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STEREOCHEMICAL SEPARATION AND CONFIGURATIONAL ASSIGNMENT BY GAS–LIQUID CHROMATOGRAPHY OF N-TRIFLUOROACETYL-L-PROLYL AMIDES OF ASYMMETRIC 1-PHENYLISOPROPYLAMINES

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SUMMARY

The gas–liquid chromatographic separation of the N-trifluoroacetyl-L-prolyl derivatives of various ring and N-alkyl substituted amphetamines is described. Of the seventeen enantiomeric pairs tested, the derivatives of the (2R) enantiomers, whose absolute configurations are the same, had shorter retention times than the derivatives of the (2S) enantiomers; the introduction of a 1-OH group to give ephedrines and pseudoephedrines did not alter the control of the relative retention times by the geometry of the carbon-2.

INTRODUCTION

N-Trifluoroacetyl-L-prolyl (TP) derivatives have been used to separate by gas–liquid chromatography (GLC) the enantiomeric mixtures of various chiral compounds. WESTLEY AND HALPERN[1], who separated many enantiomers, rationalised their results in term of a configurational rule predicting that in most cases TP derivatives of the (R) enantiomer had a shorter retention time than the corresponding diastereoisomer.

Recently, we described[2] a method for the GLC separation of some "ephedrines" and "pseudoephedrines" by means of their TP derivatives. The results confirm and extend the above correlation; the configuration of the carbon-2 (carbon-α to the reacting nitrogen atom) controls the relative retention time irrespective of the configuration of the carbon-1.

This control seems also independent of the GLC conditions, *e.g.* the separation of (+)- and (−)-amphetamine and (+)- and (−)-methylamphetamine using various GLC conditions[3–5].

We now provide information on a series of closely related ring and N-alkyl substituted 1-phenylisopropylamines.

EXPERIMENTAL

Compounds tested

N-Trifluoroacetyl-L-prolyl chloride (TPC), 0.1 *M* in $CHCl_3$ (Regis Chemical Co., Chicago, Ill., U.S.A.; (—)-N-methylamphetamine, kindly supplied by Smith, Kline and French Labs., Philadelphia, Pa., U.S.A.; (+)- and (—)-N-ethylamphetamine, (+)- and (—)-N-*n*-propylamphetamine, (+)- and (—)-N-*n*-butylamphetamine, kindly supplied by E. V. B. SHENOY, Chelsea College (these compounds were prepared by reacting the appropriate amphetamine enantiomer with the appropriate acid anhydride, followed by $LiAlH_4$ reduction[6]); (+)- and (—)-N-cyanoethylamphetamine, kindly supplied by Dr. A. P. GOOSENS[7]; (+)- and (—)-*p*-chloroamphetamine, kindly supplied by Leo Pharmaceutical Products, Denmark; (+)- and (—)-norfenfluramine, (+)- and (—)-fenfluramine, (+)- and (—)-N-allylnorfenfluramine, (+)- and (—)-N-propynylnorfenfluramine*, kindly supplied by Les Laboratoires Servier, Neuilly, France; (+)- and (—)-norephedrine, (+)- and (—)-norpseudoephedrine, kindly supplied by Wellcome Research Laboratories; (+)- and (—)-ephedrine, (+)- and (—)-pseudoephedrine, kindly supplied by Prof. J. B. LAPIDUS, Ohio State University, U.S.A.; (+)- and (—)-N-ethylnorephedrine, (+)- and (—)-N-ethylnorpseudoephedrine, see BECKETT AND TESTA[2].

Preparation of TP derivatives

To *ca.* 50 μl of the amine in chloroform solution *ca.* 10 μl of TPC solution were added. After 10–15 min the solution (1–2 μl) was injected into the chromatograph.

GLC conditions

A Perkin-Elmer F11 gas chromatograph with a flame ionization detector was used. The column was of stainless steel, 2 m long × $^1/_8$ in. O.D., packed with AW, DMCS-treated Chromosorb G (100–120 mesh) coated with 3% SE-30. Oven temperature 170°, injection block temperature *ca.* 220°, nitrogen flow rate 25 ml/min (measured at room temperature), air pressure 30 p.s.i., hydrogen pressure 15 p.s.i.

Separation factor

The separation factor R is obtained from the formula[8]:

$$R = \frac{2(t-t')}{(a+b)}$$

where t and t' are the retention times (in min) of the two peaks considered, and a and b are the width (in min) of the bases of the triangles built by the inflection tangents of the peaks.

