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Note

Gas chromatographic separation of isomers of benoxaprofen using liquid crystals

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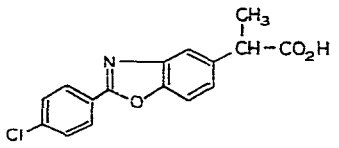
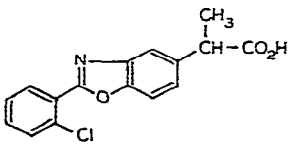
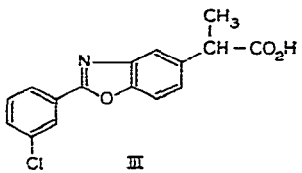
Benoxaprofen, 2-(4-chlorophenyl)-α-methyl-5-benoxazoleacetic acid (I), is a novel anti-inflammatory agent[1]. A ten-stage synthesis of the compound from the raw materials *p*-chlorobenzoyl chloride and 1-phenylethanol can result in the presence of four possible isomeric impurities (II–V). Attempts to separate low levels of these compounds from benoxaprofen using conventional gas–liquid chromatography (GLC) have proved extremely difficult. As a result the *o*-chlorophenyl and *m*-chlorophenyl isomers have been determined by GLC[2] after alkaline hydrolysis and subsequent methylation, whereas the 6- and 7-propionic acid impurities have been estimated by nuclear magnetic resonance spectroscopy[2] using a lanthanide shift reagent. We now report the use of a liquid crystal stationary phase to separate the methyl esters of isomers II–V from benoxaprofen methyl ester.



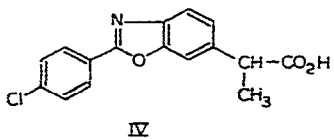
I
Benoxaprofen



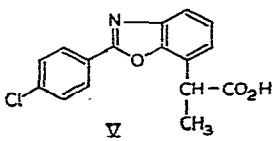
II
o-chloroisomer



III
m-chloroisomer



IV
6-isomer



V
7-isomer

EXPERIMENTAL

A 6-ft. × 4-mm-I.D. glass column was packed with 4% N,N-bis-(*p*-methoxybenzylidene)-*α*,*α*′-bi-*p*-toluidine, a liquid crystal, on Gas-Chrom Q, 100–120 mesh. The column was conditioned at 280° for 24 h before use. The column oven and detector temperatures of the gas chromatograph (Hewlett-Packard Model 5711A equipped with a flame ionisation detector) were maintained at 280° and 300°, respectively. Nitrogen was used as the carrier gas at a flow-rate of 60 ml/min.

Samples of I were methylated with ethereal diazomethane solution before on-column (25 *μ*g) injection into the gas chromatograph. Determination of low concentrations of isomers II to V required 40-fold attenuation change.

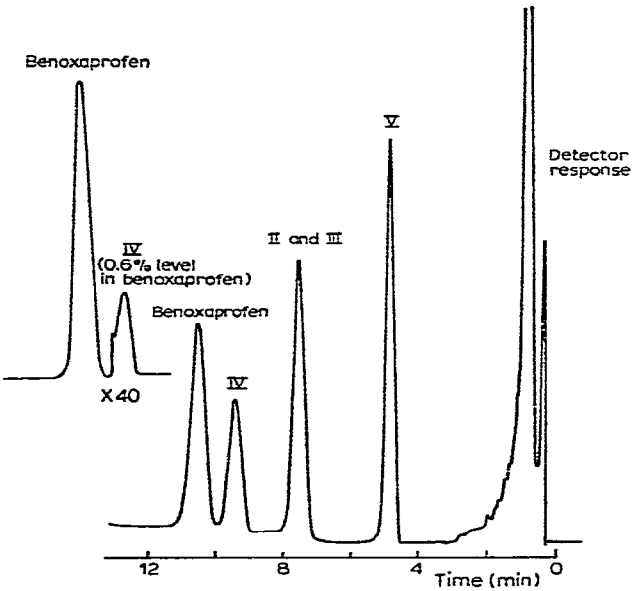


Fig. 1. Gas chromatogram of methyl esters of benoxaprofen and its isomeric impurities on 4% N,N-bis-(*p*-methoxybenzylidene)-*α*,*α*′-bi-*p*-toluidine.

RESULTS AND DISCUSSION

The liquid crystal N,N-bis-(*p*-methoxybenzylidene)-*α*,*α*′-bi-*p*-toluidine has a long nematic temperature range[3] (181–320°). Maximum selectivity is obtained from the phase at the lower end of its nematic temperature range, although the methyl esters of benoxaprofen and its isomeric impurities then have a long retention time. Consequently a column temperature of 280° was chosen. A 4% phase loading was required to obtain optimum peak symmetry. As the isomeric impurities elute before benoxaprofen, they could be estimated at low levels, as indicated in Fig. 1.

REFERENCES

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3 G. M. Janani, K. Johnston and W. L. Zielinski, Jr., *Anal. Chem.*, 47 (1975) 670.