DETERMINATION OF THE threo- AND erythro- CONFIGURATIONS OF VICINAL DIASTEREOMERIC DERIVATIVES OF HIGHER FATTY ACIDS WITH THE AID OF PMR SPECTRA

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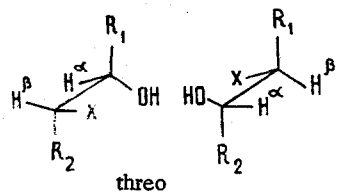
PMR spectroscopy is used successfully in the study of the sterochemistry of diastereomeric compounds in which two chiral centers lead to the existence of threo and erythro forms. Thus, for example, it has been shown that for symmetrical and unsymmetrical α-glycols [1, 2], β-diols [3], γ-glycols [4], amino alcohols [5, 6], and β-hydroxy esters [7] the chemical bonds of the methine protons of the erythro isomers are located in a weaker field than those of the threo isomers, i.e., the condition δCH(erythro) > δCH(threo) is satisfied. However, this relationship is not always observed. In individual cases — for example, for disubstituted butanes [8] and derivatives of 1,2-diphenylpropane [9] — there is not clear correlation between the configuration and the δCH value, and the relative magnitude of Δδ = δCH(erythro) — δCH(threo) has a positive or negative value according to the nature of the substituent.

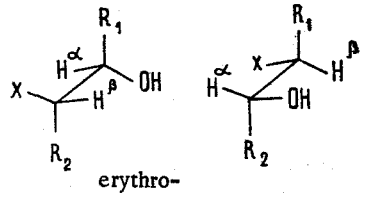
Other cases are known in which the chemical shifts of the methine protons of diastereomeric compounds are practically identical, although their spin-spin coupling constants differ, and here again there is no direct correlation between the configuration and the value of J. For such compounds as substituted 1,2-dihalopropanes, 1,2-diphenylpropanes [9], and others [8, 11], $J_{erythro} > J_{threo}$, and for acyloxylated or alkoxylated 2-amino-1,2-diphenylethanes [12], 2-dimethylamino-1,2-diphenylethanols [13], and other compounds [2, 3], $J_{erythro} < J_{threo}$.

Information on the PMR spectra of diastereomeric derivatives of higher fatty acids is sparse. The chemical shifts of the protons of individual groups have been given for some diastereomeric pairs: threo- and erythro-6,7-dihydroxy-, -9,10-dibromo- [14], and -9-chloro-10-hydroxyoctadecanoic acids [14, 15], and threo-9,10-dihydroxyoctadecanoic acid [14].

In the present paper we give the results of an investigation by the PMR method of position isomers of threo- and erythro-dihydroxy-, acetoxy-hydroxy, and -halohydroxyoctadecanoic and -docosanoic acids and their trimethylsilyl derivatives.



threo



erythro-

$X = OH,\ OCOCH_3,\ Cl,\ Br,\ OSi(CH_3)_3$ at $m = 4,\ n = 10$; $m = 7,\ n = 7$; $m = 11,\ n = 7$

$R_1 = (CH_2)_m\underline{COOH}(CH_3)$

$R_2 = (CH_2)_n CH_3$

In the PMR spectra of the above-mentioned compounds in the 3-5-ppm region there are two multiplets which are due to the two nonequivalent protons H^{α} ($\underline{CH}^{\alpha}OH$) and H^{β} ($\underline{CH}^{\beta}X$). The assignment of the signals of the methine protons was made on the basis of a comparison of the PMR spectra of the corresponding dihydroxy-, acetoxyhydroxy-, acetoxybromo-, and halohydroxyoctadecanoic and -docosanoic acids taken under standard conditions.

Table 1 gives the values of the chemical shifts of the protons in the PMR spectra of the diastereomeric compounds studied. It must be mentioned that the PMR spectra of the individual position isomers and their mixtures are identical, as we showed for the case of the halohydroxy acids as examples.

