The Higher Normal Chain DL- β -Hydroxy Acids. Synthesis and Investigation of the Crystal Behaviour of Seventeen Homologous Acids with 8 to 24 Carbon Atoms

MARCUS SKOGH

Institute of Medical Chemistry, University of Uppsala, Sweden

The only practical synthetic route to normal chain β -hydroxy acids previously available has been the Reformatzky reaction, *i.e.* the condensation between aldehydes and bromoacetic ester in the presence of zinc¹

Various side reactions occur, however, and the yields of pure β -hydroxy acids are not very satisfactory. Thaler and Geist², and Adickes and Andresen³, state that the yields of pure products in their experiments amounted to 10–12 % of the theoretical.

The development of satisfactory methods for the preparation of long normal chain β -keto esters^{4,5} opens up a new and convenient synthetic route, *viz.* hydrogenation of the β -keto esters to the corresponding β -hydroxy esters and hydrolysis of the latter.

Several methods of hydrogenation of the β -keto esters were tried in the course of the work to be described. The use of copper-chromium oxide catalyst has been reported by Adkins⁶ to be satisfactory for the hydrogenation of ethyl acetoacetate. This method was tried, but did not prove satisfactory in the case of higher β -keto esters. Some side reactions evidently occurred, involving chain-splitting of the β -hydroxy ester produced. Mozingo and Folkers⁷, by using relatively large amounts of this catalyst and temperatures of 150–180°C,

Fig. 1.

have converted ethyl acetoacetate into 1,3-butylene glycol in moderate (30 %) yield. For the preparation of β -hydroxy acids this represents an undesirable side reaction. Raney nickel was therefore tried, and good results were obtained when carrying out the reaction at a temperature of 85–210° C and a pressure of 70–140 kg per sq.cm.

After hydrolysis, the pure β -hydroxy acids were obtained in yields of 50–70 % of the theoretical, calculated on the β -keto esters used. The complete synthesis, starting from the carboxylic acid with two carbon atoms less than the final compound, gives an overall yield of 30–40 % of the theoretical. The following steps are involved:

In this way the complete series of DL- β -hydroxy acids, from the C_8 (β -hydroxyoctanoic acid) up to and including the C_{24} member (β -hydroxytetracosanoic acid), was synthesized. As indicated in Table I, several of these acids

Fig. 2.

have been described previously on one or more occasions in the literature, but in several cases the melting point data given by different authors do not agree. The melting points of the acids now prepared, when plotted against the number of carbon atoms in the chain, appear to fall on two smooth curves (Fig. 1), that of the odd-numbered acids lying above that of the acids containing an even number of carbon atoms. As pointed out by Adickes and Andresen³, this is the opposite to the manner in which the melting points of the normal chain acids alternate.

The crystal behaviour of the acids has also been studied, in order to detect the existence of polymorphism. The crystal spacings corresponding to the 00 l , and some of the stronger $hk0$ reflections, have been calculated from diffraction patterns of the powder type. The results are given in Fig. 2 and Table 3.

The long crystal spacings of the odd-numbered acids from C_9 to C_{23} , when plotted against the number of carbon atoms in the molecules, all fall on the same straight line (Fig. 2). The general appearance of the side spacing pattern from the β -hydroxy acids at room temperature remains the same throughout the series, but there are minor changes in the numerical values of the spacings. The same crystal structure is found for acids crystallized from light petroleum or benzene (low boiling light petroleum is the only solvent found from which it has been possible to crystallize the lowest members), as for specimens crystallized from the melt.

Table 1.

