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Model Compounds of Hydrophilic Polymers

6. Preparation of Threo- and Erythro-Isomers of 2-Methoxymethyl-2,4-Dimethylglutaric Acids and of Their Derivatives

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Summary

From the products of hydrolysis of dimethyl 2-methoxymethyl-2,4-dimethylglutarate, the pure stereoisomers of 2-methoxymethyl-2,4-dimethylglutaric acid and their anhydrides have been prepared. Alkaline hydrolysis of the stereoisomeric anhydrides yields the corresponding pure stereoisomeric acids which can be transformed to the corresponding pure threo- and erythro- dimethyl esters by means of diazomethane. The configuration of the stereoisomeric anhydrides was determined by analysis of ^{1}H-NMR spectra, the configuration of the other compounds was derived from the anhydride structures based on the preparative procedure controlled by ^{1}H-NMR spectra.

Introduction

Oligomers of methyl methacrylate prepared by means of alkali metal methoxides have been subject of considerable interest; their preparation (VOLKER et al. 1963), kinetics of oligomerization (FREIREICH and ZILKHA, 1972) and alkaline hydrolysis of oligomer fractions (VOLKER and SCHREYER, 1963) have been described. The "dimer" i.e. the dimethylester of 2-methoxymethyl-2,4-dimethylglutaric acid served as the model compound in NMR studies of stereoregular polymethacrylic acid and polymethylmethacrylate (FUJISHIGE 1975) and in NMR studies of ion pairs in anionic polymerization (VANCEA and BYWATER, 1979). Further studies were concerned with attempts of obtaining the pure oligomers (FUJISHIGE 1976) and with the separation of stereoisomers (FUJISHIGE 1978). The preparation of the pure stereoisomeric dimethylesters or other derivatives is not described in any of the cited papers. Only partial separation of the stereoisomeric dimethyl 2-methoxymethyl-2,4-dimethylglutarates by liquid chromatography (FUJISHIGE 1978) has been described. The preparation and identification of pure threo- and erythro- isomers of 2-methoxymethyl-2,4-dimethylglutaric acids, their anhydrides and dimethyl esters is the subject of the present paper.

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Experimental

2-methoxymethyl-2,4-dimethylglutaric acids. The mixture of threo- and erythro-dimethyl 2-methoxymethyl-2,4-dimethylglutarate (I) was prepared as previously described (VOLKER et al. 1963). The mixture of (I) (458.6 g, 1.97 mol) and of sodium hydroxide (157.95 g, 3.95 mol) dissolved in 1 200 ml of methanol was heated to boiling for 12 h; a white precipitate of disodium salts separated during the reaction. The reaction mixture was acidified by hydrochloric acid and the mixture was vacuum dried. The residue was extracted with chloroform (3x100 ml); after evaporation of the solvent 226.5 g (88% of theory) of an oily substance were obtained. By double free crystallization from benzene one pure stereoisomer of 2-methoxymethyl-2,4-dimethylglutaric acid (IIa) was obtained, of m.p. 96-97°C. For $C_9H_{16}O_5$: calc. C 52.93%, H 7.89%; found C 52.82%, H 8.01%. The absence of the other stereoisomer was proved by NMR spectroscopy and by liquid chromatography after transformation to the dimethyl ester. From the mother liquor the second isomer (IIb) could be isolated with difficulty after many repeated crystallizations; m.p. 68-71°C, elemental analysis 53.01% C, 7.83% H. The pure acid (IIb) can be more easily prepared by hydrolysis of the anhydride (IIIb).

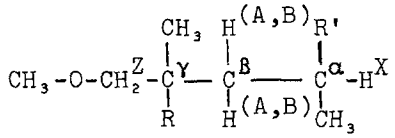
2-methoxymethyl-2,4-dimethylglutaric anhydrides The crystallization residue of (IIa) was distilled on the Perkin-Elmer column PE 200 (200 TP); the fraction of b.p. 98°C/67 Pa was collected. Distillation lead to anhydrization of the acid and the product was identified as the anhydride (IIIb). For $C_9H_{14}O_5$: calc. C 58.05%, H 7.58%, found C 58.22%, H 7.74%. The substance crystallized well from the mixture acetone-cyclohexane (1:1), m.p. 60-61°C. A selected crystal exhibited optical activity, as measured by CD. The absence of the other isomer was proved by NMR spectrometry and by liquid chromatography after transformation to the dimethyl ester. The other stereoisomer (IIIa) was prepared by heating to the boiling point of the mixture of (IIa) (10 g, 0.049 mol) with acetic anhydride (50 g, 0.49 mol) for 5 h. Distillation yielded 4.20 g of (IIIa), b.p. 82°C/133 Pa. For $C_9H_{14}O_4$: found C 58.26%, H 7.53%. The pure acid (IIa) was prepared by hydrolysis of (IIIa) by a theoretical amount of 0.1 N NaOH at 40°C during 24 h. After acidification, extraction with chloroform and evaporation of solvent the quality of the product was controlled by NMR spectroscopy, and no isomerization was found to have occurred during hydrolysis.