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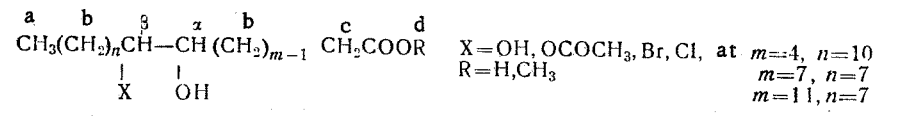
TABLE 1. Chemical Shifts in the PMR Spectra of Diastereomeric Derivatives of Higher Fatty Acids (δ, ppm, 100 MHz, benzene)



Compound	Configuration	Chemical shift									
		a	b	c	CH^{α}	$\Delta\delta CH^{\alpha} = \delta CH^{\alpha}_{erythro} - \delta CH^{\alpha}_{threo}$	CH^{β}	$\Delta\delta CH^{\beta} = \delta CH^{\beta}_{erythro} - \delta CH^{\beta}_{threo}$	d	$OCOCH_3$
Methyl esters of dihydroxy acids										
Methyl 6,7-dihydroxyoctadecanoate	erythro	0,92	1,35	2,21	3,58	0,25			3,40	
	threo	0,91	1,35	2,16	3,33				3,38	
Methyl 9,10-dihydroxyoctadecanoate	erythro	0,93	1,33	2,15	3,55	0,16			3,39	
	threo	0,92	1,32	2,16	3,39				3,39	
Methyl 13,14-dihydroxyoctadecanoate	erythro	0,92	1,33	2,15	3,57	0,22			3,38	
	threo	0,93	1,33	2,17	3,35				3,39	
Acetoxyhydroxy acids										
6(7)-Acetoxy-7(6)-hydroxyoctadecanoic	erythro	0,93	1,32	2,19	3,71	0,17	5,01			1,85
	threo	0,91	1,29	2,18	3,54		4,95			1,83
9(10)-Acetoxy-10(9)-hydroxyoctadecanoic	erythro	0,91	1,27	2,17	3,69	0,16	5,00			1,83
	threo	0,89	1,27	2,11	3,53		4,98			1,83
13(14)-Acetoxy-14(13)-hydroxydoeosanoic acid	erythro	0,91	1,29	2,15	3,71	0,11	5,05			1,81
	threo	0,91	1,28	2,16	3,60		5,01			1,82
Halohydroxy acids										
6(7)-Bromo-7(6)-hydroxyoctadecanoic	erythro	0,94	1,34	2,15	3,56	0,22	3,96	0,13		
	threo	0,93	1,34	2,15	3,34		3,83			
7-Bromo-6-hydroxyoctadecanoic acid	erythro	0,93	1,34	2,15	3,54	0,22	3,95	0,12		
	threo	0,93	1,33	2,16	3,32		3,83			
6-Bromo-7-hydroxyoctadecanoic acid	erythro	0,93	1,32	2,14	3,57	0,24	3,93	0,12		
	threo	0,94	1,33	2,16	3,33		3,81			
9(10)-Bromo-10(9)-hydroxyoctadecanoic	erythro	0,93	1,30	2,16	3,61	0,21	4,00	0,09		
	threo	0,94	1,31	2,17	3,40		3,91			
10-Bromo-9-hydroxyoctadecanoic acid	erythro	0,93	1,29	2,16	3,60	0,22	3,99	0,11		
	threo	0,94	1,31	2,15	3,38		3,88			
9-Bromo-10-hydroxyoctadecanoic acid	erythro	0,93	1,31	2,14	3,60	0,23	4,00	0,11		
	threo	0,94	1,31	2,16	3,37		3,89			
13(14)-Bromo-14(13)-hydroxydocosanoic acid	erythro	0,94	1,29	2,17	3,62	0,22	4,02	0,12		
	threo	0,93	1,29	2,16	3,40		3,90			
6(7)-Chloro-7(6)-hydroxyoctadecanoic	erythro	0,92	1,31	2,14	3,54	0,12	3,77	0,10		
	threo	0,93	1,30	2,15	3,42		3,67			
7-Chloro-6-hydroxyoctadecanoic acid	erythro	0,92	1,31	2,14	3,52	0,10	3,77	0,09		
	threo	0,93	1,30	2,15	3,42		3,68			
6-Chloro-7-hydroxyoctadecanoic acid	erythro	0,92	1,32	2,10	3,56	0,13	3,72	0,09		
	threo	0,91	1,30	2,09	3,43		3,63			
9(10)-Chloro-10(9)-hydroxydecanoic acid	erythro	0,92	1,27	2,14	3,62	0,09	3,84	0,11		
	threo	0,91	1,27	2,15	3,53		3,73			
10-Chloro-9-hydroxyoctadecanoic acid	erythro	0,91	1,25	2,14	3,60	0,11	3,82	0,09		
	threo	0,92	1,27	2,16	3,49		3,73			
9-Chloro-10-hydroxyoctadecanoic acid	erythro	0,92	1,26	2,15	3,61	0,09	3,81	0,10		
	threo	0,92	1,26	2,14	3,52		3,71			
13(14)-Chloro-14(13)-hydroxydocosanoic acid	erythro	0,92	1,28	2,15	3,62	0,09	3,83	0,08		
	threo	0,93	1,29	2,15	3,53		3,75			

