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GAS–LIQUID CHROMATOGRAPHY, THIN-LAYER CHROMATOGRAPHY AND CARBON-13 NUCLEAR MAGNETIC RESONANCE SPECTROMETRY IN THE ANALYSIS OF DIASTEREOMERIC MIXTURES OF R–CH(OH)–CH(CH_3)–CH=CH_2 ALCOHOLS

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SUMMARY

Gas–liquid chromatography, thin-layer chromatography and ^{13}C NMR spectrometry have been employed to identify and analyse diastereomeric mixtures of the β-methylalcohols R–CH(OH)–CH(CH_3)–CH=CH_2 where R = CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9, *n*-C_5H_{11}, *iso*-C_3H_7, *sec.*-C_4H_9, *tert.*-C_4H_9. The existence of a relationship between the analytical data and diastereomeric configuration of the alcohols is pointed out for all the three methods adopted.

INTRODUCTION

The formation of stereochemically defined β-methylalkanols of the type R–CH(OH)–CH(CH_3)–CH=CH_2, prepared by addition of metal enolates or allylmetal compounds to aldehydes, is very important in the synthesis of macrolides and polyether antibiotics, as well as of some pheromones[1,2]. So far, mixtures of diastereomeric alcohols have been obtained by addition of many crotylmetal compounds to aldehydes[1,3–5].

In the present work, gas–liquid chromatography (GLC), thin-layer chromatography (TLC) and ^{13}C NMR spectrometry have been used to identify and analyse the diastereomeric mixtures of R–CH(OH)–CH(CH_3)–CH=CH_2, where R = CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9, *n*-C_5H_{11}, *iso*-C_3H_7, *sec.*-C_4H_9, *tert.*-C_4H_9.

EXPERIMENTAL

Materials

The diastereomeric mixtures of R–CH(OH)–CH(CH_3)–CH=CH_2 were prepared by the addition reaction of dibutylcrotyltin chloride with aldehydes RCHO[5].

Pure samples of *threo*- and *erythro*-homoallylic alcohols were obtained by separation of the mixtures with a Hewlett-Packard Scientific 700 gas chromatograph/thermal energy analyser equipped with a 3 m × 6.4 mm O.D. column packed with

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10% (w/w) Carbowax 20M on Chromosorb P (30–60 mesh). The helium carrier gas flow-rate was 20 ml/min, the injector temperature was 240°C, the detector temperature was 250°C and the oven temperature was in the range 100–130°C according to the alcohol to be analysed.

Gas chromatography

Pure *threo-* and *erythro*-alcohols were dissolved in diethyl ether (1%) solution. The samples were analysed with a Perkin-Elmer Model Sigma 3B gas chromatograph equipped with flame ionization detection (FID) and a 2 m × 3.2 mm O.D. column packed with 10% (w/w) LAC 860 on Chromosorb. The nitrogen carrier gas flow-rate was 20 ml/min, and the injector, detector and oven temperatures were 250, 270 and 105°C respectively. The retention times of the alcohols were measured with respect to the diethyl ether. The relative detector response factors for the *threo* and *erythro* isomers have the same values.

Thin-layer chromatography

The pure *threo-* and *erythro*-alcohols were dissolved in diethyl ether and 1–10 μl of the samples were applied with a microsyringe 1.5 cm from the lower edge of the plate (Kieselgel 60 F_{254}, 10 × 5 cm plates, Merck art. 5720) and dried by an air blower. Ascending development at room temperature was effected in a glass chamber equilibrated with the solvent. The following solvent systems were employed: S_1 = 10% solution of diethyl ether in light petroleum (b.p. 40–60°C); S_2 = 20% solution of diethyl ether in light petroleum; S_3 = 10% solution of ethyl acetate in hexane and S_4 = 10% solution of ethyl acetate in light petroleum.

Usually 10–15 min were required for the solvent front to cover a distance of 8 cm. The plates were then dried and the spots were detected in an iodine vapour chamber or by spraying with 50% sulphuric acid and kept for 15 min at 110°C. In both cases the alcohols were revealed as brown spots on a white background.