Pure stereoisomers of dimethyl 2-methoxymethyl-2,4-dimethylglutarate (Ia, Ib) were obtained by the reaction of the pure isomers of the corresponding acids (IIa and IIb) with diazomethane in ether solution (HOUBEN-WEYL 1963). Both isomers have identical boiling

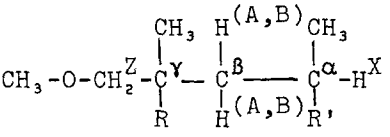
points (87°C/93 Pa). Refractive index of Ia: n_D^{20} = 1.4380; Ib: n_D^{20} = 1.4372.

^{1}H-NMR spectra were measured on the spectrometer PS-100 (JEOL) at 100 MHz. The samples were measured as 10% (w/v) solutions in $CDCl_3$ with HMDS as internal standard. The cited values of chemical shifts are related to TMS. The values of coupling constants were obtained by 1st order analysis.

Assignment of stereoisomer configuration. The ^{1}H-NMR spectra of the separated stereoisomers (Ia,b), (IIa,b) and (IIIa,b) are shown in Figs 1-3, the spectral parameters are summarized in Table 1. The spectra of the stereoisomeric pairs of acids and dimethyl esters differ by the structure of the multiplet bands to such an extent that they can be well utilized for monitoring the separation process. However, they cannot be used directly for the assignment of the configurational structure, because the shape of the multiplets is determined mainly by the conformational structure of the stereoisomers which is unknown. The situation is different for the anhydrides (IIIa,b) where a reasonable assumption can be made about the conformation of the anhydride heterocycle. The configurational assignment is based on the existence of the splitting of 1.2 Hz observed in the spectrum 3b on the bands of one of the protons of the $-O-CH_2-$ group at 3.65 and 3.73 ppm, and also on the bands of one of the protons on the C_β carbon at 1.51, 1.65 and 1.78 ppm. This splitting indicates coupling over 4 single bonds, $^4J_{HH}$, between two protons of both these CH_2 groups. It is known that $^4J_{HH}$ attains measurable values only in those cases when the coupled protons lie in plane and are bound by bonds arranged in W shape. In the studied anhydrides this situation can occur when the $-O-CH_2-$substituent assumes an axial position on the anhydride heterocycle. If we assume that in the studied anhydrides, the form with one axial substituent is strongly preferred with respect to the form with two axial substituents, then the axial position of the $-O-CH_2-$ substituent is expected to predominate in the erythro-isomer. Therefore we suppose that the spectrum 3b (compound IIIb) corresponds to the erythro-isomer and the spectrum 3a (compound IIIa) to the threo-isomer of 2-methoxymethyl-2,4-dimethylglutaric anhydride. The assignments of compound (IIa) (Fig.2a) to the threo-, and of compound (IIb) (Fig.2b) to the erythro-isomer of the corresponding acid, and of compound (Ia) to the threo-, and of compound (Ib) to the erythro-isomer of the corresponding dimethyl esters follows from the synthetic procedure described above. This assignment of configuration differs from that in ref. (FUJISHIGE 1978) proposed for the partly enriched isomeric forms of (I).



a) threo- (I,II,III)



b) erythro- (I,II,III)

I -R, -R' : $-CO-O-CH_3$

II -R, -R' : $-CO-OH$

III -R—R'— : $-CO-O-CO-$

TABLE 1

Chemical shifts and coupling constants in ^1H-NMR spectra of the stereoisomers of 2-methoxymethyl-2,4-dimethylglutaric acid and derivatives

