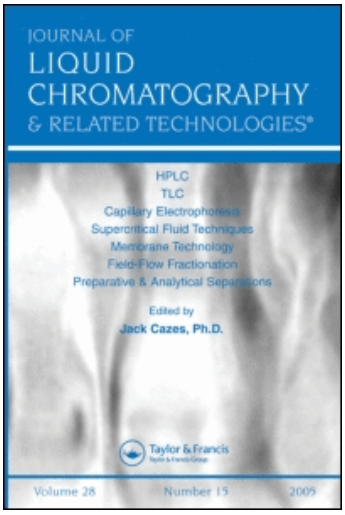

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Direct Resolution of Isomeric and Diastereoisomeric Mixtures of Amides, Lactones, Alcohols, Carbazones and Pyrethenoid Derivatives

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DIRECT RESOLUTION OF ISOMERIC AND DIASTEREOISOMERIC MIXTURES OF AMIDES, LACTONES, ALCOHOLS, CARBAZONES AND PYRETHENOID DERIVATIVES

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Abstract

The resolution of a wide range of compounds of different functionalities has been achieved by high performance liquid chromatography (HPLC) on chiral stationary phases based on N-formulated aminoacid derivatives. The separation factors (α) of 1.11 - 1.25 have been achieved. The alcohol derivatives of the insecticides investigated were not resolved into their enantiomeric molecules, however such solutes were resolved into their diastereoisomers. The mechanism of chiral recognition is a subject of future investigations.

Introduction

The chromatographic resolution of an enantiomeric mixture has posed a greater challenge than, for example, the separation of geometric isomers. A number of approaches including the direct and indirect high performance liquid chromatographic

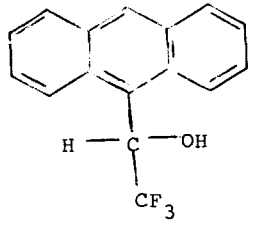
technique and gas chromatography (GC) have been used. Some of these techniques have been reviewed (1 - 3).

An almost ideal procedure is the direct resolution of enantiomers of interest upon a column packed with a suitable chiral phase which is chemically bonded and is mechanically stable and suitable for use with commonly available solvents. In recent years, considerable progress has been made towards the development of fairly general chiral packings. Two such materials, capable of resolving a wide range of chiral compounds, were developed by Pirkle *et al.* (4) and are now commercially available. Although the HLPC chiral stationary phases (CSPs) of Pirkle *et al.* (4) have been employed in the direct resolution of a variety of chiral molecules, difficulties have been reported (5) with certain structural types and functionalities viz, amines and carboxylic acids.

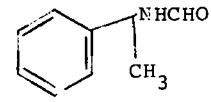
In our previous report (6), we reported the synthesis of chiral bonded materials which were successfully employed for the resolution of racemic esters of aminoacids. This paper reports the expansion of our previous approach to a series of racemic mixtures of a wide variety of compounds which were resolved as their secondary or tertiary derivatives (I - VI), and also certain compounds which were resolved as their diastereisomeric mixture (VII - X). These compounds are difficult to resolve on ordinary silica gel (straight phase) or octadecylsilane modefied gel (ODS). The resolution of these compounds is of pharmacological interest since the (R-) and (S-) enantionrers have different pharmacological behaviour *in vivo* when used on man or as pest control in agrochemicals.

The procedure described here has the advantage of a direct enantiomeric approach since it avoids the difficulties that are inherent in the diastereoisomeric approach to the separation of racemic mixtures.

Structures of compounds resolved as their enantiomeric molecules.



(I)



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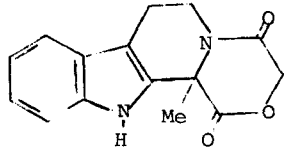

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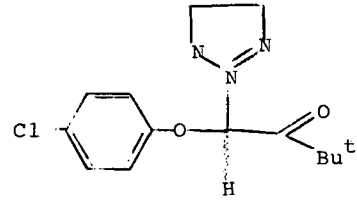

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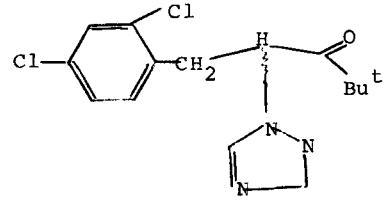

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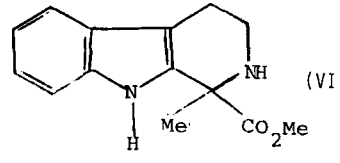
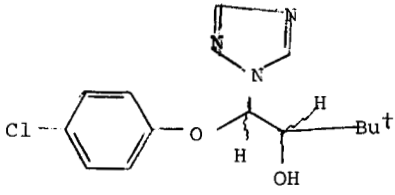
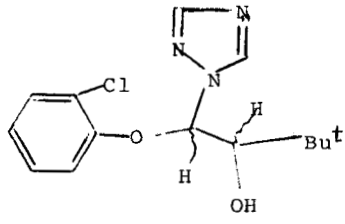


(VI)

Structures of c ompounds resolved as their diastereoisomeric molecules.