It follows from an analysis of the facts presented that for the dihydroxy, halohydroxy, and acetoxyhydroxy acids and their esters the signal of the $\underline{CH}^{\alpha}(OH)$ methine proton for the erythro form is shifted downfield in comparison with the threo form, i.e., $\delta(\underline{CH}^{\alpha}OH)_{erythro} > \delta(\underline{CH}^{\alpha}OH)_{threo}$ as in the case of α-glycols and β-diols [1-3]. The relative shift $\Delta\delta(CH^{\alpha}OH) = \delta_{erythro} - \delta_{threo}$ amounts to 8-11 Hz for the chlorohydroxy, 10-17 Hz for the acetoxyhydroxy, 16-20 Hz for the dihydroxy, and 20-22 Hz for the bromohydroxyoctadecanoic and -docosanoic acids (and esters).

The value of $\delta\underline{CH}(OCOCH_3)$ for all series of acetoxyhydroxy acids is approximately the same, amounting to 5-5.09 ppm. For the series of halohydroxy acids the signals of the δCH^{β}-(Hal) protons of the erythro derivatives are found in lower fields than those of the threo

derivatives, and $\Delta\delta(CH^{\beta}Hal) = \delta_{erythro} - \delta_{threo}$ has approximately the same value for the bromohydroxy and for the chlorohydroxy acids, amounting to 8-11 Hz.

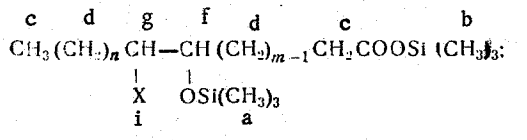
A comparison of the chemical shifts of the $\underline{CH}^{\beta}(Hal)$ protons shows that the values of $\delta\underline{CH}^{\beta}(Br)$ (3.87-4.06 ppm) are somewhat greater than $\delta\underline{CH}^{\beta}(Cl)$ (3.72-3.89 ppm). Thus, for the halohydroxy acids no correlation is observed between the electronegativity of the substituent (Cl, Br) and the values of $\delta CH(Hal)$, just as for the case of the 2,3-dibromo- and 2,3-dichlorobutanes [8] and the halogen-substituted 1,2-diphenylethanes [16].

The difference in the chemical shifts of the $\underline{CH}^{\alpha}(OH)$ and $\underline{CH}^{\beta}(X)$ (X = OH, Cl, Br) methine protons for the erythro and threo derivatives is apparently explained by the fact that in the erythro form each of the methine protons experiences the descreening action of β substituents to a greater degree than in the threo form.

When an alcoholic hydroxyl in the compounds investigated is replaced by an $OSi(CH_3)_3$ group, the values of $\delta\underline{CHOSi}(CH_3)_3$ for the threo and erythro forms scarcely differ for the case of the acetoxyhydroxy acids, while in the case of the dihydroxy acids for the threo form the signal is shifted downfield somewhat, $\Delta\delta\underline{CHOSi}(CH_3)_3 = \delta_{threo} - \delta_{erythro}$ amounting to 5-10 Hz. The greatest difference is observed in the PMR spectra of the silylated diastereomeric bromohydroxy acids: The $\underline{CHOSi}(CH_3)_3$ and CHBr methine protons of the threo derivatives give individual multiplets, and for the erythro derivative these protons give a common unresolved multiplet shifted downfield. The relative change in the chemical shift $\Delta\delta CHOSi(CH_3)_3 = \delta_{erythro} - \delta_{threo}$ amounts to 9-13 Hz. Thus, the PMR spectra of the TMS derivatives permit a clear conclusion to be drawn concerning the configuration only in the case of the bromohydroxy acids, and for the TMS derivatives of the dihydroxy and acetoxyhydroxy acids the differences in the PMR spectra of the threo and erythro forms are small (Table 2).

