods is difficult.

In contrast, preparative HPLC provides a simple and rapid technique for the isolation of both isomers in high purity. A feature of the technique is that the use of peak shaving/re-

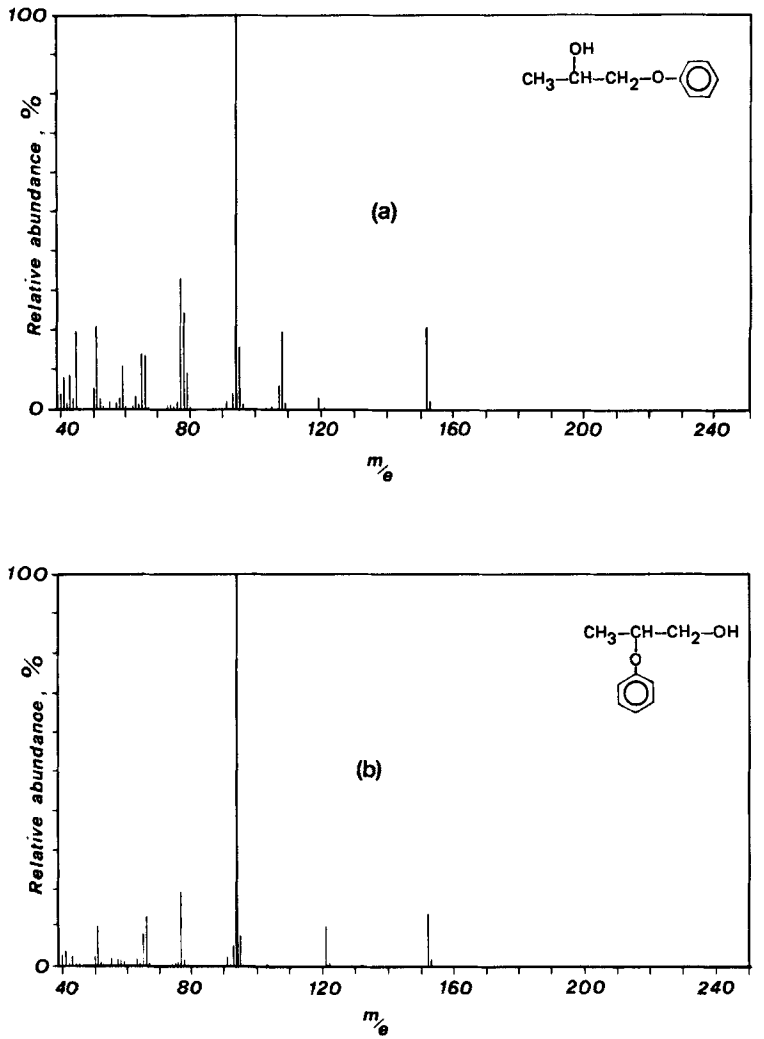

FIGURE 7 : (a) Mass spectrum of major isomer purified by HPLC

(b) Mass spectrum of minor isomer purified by HPLC

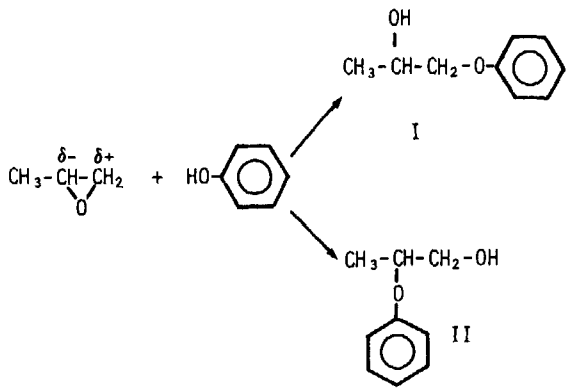

FIGURE 8 : Reaction of phenol with propylene oxide.

cycling eliminates the need for complete chromatographic resolution enabling the analysis time to be reduced and therefore solvent consumption kept to a minimum. A further advantage is that contamination of the isolates with undesirable reaction by-products or impurities is avoided, provided high purity solvents are used.

This was strikingly demonstrated when I was synthesised by first oxidising commercial 1-phenoxy-2-propanol, isolating the ketone formed from I, then reducing this to give a product which was 99% pure I by GLC. After only a few months the material had developed a most unpleasant odour and HPLC analysis showed the presence of trace amounts of several impurities, although the GLC purity was still 99%. On the other hand, the isomers separated by preparative HPLC have retained their faintly pleasant odours after a period of more than 2 years and HPLC analysis confirms the absence of these trace impurities.

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