VII



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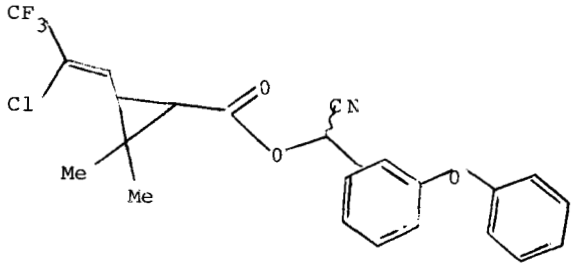

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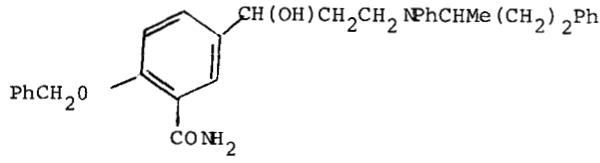

(X)

Materials and Methods.

Column packings were made up of

i) N-formylated-L-isoluecine aminopropylated silica gel(APSG) and

ii) N-formylated-L-phenylalanine (APSG) as the chiral moieties.

Test solutes were obtained from various sources. 2,2,2, trifluoro-1-(-9-anthryl) ethanol was obtained commercially (Regis, Morton Corove, 1L; USA) α-methylbenzylamine was obtained from DBH, U;K and was N-formylated using standard procedures. The aminolactone derivative and the methoxy-derivative of azacarbozole were provided by Dr. Richard Herbert of Leeds University, U.K. Tridimefon, PP296 and Diclobutrazole PP536 are agrochemicals and are commercially available. Labitalol was provided by the kind donation of Glaxo Pharmaceuticals, Ware, Herts, U.K.

Chromatography was performed using a laboratory Data control (LDC) HPLC system as previously described (6). The columns were of stainless steel (25 x 4.6 mm i.d) packed with aminopropylated. Silica gel (APSG) of 5μm Spherisorb (Phase Separations Ltd, Deeside, Clywd. U.K.), modified with N-formylated aminoacids prepared according to procedures described elsewhere(6). Except where indicated, the mobile phase was 1 - 3% isopropanol in n-hexane.

Results And Discussion.

The results of the enantiomeric separations achieved for the racemic molecules tested are shown in Table I. Compounds which were resolved as their diasterioe isomeric molecules are listed in table II. Chromatograms of resolved solutes are shown in Figs. 1 - 6. For the racemates resolved, it was consistently noted that the presence of a carbonyl

Table I

Capacity ratios, selectivity and resolutions for racemic test solutes resolved on N-formylated aminoacid chiral Packings[a].

Mixture No	K'D	K'L		R_s
1.	6.60	7.10	1.10	1.43[b]
2.	2.80	3.33	1.20	1.46
3.	3.60	4.10	1.14	0.41
4.	2.50	3.13	1.25	2.36
5.	2.46	2.73	1.11	0.46
6.	9.40	11.30	1.10	1.52

a. Solutes were resolved on M-formylisoleucine APSG.

b. Solutes was resolved on N-formylphenylalamine APSG.

TABLE II

Capacity ratios, selectivities and resolutions for racemic solutes resolved only as their diastereisomeric molecules on N-formylisoleucine APSG[a].

Mixture No	K'D	K'L		R_s
7	5.01	5.59	1.12	2.33
8	5.08	6.31	1.24	3.08
9	4.73	6.0	1.30	2.31
10	4.73	6.0	1.30	2.31

a. All solutes were resolved on both types of packings.