Multiple development of the plates was also carried out. The diastereomeric mixtures of each alcohol (1% diethyl ether solution) were applied (1–10 μl) and TLC was carried out with all the solvent systems (S_1–S_4). The plates were then removed from the chamber and the solvent was allowed to evaporate; they were then returned to the same solvent and developed a number of times depending on the separation to be achieved[6].

^{13}C NMR spectrometry

The spectra of diastereomeric mixtures of the β-methylalcohols were recorded at a fixed temperature (303K) on a Bruker WH 90 spectrometer operating in Fourier Transform (FT) mode. The off-resonance decoupling technique permitted the assignment of the ^{13}C NMR signals, since the typical multiplet structure of the carbon resonance lines was retained. In order to determine the mixture composition, sufficiently long pulse intervals (at least 25 s) were used to avoid partial saturation of ^{13}C resonances, and the gated decoupling method was employed to eliminate the nuclear Overhauser effect (NOE)[7].

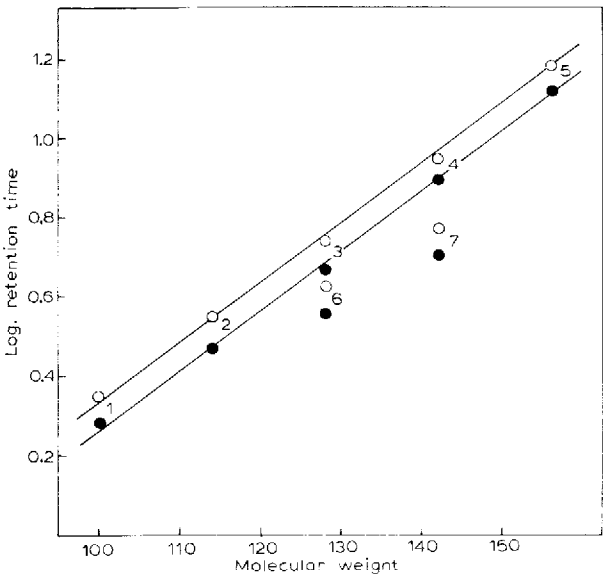

Fig. 1. Plot of log t_R against the molecular weight for β-methylalcohol (1–7 in Table I). ●, *threo*-isomer; ○, *erythro*-isomer.

RESULTS AND DISCUSSION

GC

The retention times of the *threo*- and *erythro*-alcohols are reported in Table I and a plot of log t_R *versus* molecular weight is given in Fig. 1. Linearity is found only for the homologous series of compounds 1–5 (*cf.*, Table I), as expected.

The four diastereomeric alcohols with R = *sec.*-C_4H_9 could not be separated under the conditions employed, only three peaks were detected, having retention times of 5.9, 7.8 and 8.0 min. The corresponding collected fractions were designated as A, B and C respectively and used in the other analytical methods (see below).

The results obtained reveal the existence of a relationship between the configuration of the alcohols and the relative retention times, *i.e.*, t_R (*erythro*) > t_R (*threo*).

TABLE I

GLC RETENTION TIMES, t_R, OF THE EXAMINED ALCOHOLS R–CH(OH)–CH(CH_3)–CH=CH_2

Alcohol No.	*R*	t_R *(min)*	
		Threo-isomer	*Erythro-isomer*
1	CH_3	2.0	2.3
2	C_2H_5	3.0	3.6
3	*n*-C_3H_7	4.8	5.6
4	*n*-C_4H_9	8.1	9.1
5	*n*-C_5H_{11}	13.7	15.7
6	*iso*-C_3H_7	3.7	4.4
7	*tert.*-C_4H_9	5.3	6.2