Optical rotatory dispersion

Optical rotatory dispersion (ORD) measurements of (+)-fenfluramine, (+)-N-allyl- and (+)-N-propynylnorfenfluramine, as salts in 0.1 *N* HCl and as bases in dioxan, were made using a Bellingham Stanley/Bendix-Ericsson Polarimatic 62 equipped with a 250-W Supersil xenon lamp with constant nitrogen purging, and operation at room temperature.

* Signs of rotation refer to the salts in water.

RESULTS AND DISCUSSION

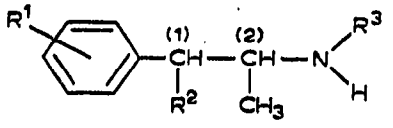
The absolute configurations of (+)- and (−)-amphetamine and their derivatives are known (*e.g.* ref. 9 and refs. cited therein), as are the configurations of the various ephedrines and pseudoephedrines[2]. BECKETT AND BROOKES[9] have established the absolute configurations of the optical isomers of fenfluramine and norfenfluramine. Similarity of the ORD curves shows that (+)-N-allyl- and (+)-N-propynylnorfenfluramine have the same configuration as (+)-fenfluramine.

The GLC results are summarized in Table I. For all compounds tested, the

TABLE I

RETENTION TIMES AND SEPARATION FACTORS OF THE TP DERIVATIVES OF VARIOUS ENANTIOMERIC 1-PHENYLISOPROPYLAMINES

Compounds, general formula:



Chemical names: (A) = amphetamine; (MA) = N-methylamphetamine; (EA) = N-ethylamphetamine; (PA) = N-*n*-propylamphetamine; (BA) = N-*n*-butylamphetamine; (CEA) = N-cyanoethylamphetamine; (CA) = *p*-chloroamphetamine; (NF) = norfenfluramine; (F) = fenfluramine; (ANF) = N-allylnorfenfluramine; (PNF) = N-propynylnorfenfluramine; (NE) = norephedrine; (NPE) = norpseudoephedrine; (E) = ephedrine; (PE) = pseudoephedrine; (ENE) = N-ethylnorephedrine; (ENPE) = N-ethylnorpseudoephedrine. GLC details in text.

Compound	R^1	R^2	R^3	*Configuration*	*Retention times (min)*	*Separation factor R*
(−)-A	H	H	H	(R)	29	1.50
(+)-A				(S)	32	
(−)-MA	H	H	methyl	(R)	52	0.80
(+)-MA				(S)	55	
(−)-EA	H	H	ethyl	(R)	58	1.25
(+)-EA				(S)	63	
(−)-PA	H	H	*n*-propyl	(R)	71	0.80
(+)-PA				(S)	75	
(−)-BA	H	H	*n*-butyl	(R)	94	0.64
(+)-BA				(S)	98	
(−)-CEA	H	H	cyanoethyl	(R)	155	0.45
(+)-CEA				(S)	160	
(−)-CA	*p*-chloro	H	H	(R)	56	2.1
(+)-CA				(S)	65	
(−)-NF	*m*-CF_3	H	H	(R)	26	0.75
(+)-NF				(S)	27.5	
(−)-F	*m*-CF_3	H	ethyl	(R)	46	1.14
(+)-F				(S)	50	

(Continued on p. 288)

TABLE I *(continued)*

Compound	R^1	R^2	R^3	*Configuration*	*Retention times (min)*	*Separation factor R*
(−)-ANF (+)-ANF	*m*-CF_3	H	allyl	(R) (S)	58.5 62	0.87
(−)-PNF (+)-PNF	*m*-CF_3	H	propynyl	(R) (S)	59.7 60.5	0.2[a]
(+)-NE (−)-NE	H	OH	H	(1S:2R) (1R:2S)	62 70	1.33
(−)-NPE (+)-NPE	H	OH	H	(1R:2R) (1S:2S)	64 71	1.15
(+)-E (−)-E	H	OH	methyl	(1S:2R) (1R:2S)	98 105	0.78
(−)-PE (+)-PE	H	OH	methyl	(1R:2R) (1S:2S)	101 105	0.45
(+)-ENE (−)-ENE	H	OH	ethyl	(1S:2R) (1R:2S)	114 121	0.78
(−)-ENPE (+)-ENPE	H	OH	ethyl	(1R:2R) (1S:2S)	113 118	0.56

[a] $R = 0$ when analysed together.