Systematic name	Yield %	m. p. °C	m.p. from literature °C
DL-3-hydroxyoctanoic acid	34	37	38—38.5 (3)
DL-3-hydroxynonanoic acid	37	58.8—59.0	60 (3)
DL-3-hydroxydecanoic acid	54	56.4—56.6	56—56.5 (3); 53—54 (2)
DL-3-hydroxyhendecanoic acid	59	71.2—71.4	73—73.5 (3); 73 (8)
DL-3-hydroxydodecanoic acid	48	68.8—69.1	70—70.5 (3); 78—79 (8)
DL-3-hydroxytridecanoic acid	66	80.4—80.6	81 (8)
DL-3-hydroxytetradecanoic acid	72	77.8—77.9	72—73 (2)
DL-3-hydroxypentadecanoic acid	63	86.7—87.0	
DL-3-hydroxyhexadecanoic acid	61	84.5—84.7	83—83.5 (9)
DL-3-hydroxyheptadecanoic acid	50	91.1—91.3	
DL-3-hydroxyoctadecanoic acid	55	89.4—89.6	89 (10); 90 (11)
DL-3-hydroxynonadecanoic acid	69	95.1—95.3	
DL-3-hydroxyeicosanoic acid	47	93.2—93.4 ^a	
DL-3-hydroxyheneicosanoic acid	81	97.9—98.1	
DL-3-hydroxydocosanoic acid	69	95.8—96.0	
DL-3 hydroxytricosanoic acid	68	100.6—100.9	
DL-3-hydroxytetracosanoic acid	67	98.7—98.9	

^a After resolidification most of the sample in the tube melted between 91.9—92.5, but a small residue did not melt until 93.6°.

The long spacings of specimens of the even-numbered acids C_8 — C_{20} obtained from solvents when plotted fall on a straight line (*cf.* Fig. 2), which lies slightly above the line for the odd-numbered acids. The side spacing patterns are very similar to those of the latter acids. However, melted specimens of the C_{14} , C_{16} , C_{18} , and C_{20} acids show, in addition to the form mentioned (marked β in Fig. 2), the presence of a second crystalline form with slightly shorter long spacings. This form (γ in Fig. 2) is the only one found for specimens of the C_{22} and C_{24} acids crystallized from light petroleum and benzene. Previously-melted specimens of the two acids just mentioned also show the spacings of the γ modification, but melted specimens of all C_{18} to C_{24} acids show a few very weak lines, which appear to correspond to a third modification of a still shorter long spacing. (ζ)

As indicated in Table 1, specimens obtained by crystallization from solvents, and on solidification of the molten acid, show the same m.p., with the exception of the C_{20} acid. It was mentioned above that previously-melted specimens of several of the higher even-numbered acids showed the presence of two crystalline forms at room temperature, and it was therefore of interest to follow the appearance of the diffraction pattern right up to the melting point.

Table 2.

Number of carbon atoms in β -keto ester	Hydrogenation					Hydrolysis					Crystallization			
	Keto- ester g	Solvent	ml	Raney nickel ml	Hydrogen pressure kg/sq. cm. (initially)	Reaction- temp °C	Reaction-time hrs	Potassium hydroxide g	Ethanol ml	Time of reflux hrs	Solvent	Number of carbon atoms in β -hydroxy acid	Yield g	
9	0.9	methanol	12	1	140	210	5	5		5.5	light petroleum, b.p. 35–60°	8	0.26	
10	1	»	10	1	115	145	2.5	5	22	12	} b.p. 60–80°	9	0.35	
11	2	ethanol	6	1	120	120	4.5	10	50	6		10a)	1.02	
12	1	methanol	10	1	135	210	4	5	80	9		11	0.55	
13	0.74	»	10	1	115	145	2.5	5	25	4.5		12	0.34	
14	2	»	8	1	70	85	4	10	50	5		13	1.25	
15	2	{ dioxan	10	1	100	100	2.5	10	50	8		14	1.37	
16	2	methanol	20	1	100	100	5.5	10	50	6		15	1.20	
17	2	{ dioxan	10	1	100	100	7	10	50	5		16	1.17	
18	1	methanol	15	1	120	145	2.5	5	25	12		17	0.47	
19	2	»	15	1	120	145	1	10	50	5		18	1.05	
20	0.6	»	10	1	110	145	4	5	25	7	19	0.40		
21	1	»	10	1	140	190	5	5	35	5	20	0.45		
22	0.5	»	10	1	110	145	3.5	5	25	6	21	0.39		
23	0.6	»	12	1	115	145	2.5	5	25	5	} b.p. 80–100°	22	0.40	
24	0.7	»	11	1	135	145	5.5	3	30b)	4		benzene light petroleum, b.p. 80–100°	23	0.50
25	0.4	»	9	1	140	210	3	5	25	5.5		24	0.26	

a) Prepared by S. Stållberg-Stenhagen, *cf.* ref. 13.

b) Methanol.