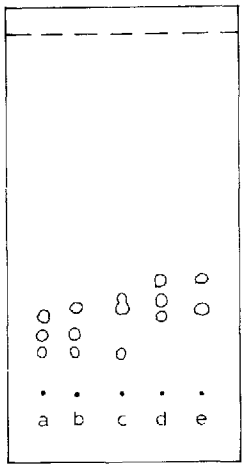

Fig. 2. TLC separation of R–CH(OH)–CH(CH_3)–CH=CH_2 mixtures using solvent system S_2. (a) R = CH_3, C_2H_5, *n*-C_3H_7 (R_F = 0.11, 0.17, 0.21); (b) R = CH_3, C_2H_5, *n*-C_4H_9 (R_F = 0.11, 0.17, 0.23); (c) R = CH_3, *n*-C_4H_9, *n*-C_5H_{11} (R_F = 0.11, 0.23, 0.25); (d) R = *n*-C_3H_7, *n*-C_5H_{11}, *tert.*-C_4H_9 (R_F = 0.21, 0.25, 0.31); (e) R = *iso*-C_3H_7, *tert.*-C_4H_9 (R_F = 0.23, 0.31).

This finding is in agreement with previous reports[8,9] since in the *threo* configuration the vinyl group is more able to form an intramolecular hydrogen bond with the hydroxyl group.

TLC

The R_F differences between the *threo*- and *erythro*-isomers of each alcohol are in the range 0.01–0.02, for all the solvent systems used. As a consequence, this method cannot be adopted for resolving these mixtures.

Nevertheless, it is to be noted that the R_F (*threo*) values are always greater than the R_F (*erythro*) values. This trend was confirmed by the results obtained with multiple development (see below). In addition, in the light of previous reports[10–13],

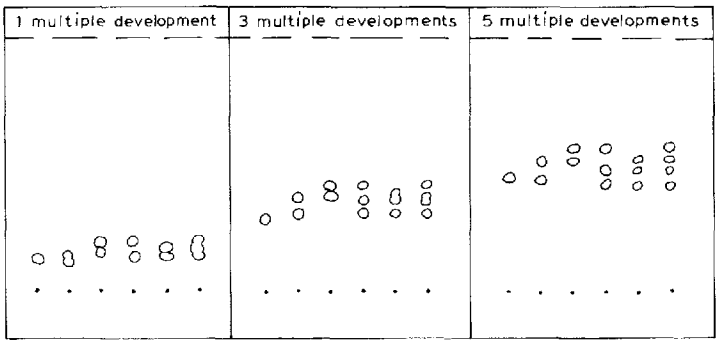

Fig. 3. TLC separation of diastereomeric alcohols, using solvent system S_1. (a) R = *n*-C_3H_7, *threo/erythro* mixture; (b) R = *iso*-C_3H_7, *threo/erythro* mixture; (c) R = *sec.*-C_4H_9, A and B mixture; (d) R = *sec.*-C_4H_9, A and C mixture; (e) R = *sec.*-C_4H_9, B and C mixture; (f) R = *sec.*-C_4H_9, sample of the original alcohol prepared. A, B and C represent the three fractions collected by GC.

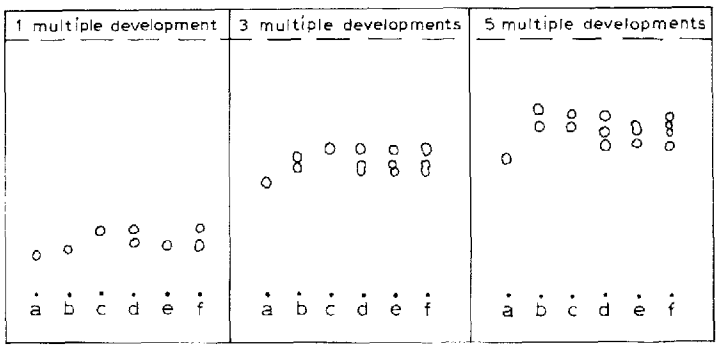

Fig. 4. TLC separation of diastereomeric alcohols, using solvent system S_3. Details as in Fig. 3.

TLC with ascending development offers a good, rapid resolution of alcohol mixtures having different R groups, as shown in Fig. 2, where the corresponding R_F values are also reported.

The multiple developments performed for alcohols with R = *n*-C_3H_7, *iso*-C_3H_7 and *sec*.-C_4H_9 using the solvent systems S_1 and S_3 are shown in Figs. 3 and 4 respectively. Analogous results have been obtained with the solvent systems S_2 and S_4. A good separation of the examined diastereomeric mixtures takes place only when R is a branched group, *cf.*, samples b–f in Figs. 3 and 4.