However, when the PMR spectra of the dihydroxy-, acetoxyhydroxy-, and halohydroxyoctadecanoic and -docosanoic acids and their TMS derivatives are compared (see Tables 1 and 2), an interesting relationship is observed. For all the compounds investigated, when a CHOH group

TABLE 2. Chemical Shifts in the PMR Spectra of the Trimethylsilyl-Substituted Diastereomeric Derivatives of Higher Fatty Acids (δ, ppm, 100 MHz, benzene)



X = $OSi(CH_3)_3$, $OCOCH_3$, Br; at $m=4, n=10$; $m=7, n=7$; $m=11, n=7$

Derivative	Configuration	Chemical shift							
		a	b	c	d	e	f	g	i
TMS-6,7-dihydroxyoctadecanoic acid	erythro	0,18	0,26	0,91	1,31	2,21	3,60		
	threo	0,18	0,28	0,91	1,32	2,23	3,70		
TMS-9,10-dihydroxyoctadecanoic acid	erythro	0,22	0,28	0,92	1,32	2,20	3,66		
	threo	0,18	0,26	0,91	1,31	2,18	3,72		
TMS-13,14-dihydroxydocosanoic acid	erythro	0,22	0,28	0,93	1,31	2,20	3,68		
	threo	0,18	0,25	0,90	1,30	2,20	3,73		
TMS-6(7)-acetoxy-7(6)-hydroxyoctadecanoic acid	erythro	0,16	0,27	0,92	1,31	2,18	3,73	5,03	1,83
	threo	0,18	0,26	0,92	1,32	2,20	3,78	5,06	1,80
TMS-9(10)-acetoxy-10(9)-hydroxyoctadecanoic acid	erythro	0,17	0,26	0,91	1,29	2,19	3,83	5,07	1,84
	threo	0,20	0,27	0,92	1,31	2,19	3,82	5,11	1,81
TMS-13(14)-acetoxy-14(13)-hydroxydocasanoic acid	erthro	0,19	0,27	0,92	1,29	2,18	3,83	5,09	1,82
	threo	0,21	0,28	0,92	1,30	2,15	3,85	5,08	1,81
TMS-6(7)-bromo-7(6)-hydroxyoctadecanoic acid	erthro	0,15	0,25	0,91	1,28	2,15	3,84		
	threo	0,08	0,25	0,91	1,29	2,13	3,75 / 3,89		
TMS-9(10)-bromo-10(9)-hydroxyoctadecanoic acid	erthro	0,17	0,24	0,90	1,27	2,15	3,90		
	threo	0,11	0,25	0,91	1,28	2,14	3,80 / 3,96		
TMS-13(14)-bromo-14(13)-hydroxydocosanoic acid	erthro	0,17	0,25	0,92	1,27	2,17	3,95		
	threo	0,10	0,24	0,91	1,26	2,17	3,82 / 3,98		

TABLE 3. Difference in the Values of the Chemical Shifts of the Methine Protons in the PMR Spectra of the Dihydroxy, Acetoxyhydroxy, and Bromohydroxy Acids and Their TMS derivatives for the threo and erythro Forms (δ, ppm, 100 MHz, benzene)