	δ (ppm)					
	Ia	Ib	IIa	IIb	IIIa	IIIb
$C^{\alpha}-CH_3$	1.14	1.11	1.15	1.15	1.33	1.27
$C^{\gamma}-CH_3$	1.18	1.16	1.27	1.24	1.31	1.27
H^A	1.56	1.70	1.32	1.58	1.67	1.65
H^B	2.15	1.99	2.17	2.07	2.13	2.07
H^X	2.54	2.46	2.62	2.56	2.74	3.20
H^Z	3.35	3.36	3.34	3.56	3.48	3.55
$-O-CH_3$	3.25	3.28	3.32	3.35	3.32	3.30
$-CO-O-CH_3$	3.62 3.63	3.62 3.64	-	-	-	-
	J (Hz)					
$^2J_{AB}$	-14	-14	-14	-14	-14	-14
$^3J_{AX}$	3.5	4.5	2.5	3	5.5	14
$^3J_{BX}$	9	8.5	12	12	13	6
$^4J_{AZ}$	-	-	-	-	-	1.2

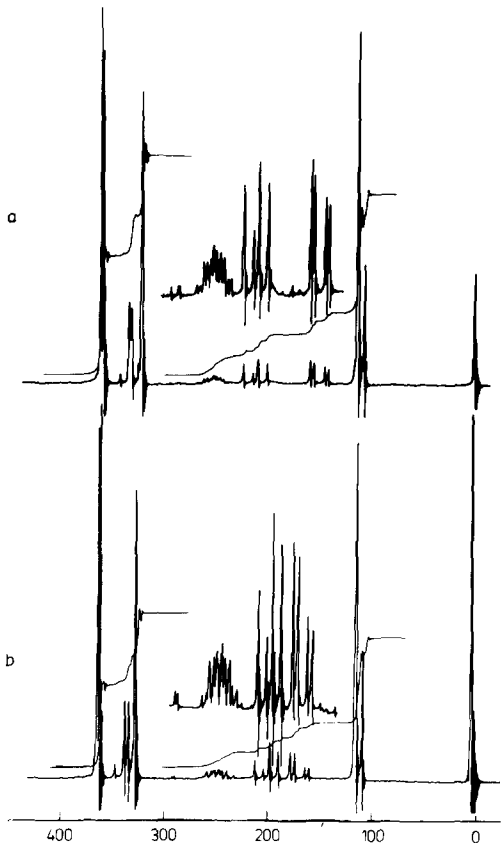


Fig.1. ^{1}H-NMR spectra (100 MHz) of dimethyl 2-methoxymethyl-2,4-dimethylglutarate
a threo-isomer (Ia),
b erythro-isomer (Ib)

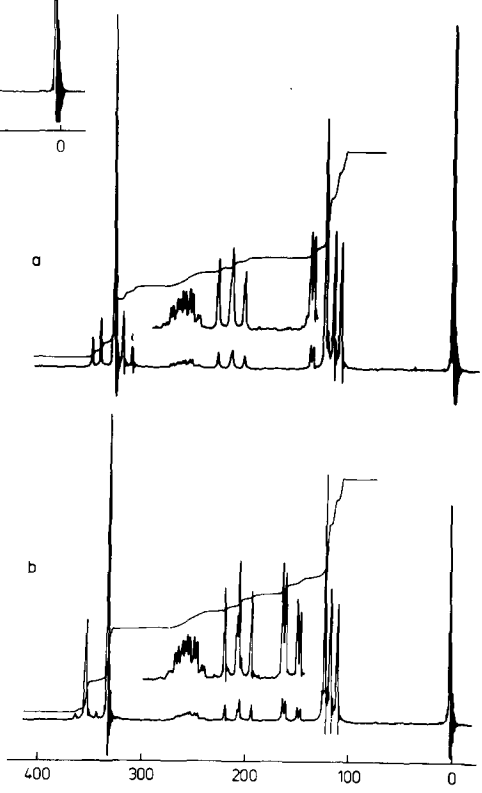


Fig.2. ^{1}H-NMR spectra (100 MHz) of 2-methoxymethyl-2,4-dimethylglutaric acid
a threo-isomer (IIa),
b erythro-isomer (IIb)