A significant example of the separation and identification is given by the ΔR_F value (0.06) between the *threo*- and *erythro*-alcohols with R = *iso*-C_3H_7 found after the third multiple development with both systems S_1 and S_3, *cf.*, sample b, Figs. 3 and 4. The individual R_F values are: 0.36 (*threo*) and 0.30 (*erythro*) with system S_1; 0.56 (*threo*) and 0.50 (*erythro*) with system S_3.

This method allows the complete separation of the four diastereomeric alcohols with R = *sec*.-C_4H_9, after five multiple developments (sample f, *cf.*, Figs. 3 and 4): four spots are found having R_F 0.56, 0.51, 0.47 and 0.42 with system S_1 and R_F 0.70, 0.66, 0.63 and 0.59 with system S_3.

A comparison of sample f with c, d and e (*cf.*, Figs. 3 and 4) allows one to establish that the fractions A and B are pure diastereoisomers, whereas C is a mixture of the other two.

^{13}C NMR spectrometry

The carbon-13 chemical shifts of the examined alcohols are listed in Table II. The signal of each carbon is split into a doublet whose intensity ratio is dependent on the *threo/erythro* composition.

In order to identify the *threo*- and *erythro*-isomers in a given mixture of alcohols, pure samples of the *threo*- and *erythro*-isomers of alcohol 3 (*cf.*, Table I) (separated by GC) were mixed in the ratio 2:1. The spectrum of this system in the olefinic region shows two inner lines, $\delta(=CH)$ 141.0 ppm and $\delta(=CH_2)$ 115.4 ppm, *cf.*, Table II), corresponding to the *threo*-isomer and other two outer lines, $\delta(=CH)$ 142.0 ppm and $\delta(=CH_2)$ 114.5 ppm, corresponding to the *erythro*-isomer, as shown in Fig. 5. The spectra of all the other alcohols examined show an analogous pattern.

We have observed that along this series the differences, $\Delta\delta$(ppm), between the

TABLE II

^{13}C NMR CHEMICAL SHIFTS* OF THE CARBINOLS

Carbinol	*Diastereoisomer*	*Carbon atom*										
		1	*2*	*3*	*3'*	*4*	*5*	*5'*	*6*	*7*	*8*	*9*
$\overset{1}{CH_2}=\overset{2}{CH}-\overset{3}{CH}(\overset{3'}{CH_3})-\overset{4}{CH}(OH)-\overset{5}{CH_3}$**	*erythro*	114.4	141.2	45.3	15.9	70.8	19.8					
	threo	114.8	141.4	45.6	15.3	71.0	20.5					
$\overset{1}{CH_2}=\overset{2}{CH}-\overset{3}{CH}(\overset{3'}{CH_3})-\overset{4}{CH}(OH)-\overset{5}{CH_2}-\overset{6}{CH_3}$**	*erythro*	114.1	142.1	44.3	15.6	76.6	27.6		10.6			
	threo	114.8	141.0	44.0	16.3	76.6	27.4		10.6			
$\overset{1}{CH_2}=\overset{2}{CH}-\overset{3}{CH}(\overset{3'}{CH_3})-\overset{4}{CH}(OH)-\overset{5}{CH_2}-\overset{6}{CH_2}-\overset{7}{CH_3}$	*erythro****	114.5	142.0	44.5	15.0	74.8	36.9		19.6	14.2		
	*threo****	115.4	141.0	44.5	16.4	74.8	36.9		19.4	14.2		
$\overset{1}{CH_2}=\overset{2}{CH}-\overset{3}{CH}(\overset{3'}{CH_3})-\overset{4}{CH}(OH)-\overset{5}{CH_2}-\overset{6}{CH_2}-\overset{7}{CH_2}-\overset{8}{CH_3}$												
	*erythro****	113.0	142.0	44.4	15.2	75.1	34.4		28.7	23.1	14.2	
	*threo****	114.4	141.0	44.4	16.4	75.1	34.3		28.6	23.1	14.2	
$\overset{1}{CH_2}=\overset{2}{CH}-\overset{3}{CH}(\overset{3'}{CH_3})-\overset{4}{CH}(OH)-\overset{5}{CH_2}-\overset{6}{CH_2}-\overset{7}{CH_2}-\overset{8}{CH_2}-\overset{9}{CH_3}$												
	*erythro****	114.5	142.0	44.4	14.9	75.0	34.7		32.4	26.2	23.1	14.2
	*threo****	115.4	141.0	44.4	16.4	75.0	34.7		32.4	26.0	23.1	14.2