With an automatically recording X-ray camera¹², this was done for the whole series of acids crystallized from the melt, and for the C₉, C₁₄, C₂₀, C₂₂ and C₂₄ acids crystallized from solvents. In all cases where two crystalline forms co-existed at room temperature, the form with the shorter long spacing gradually disappeared within a certain temperature interval, transforming into the one with the longer spacing.

Except for the C₂₀ acid obtained from the melt, the longer (β) form persisted up to the melting point, as could be expected from the melting point data. The C₂₀ acid crystallized from light petroleum behaved in the same manner, but a previously-melted specimen, first transformed into the γ form, and then gradually back into a shorter form, evidently not identical with the ζ -form.

Table 3. X-ray diffraction data of β -hydroxy acids.

β -hydroxy acid	Number of carbon atoms in		Long crystal spacing in Å		Side spacings in Å	
	β	γ	S		M	
			γ	ζ	γ	ζ
8	22.4				<i>4.64, 4.42, 3.88, 3.53</i>	<i>4.64, 4.40, 4.07, 3.87, 3.53</i>
9	24.4				<i>4.68, 4.31, 3.90, 3.44</i>	<i>4.68, 4.32, 3.90, 3.46</i>
10	27.5				<i>4.64, 4.45, 3.89, 3.55</i>	<i>4.64, 4.45, 3.89, 3.55</i>
11	29.1				<i>4.68, 4.38, 3.83</i>	<i>4.68, 4.38, 3.83</i>
12	32.0				<i>4.64, 4.47, 3.89, 3.55</i>	<i>4.64, 4.47, 4.08, 3.93, 3.58</i>
13	33.8				<i>4.67, 4.41, 3.90</i>	<i>4.66, 4.41, 3.90</i>
14	36.8	35.2			<i>4.63, 4.49, 4.05, 3.89, 3.55</i>	<i>4.63, 4.46, 4.08, 3.90</i>
15	38.5				<i>4.66, 4.44, 3.89</i>	<i>4.66, 4.45, 3.89</i>
16	41.4	40.0			<i>4.66, 4.49, 3.88</i>	<i>4.40, 4.26, 4.09, 3.89</i>
17	43.2				<i>4.64, 4.46, 3.89</i>	<i>4.66, 4.45, 3.88</i>
18	46.5	44.6	36.0		<i>4.11, 3.89</i>	<i>4.11, 3.87</i>
19	48.2		38.3		<i>4.61, 4.47, 3.88</i>	<i>4.66, 4.45, 3.86</i>
20	50.9	49.0	40.0		<i>4.62, 4.49, 4.09, 3.86</i>	<i>4.10, 3.83</i>
21	53.0		42.0		<i>4.63, 3.89, 3.56</i>	<i>4.66, 4.46, 3.86</i>
22		53.6	43.9		<i>4.10, 3.85</i>	<i>4.12, 3.85</i>
23	57.3		45.6		<i>4.64, 4.51, 3.88</i>	<i>4.66, 4.47, 3.85</i>
24		58.4	47.5		<i>4.10, 3.82</i>	<i>4.12, 3.82</i>

S = Specimens crystallized from solvents.

M = Specimens crystallized from the melt.

Strong side spacings in italics.

Crystal spacings are given in Table 3. Fig. 3 shows the relative intensities of the low order 00l reflections, estimated visually from diffraction patterns of acids crystallized from solvents.

EXPERIMENTAL *

As all the β -hydroxy acids were produced by a series of more or less identical procedures, a detailed description is given only of the synthesis of the C_8 and the C_{23} acids. Other experimental data are collected in Table 2 and the analyses are given in Table 4.

DL-3-Hydroxyoctanoic acid. Methyl 3-ketooctanoate (0.9 g), dry methanol (12 ml), and a suspension of finely-dispersed Raney nickel in ethanol (1 ml) were placed in a high-pressure vessel, which was then filled with hydrogen from an ordinary commercial hydrogen container, giving a pressure of 140 kg/sq.cm. The temperature was raised up to

* For reference to melting point determination and X-ray technique employed, see Stållberg-Stenhagen, S., and Stenhagen, E. *J. Biol. Chem.* **173** (1948) 389.

Fig. 3.

210° C, and the hydrogenation was allowed to continue at this temperature for about 5 hours under continuous shaking of the mixture.