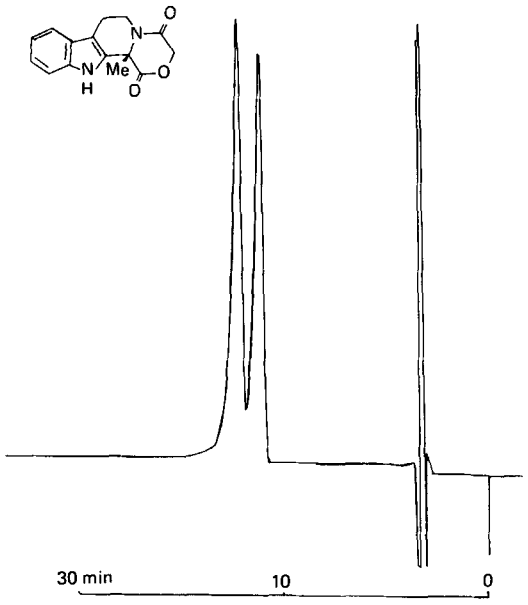

Fig. 1: Resolution of racemic aminolactone derivative (Sample III) on N-formylisoleucine APSG. Conditions: 60% CH_2Cl_2 in n-hexane, Flow rate, $2cm^3min^{-1}$, U.V detector at 254nm, 0.1 AUFS.

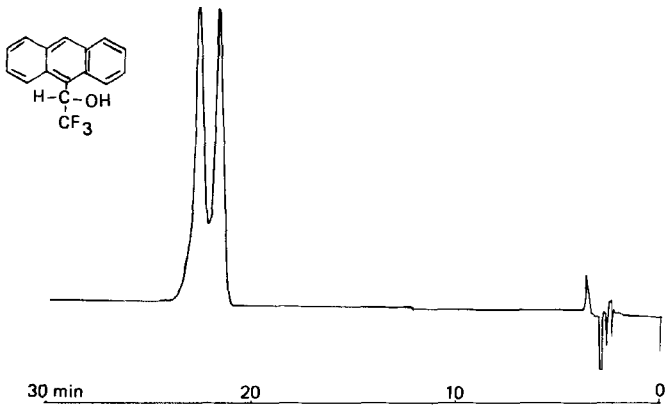

Figure 2: Resolution of racemic trifluoroanthryl alcohol on N-formylphenylalanine APSG conditions: Flowrate $1cm^3min^{-1}$, eluent. 1% Pr^iOH in n-hexane, U.V. detector at 254 nm, 0.5 AUFS.

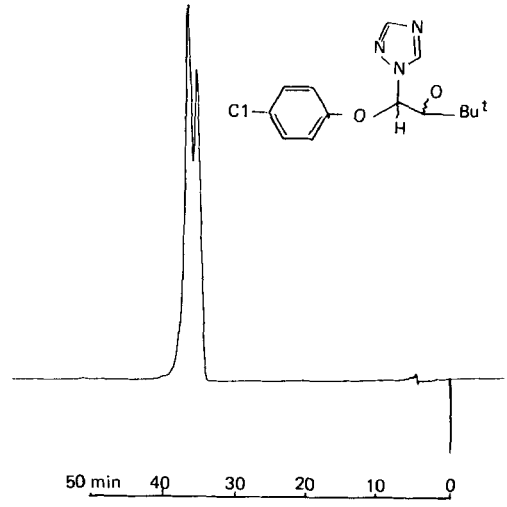

Fig. 3: Partial resolution of racemic Triadimefon on N-formylisoleucine APSG.
Conditions: Flow rate, 0.7cm^3 min^{-1}, eluent, 0.5% Pr^{i}OH in n-hexane, U.V. detector at 254nm, 0.1 AUFS.

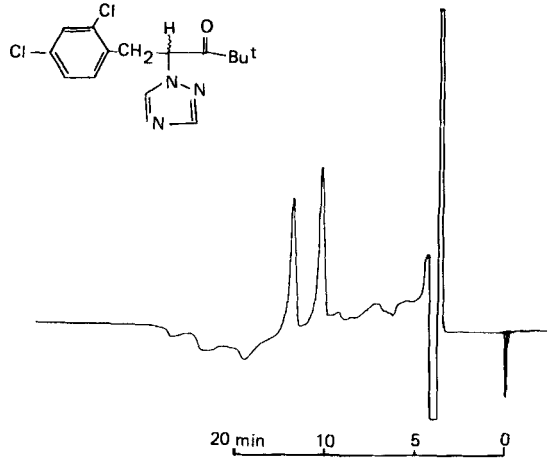

Fig. 4: Resolution of racemic ketoanalogue of PP296 (Sample V on N-formylisoleucine APSG.
Conditions; Flow rate, 2cm^{3}min^{-1}, eluent, 3% Pr^{i}OH in n-hexane, U.V. detector at 254nm, 0.1 AUFS.