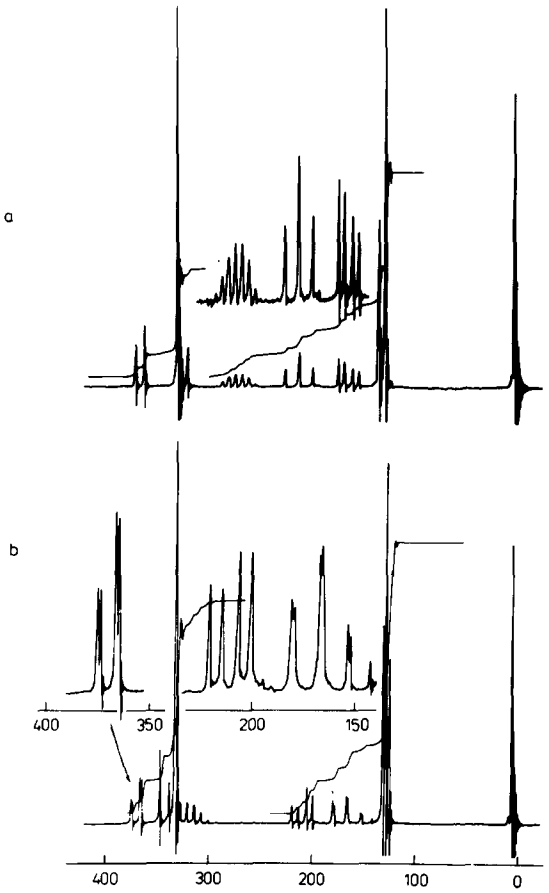


Fig.3. ^{1}H-NMR spectra (100 MHz) of 2-methoxymethyl-2,4-dimethylglutaric anhydride
a threo-isomer (IIIa),
b erythro-isomer (IIIb)

Results and Discussion

It was confirmed by NMR analysis that even on a highly efficient column, enrichment by one of the isomers cannot by obtained by distillation of a 1:1 mixture of the threo- and erythro- isomers of dimethyl 2-methoxymethyl-2,4-dimethylglutarate. With the same stereoisomer mixture, also GLC experiments always exhibited only a single wave on the nonpolar phase. Therefore, concerning fugacity, the interactions of the functional groups in both isomers are equal and separation methods based on expected differences in fugacity are inefficient. Different results are obtained after modification of the functional groups by hydrolysis. Carboxyl groups are characterized by high polarity and strong mutual interaction. This made possible the separation of stereoisomers in the form of acids by free crystallization from benzene solution; the threo-isomer crystallized preferentially. The erythro-isomer crystallized less readily, the crystals were contamined by the other isomer and had to be recrystallized many times before the pure compound was obtained.

It was found that the 2-methoxymethyl-2,4-dimethylglutaric acids split off water upon heating under formation of cyclic anhydrides which can be very easily purified by distillation and subsequent crystallization (the anhydrides can also be prepared in conventional way by reaction with acetic anhydride or by reaction of the acids with thionyl chloride). The pure anhydride stereoisomers may be utilized for NMR determination of configuration, as their conformational structure is limited by formation of the heterocycles. It was found that the pure anhydrides do not isomerize during alkaline hydrolysis. Therefore they may be used for the preparation of pure acid isomers of defined configuration; these configurationally defined acids can be further transformed to the corresponding dimethyl esters by reaction with diazomethane.

According to a preliminary observation of CD, an individual crystal of the erythro-anhydride appears as optically active; it might be possible to separate the enantiomers by crystallization.

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References

FREIREICH, S. and ZILKHA, A.: J.Macromol.Sci.-Chem. A6 (7), 1383 (1972)
FUJISHIGE, S.: Makromol.Chem. 176, 225 (1975)
FUJISHIGE, S.: Makromol.Chem. 177, 375 (1976)
FUJISHIGE, S.: Makromol.Chem. 179, 2251 (1978)
HOUBEN-WEYL: Methoden der organischen Chemie, Vol. XIV/2, p.736, Stuttgart, G.Thieme Verlag, 1963
VANCEA, L. and BYWATER, S.: 26th International IUPAC Symposium on Macromolecules, Mainz, Preprints Vol.I, p.140 (1979)
VÖLKER, T., NEUMANN, A. and BAUMANN, U.: Makromol.Chem. 63, 182 (1963)
VÖLKER, T. and SCHREYER, G.: Makromol.Chem. 63, 202 (1963)

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