$^{1}CH_2=^{2}CH-^{3}CH(^{3'}CH_3)-^{4}CH(OH)-^{5}CH(^{5'}CH_3)-^{6}CH_3$**

erythro	113.9	142.5	41.8	15.4§	79.7	30.9	16.7§	20.1§	
threo	115.0	140.8	41.5	15.7§	80.0	31.2	17.8§	19.8§	

$^{1}CH_2=^{2}CH-^{3}CH(^{3'}CH_3)-^{4}CH(OH)-^{5}CH(^{5'}CH_3)-^{6}CH_2-^{7}CH_3$**

erythro§§	*SSS,RRR*	113.9	142.8	41.2	13.6§§§	79.0	37.8§§§	16.0§§§	24.4§§§	11.4
		(113.9)	(142.5)	(41.9)		(78.3)				(11.4)
	RSS,SRR	113.9	142.2	42.7	12.7	77.6	37.5	16.8	26.8	11.4
threo§§	*SRS,RSR*	115.2	141.7	41.8	13.3	77.4	37.2	17.2	26.8	11.7
		(115.2)	(141.2)	(41.5)		(78.2)				(11.7)
	SSR,RRS	115.2	140.7	41.2	14.5§§§	79.0	38.1§§§	18.0§§§	23.8§§§	11.7

$^{1}CH_2=^{2}CH-^{3}CH(^{3'}CH_3)-^{4}CH(OH)-^{5}C\equiv^{6}(CH_3)_3$**

erythro	112.5	144.9	40.5	16.1	81.6	36.1	27.1	
threo	114.2	141.1	40.5	21.6	82.8	36.1	27.1	

* In ppm from internal tetramethylsilane for pure liquids.

** See also ref. 5.

*** Chemical shifts in $C^2H_2Cl_2$.

§ The assignment is only tentative.

§§ This formalism is used in order to compare this system with the others. The calculated barycentres of the resonance lines of the pairs of diastereoisomers are given in parentheses.

§§§ These figures may be interchanged within each column.

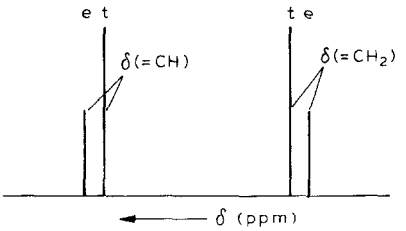

Fig. 5. ^{13}C NMR pattern of the olefinic carbon signals. t = *threo*-isomer; e = *erythro*-isomer.

chemical shifts $\delta(=CH)$ and $\delta(=CH_2)$ of the inner lines lie in a narrower range in comparison with the outer lines: $\Delta\delta$(inner) = 26.2 ± 0.6 ppm, $\Delta\delta$(outer) = 29.6 ± 2.8 ppm.

It is to be noted that the *threo*-form is stabilized in the eclipsed structure owing to intramolecular interactions between –OH and $-CH=CH_2$ groups[8]. Thus, it is likely that the chemical environment around the olefinic carbons in such isomers does not change very much on varying the steric hindrance of the R group. On the contrary, changes are to be expected for the *erythro*-isomer. Hence the pattern depicted in Fig. 5 applies to all the alcohols examined, that is the inner lines belong to the *threo*-isomer and the outer to the *erythro*-isomer.

Integration of these signals, as indicated above, allows a quantitative analysis of the *threo/erythro* mixtures. The results obtained are in good agreement with the GC data. For example, the *threo/erythro* composition of alcohols 3–5 (*cf.*, Table I) detected by GC and ^{13}C NMR are: 53/47 (GC), 53/47 (^{13}C NMR); 50/50, 49/51; 55/45, 54/46 respectively.

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