When the contents had cooled down to room temperature, the catalyst was filtered off, and the solvents evaporated. Potassium hydroxide (5 g) in ethanol (25 ml) was added, and the material refluxed for 9 hours. After concentrated hydrochloric acid (8 ml) had been added, the solution was extracted with ether, and the ether washed with dilute hydrochloric acid, and several times with water. The ether layer was dried over sodium sulphate, and the solvent evaporated. The residue was dissolved in light petroleum (b.p. 35–60° C), from which 0.23 g of pure acid crystallized when placed in a refrigerator.

DL-3-hydroxytricosanoic acid. Methyl 3-ketotricosanoate ** (0.7 g) in dry methanol (11 ml) was hydrogenated with Raney nickel (1 ml) in the same manner as described above. The initial hydrogen pressure was 135 kg/sq.cm and the reaction temperature was kept constant at 145° C for 5.5 hours. The apparatus was allowed to cool down before being disconnected, whereafter the contents were extracted with ether and filtered. The ether was evaporated, and the remainder hydrolysed with potassium hydroxide (3 g) in methanol (30 ml) and water (3 ml) under reflux for 4 hours. Excess hydrochloric acid was added and the mixture heated and then extracted with warm benzene. The benzene layer was washed twice with water and partly distilled off. 0.5 g of pure hydroxy acid crystallized from the benzene.

All hydroxy acids, except C_8 , C_{21} and C_{23} , were treated with active charcoal in ethanol solution before crystallization.

** This β -keto ester was prepared by Miss G. Stållberg, who also carried out the greater part of the synthesis of C_{23} hydroxy acid.

Table 4. Analysis of DL- β -hydroxy acids. Per cent composition.

Formula	C		H	
	Calcd.	Found	Calcd.	Found
$C_8H_{16}O_3$	59.97	59.90	10.07	10.01
$C_9H_{18}O_3$	62.04	61.95	10.41	10.39
$C_{10}H_{20}O_3$	63.80	63.90	10.71	10.81
$C_{11}H_{22}O_3$	65.31	65.52	10.96	10.92
$C_{12}H_{24}O_3$	66.63	66.53	11.18	11.21
$C_{13}H_{26}O_3$	67.78	67.80	11.38	11.27
$C_{14}H_{28}O_3$	68.81	68.74	11.55	11.50
$C_{15}H_{30}O_3$	69.72	69.95	11.70	11.69
$C_{16}H_{32}O_3$	70.54	70.43	11.84	11.87
$C_{17}H_{34}O_3$	71.28	71.09	11.97	11.95
$C_{18}H_{36}O_3$	71.95	71.90	12.08	12.12
$C_{19}H_{38}O_3$	72.56	72.53	12.18	12.22
$C_{20}H_{40}O_3$	73.12	73.11	12.27	12.22
$C_{21}H_{42}O_3$	73.63	73.62	12.36	12.41
$C_{22}H_{44}O_3$	74.10	73.80	12.44	12.39
$C_{23}H_{46}O_3$	74.54	74.55	12.51	12.51
$C_{24}H_{48}O_3$	74.94	75.14	12.58	12.59

Throughout the whole series the crystals appear as very thin rhombic plates.

The acids with an even number of carbon atoms are much more soluble in light petroleum than are the odd-numbered ones. The solubility decreases with increasing length of the carbon chain. The DL-3-hydroxytricosanoic acid was not soluble enough to allow crystallization even from high-boiling light petroleum.

SUMMARY

A series of normal chain DL- β -hydroxy acids, containing from 8 to 24 carbon atoms, has been synthesized by high pressure hydrogenation of the corresponding methyl β -keto esters, using Raney nickel as a catalyst. The crystal spacings have been determined by the X-ray powder technique, and the crystal polymorphism has been studied at various temperatures by using an automatically recording X-ray camera.

The yield of β -hydroxy acid obtained from the corresponding β -keto ester ranges from 50 to 70 % of the theoretical.

I am indebted to Dr. E. Stenhagen for advice, and to Mrs. S. Stållberg-Stenhagen for placing the β -keto esters used at my disposal.

The analyses were carried out by Mr. W. Kirsten in the Microanalytical Laboratory of this Institute.

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