TP derivative of the (2R) enantiomer had a shorter retention time than the (2S) enantiomeric derivative (Figs. 1 and 2). But care must be taken in correlating results with the Cahn–Ingold–Prelog convention. Here, because of the similarity of the *a*, *b*, *c* and *d* groups around the carbon-2, the sequence is the same in all compounds; thus (2R) and (2S) always correspond to the same absolute configurations.

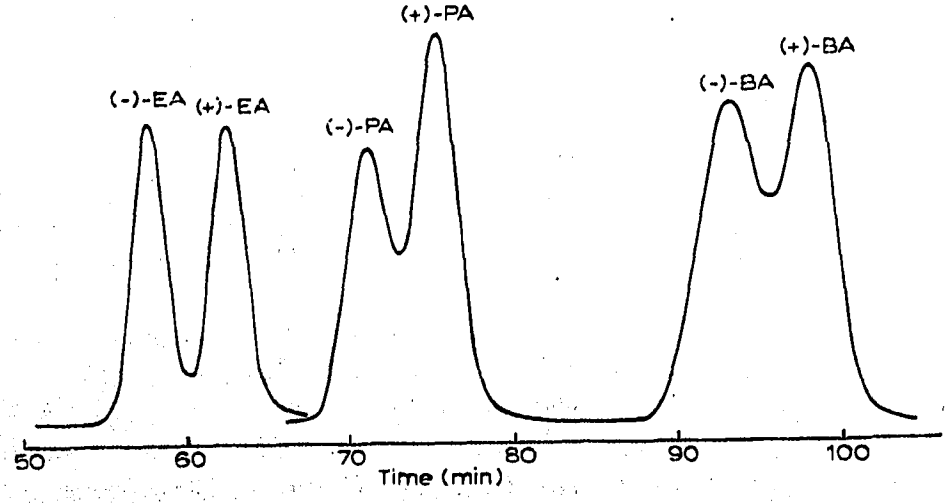


Fig. 1. Graphical combination of three chromatograms, each of them showing the separation of one enantiomeric pair: ethylamphetamine (EA), *n*-propylamphetamine (PA) and *n*-butylamphetamine (BA).

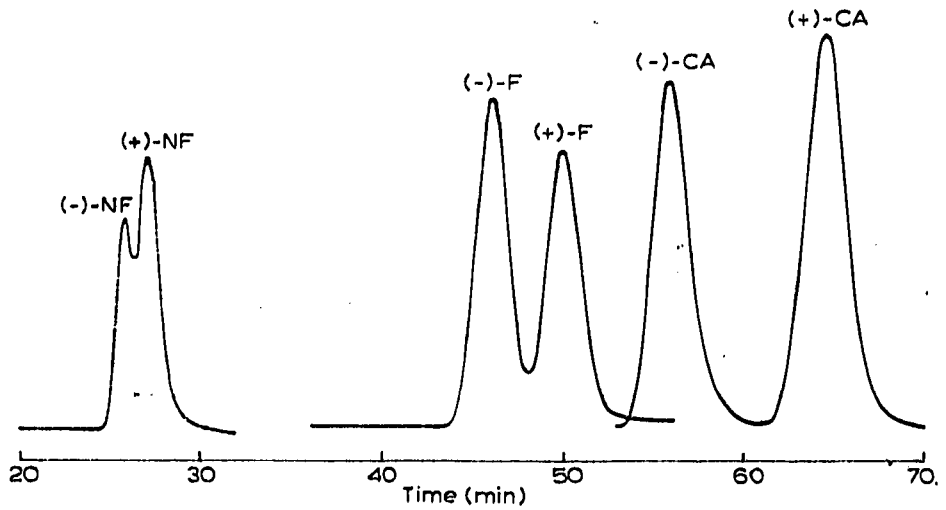


Fig. 2. Graphical combination of three chromatograms, each of them showing the separation of one enantiomeric pair: norfenfluramine (NF), fenfluramine (F) and *p*-chloroamphetamine (CA).

The effective distance between two enantiomeric peaks, which is best represented by the separation factor R, is dependent on the various structural factors involved. These factors can increase R by helping the separation of the two peaks, or they can decrease R by bringing the two peaks closer to each other. But never were they found to be large enough to invert the relative retention times.

The results indicate that the rule of WESTLEY AND HALPERN seems independent of the GLC conditions, and that it can be applied to the compounds tested in the present paper. It is thus reasonable to assign the (2R) configuration to substituted 1-phenylisopropylamines of type I, when both isomers are available, to the TP derivative with the shorter retention time of the isomeric pair, provided R^1, R^2 and R^3 are relatively small groups.

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