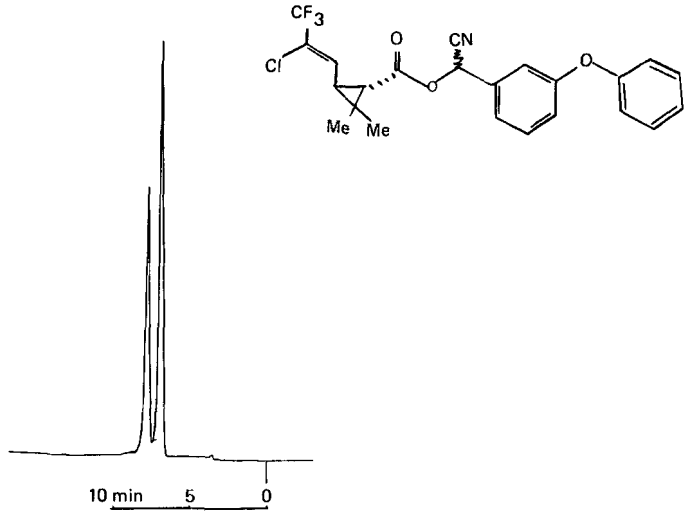

Fig. 5 : Resolution of the diastereoisomers of PP536 (sample IX) on N-formylisoleucine APSG Flow rate $1cm^3min^{-1}$, eluent, Arklone P, U.V. detector at 254 nm, 0.1 AUFS.

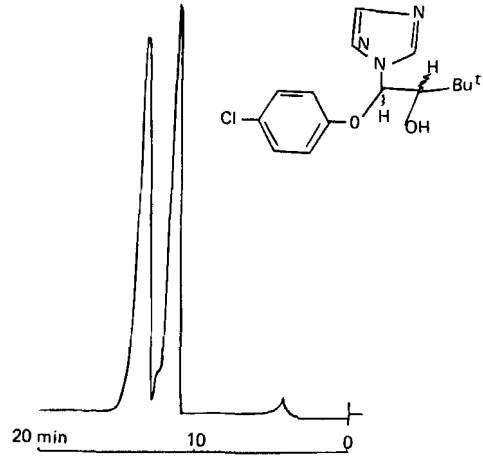

Fig. 6: Resolution of the diastereoisomers of Triadimenol on N-formylisoleucine APSG. Conditions : Flow rate, $2cm^3min^{-1}$, detector at 254,nm, 0.1 AUFS.

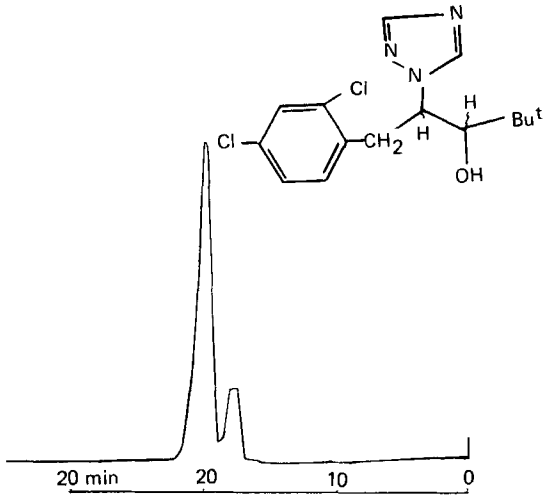

Fig. 7: Resolution of the diastereoisomers of Dichlobutrazole (87:3) on N-formyl-isoleucine APSG.
Conditions: Flow rate 1cm^3 min^{-1}, eluent 2% Pr^{i}OH in n-hexane, U.V. detector at 254 nm, 0.05 AUFS.

group near the chiral carbon enhanced chiral discrimination. For example, resolutions were achieved for compound IV while the alcohol VII shows no chiral resolution under several mobile phase conditions. However, the diastereoisomeric mixture of compound VII, (2R, 3R, 2S, 3S) was resolved as two unequal components Fig. 7. Failure to achieve enantiomeric resolutions for this compound and those other compounds resolved as their diastereoisomeric derivatives cannot immediately be explained. The result may be due to the general unsuitability of the available interaction site(s) in the solutes with that of the packings, and this also indicates the unpredictable specificity associated with

chiral HPLC packings. The resolution of these type of compounds have been reported elsewhere (7).

Dalgliesh (8) has proposed a three-point interaction model as a requirement for achieving the necessary chiral recognition. The three-point interaction model has further been explained by Pirkle *et al.* (9, 10, 11), and other workers (5, 12) in relation to chiral CSPS, and by Hara and Dobashi (13, 14) and Pirkle (15) in relation to amide bonded chiral phases respectively. For our present investigations it is difficult to immediately identify simple discrete bonds to assymetric carbon as adequate explanations upon which the Dalgleish premise was based in explaining the mechanism of chiral interaction between the surface of the packing and the solutes. It is not an easy business to afford adequate explanations for the mechanism of separation of the solutes, however further investigations would afford us better idea of the nature of chiral recognition factors in this process.

Acknowledgements

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