Compound	Configuration	Chemical shift		
		$\underline{C}HOH$	$\underline{C}HOSi(CH_3)_3$	$\Delta\delta = \delta\underline{C}HOSi(CH_3)_3 - \delta\underline{C}HOH$
Methyl 6,7-dihydroxyoctadecanoate	erythro	3,58		
	threo	3,33		
TMS-6,7-dihydroxyoctadecanoic acid	erythro		3,60	0,02
	threo		3,70	0,37
Methyl 9,10-dihydroxyoctadecanoate	erythro	3,55		
	threo	3,39		
TMS-9,10-dihydroxyoctadecanoic acid	erythro		3,66	0,09
	threo		3,72	0,33
Methyl 13,14-dihydroxydocosanoate	erythro	3,57		
	threo	3,35		
TMS-13,14-dihydroxydocosanoic acid	erythro		3,68	0,11
	threo		3,73	0,38
6(7)-Acetoxy-7(6)-hydroxyoctadecanoic acid	erythro	3,71		
	threo	3,54		
TMS-6(7)-acetoxy-7(6)-hydroxydecanoic acid	erythro		3,77	0,06
	threo		3,78	0,24
9(10)-Acetoxy-10(9)-hydroxydecanoic acid	erythro	3,69		
	threo	3,53		
TMS-9(10)-acetoxy-10(9)-hydroxydocosanoic acid	erythro		3,83	0,14
	threo		3,82	0,29
13(14)-Acetoxy-14(13)-hydroxydocosanoic acid	erythro	3,71		
	threo	3,60		
TMS-13(14)-acetoxy-14(13)-hydroxydocosanoic acid	erythro		3,86	0,15
	threo		3,85	0,25
6(7)-Bromo-7(6)-hydroxyoctadecanoic acid	erythro	3,56		
	threo	3,34		
TMS 6(7)-bromo7(6)-hydroxyoctadecanoic acid	erythro		3,84	0,28
	threo		3,75	0,41
9(10)-Bromo-10(9)-hydroxyoctadecanoic acid	erythro	3,60		
	threo	3,40		
TMS- bromo-10(9)-octadecanoic acid	erythro		3,90	0,30
	threo		3,80	0,40
13(14)-Bromo-14(13)-hydroxydocosanoic acid	erythro	3,62		
	threo	3,40		
TMS-13(14)-bromo-14(13)-hydroxydocosanoic acid	erythro		3,95	0,32
	threo		3,82	0,42

is replaced by a $CHOSi(CH_3)_3$ group the signal of the methine protons shifts downfield, i.e. $\delta\underline{C}HOSi(CH_3)_3 - \delta\underline{C}HOH > 0$, and in all cases the greatest value of this change is found for the threo derivatives (Table 3).

In the PMR spectra of the TMS derivatives of all the compounds investigated a sharp singlet of the methyl protons of the $COOSi(CH_3)_3$ group was observed at 0.29-0.33 ppm. The position of the second singlet of the methyl protons of the $CHOSi(\underline{C}H_3)_3$ group for the TMS derivatives of the threo and erythro-dihydroxy- and -acetoxyhydroxy acids was approximately the same — at δ 0.23-0.27 ppm — but in the case of the halohydroxy acids for the threo derivatives the values of $\delta CHOSi(\underline{C}H_3)_3$ were shifted somewhat upfield as compared with the erythro derivatives, $\Delta\delta CHOSi(\underline{C}H_3)_3 = \delta erythro - \delta threo$ amounting to 14-16 Hz.

An analysis of the PMR spectra of the diastereomeric dihydroxy-, acetoxyhydroxy-, and halohydroxyoctadecanoic and -docosanoic acids and their TMS derivatives shows that the difference in the chemical shifts of the vicinal methine protons may serve as a good criterion for determining the threo and erythro configurations of higher fatty acid derivatives.

EXPERIMENTAL

The PMR spectra were taken on a Varian HA-100 D/15 (100 MHz) instrument in benzene. TMS was used as internal standard. The accuracy of the measurements of the chemical shifts was 0.01-0.02 ppm. The concentration of the solutions was 8-10%. We had synthesized the threo- and erythro-halohydroxy acids previously [17], and the threo- and erythro-dihydroxy- and -acetoxyhydroxy acids were obtained in accordance with previous work [18].

The trimethylsilyl derivatives of the corresponding compounds were obtained by treating them with hexamethyldisilazane and chlorotrimethylsilane (2:1) in pyridine solution [19]. The acids were methylated with diazomethane in ethereal solution at room temperature.

The analytical results for all the compounds obtained corresponded to the calculated figures.

CONCLUSIONS

The PMR spectra of vicinal diastereomeric dihydroxy-, acetoxyhydroxy-, and halohydroxy-octadecanoic and -docosanoic acids and their trimethylsilyl derivatives have been considered. It has been shown that the signals of the methine protons of the erythro isomers appear at lower fields than those of the threo isomers. On passing from the dihydroxy, acetoxyhydroxy, and halohydroxy acids to their TMS derivatives, the signal of the methine proton shifts downfield, and $\Delta\delta = \delta\underline{C}H\underline{O}Si(CH_3)_3 - \delta\underline{C}H\underline{O}H$ is greater for the threo form than for the erythro form. The difference in the chemical shifts of the vicinal methine protons of the dihydroxy, acetoxyhydroxy, and halohydroxy acids and their TMS derivatives can be used to determine the threo and erythro configurations of the corresponding diastereometric derivatives of higher fatty acids.

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