ACTA CHEMICA SCANDINAVICA 6 (1952) 1157–1174

The Monoketo- and Monohydroxyoctadecanoic Acids

Preparation and Characterization by Thermal and X-ray Methods

SUNE BERGSTRÖM
Department of Physiological Chemistry, University of Lund,

GUNHILD AULIN-ERDTMAN* and BRITA ROLANDER
Department of Biochemistry, Medical Nobel Institute, Stockholm,

EINAR STENHAGEN and SVEN ÖSTLING
Institute of Medical Chemistry, University of Uppsala, Sweden

In connexion with work on the autoxidation of unsaturated fatty acids [1–3], hydroxyoctadecanoic acids were isolated from the hydrogenated reaction products. In these cases the hydroxyl group should be located in the neighbourhood of the original double bond, and in order to identify the acids a number of DL-hydroxyoctadecanoic acids with the hydroxyl group near the middle of the chain were synthesized. In several other instances [*cf.* 4–7] monohydroxyoctadecanoic acids have remained unidentified owing to lack of reference compounds, and we have therefore prepared the complete series of the seventeen DL-monohydroxyoctadecanoic acids. Several of the isomers have been prepared earlier, although in some cases the methods used do not seem to ensure the structure or purity of the product.

In the course of the work to be described many cases of polymorphism have been observed among the hydroxy-acids and their methyl esters. The corresponding keto-compounds are less complicated in this respect, and for identification purposes it might therefore in certain cases be advantageous to convert the hydroxy-acid into the corresponding keto-acid. Optically active hydroxy-acids, for which synthetic material for comparison is lacking at present, will at any rate be best identified in this manner. We have therefore studied the crystal behaviour, by thermal and X-ray methods, of all the monoketo- and DL-monohydroxyoctadecanoic acids and their methyl esters. Acids that possess practically identical melting points may be distinguished

* Present address: Cellulosaindustriens Centrallaboratorium, Stockholm Ö.

by their X-ray diffraction patterns, and the data given in this paper should permit the identification of any keto- or hydroxyoctadecanoic acid, using only milligram quantities of material.

A further reason for the extension of the preparative work to include all positional isomers (66 compounds in all) was the fact that we wanted to study the influence of the position of the keto and hydroxyl group respectively on the monolayer properties and on the infra-red spectra. The results of these physico-chemical studies will be reported later.

Except the case of the 2- and 18-isomers the hydroxy-acids have been prepared via the methyl esters obtained by high pressure hydrogenation of the methyl esters of the corresponding keto-acids over Raney nickel. In some instances we have reduced the keto-ester over W 6-Raney nickel [8] at ordinary pressure and room temperature. The 2-hydroxyoctadecanoic acid was prepared by alkali treatment of the α-bromoacid whereas the 18-isomer was obtained by hydrogenolysis over Raney nickel of the monothiol ester of octadecane-1,18-dioic acid.

2-Ketooctadecanoic acid was prepared in 80 per cent yield by oxidation of methyl 2-hydroxyoctadecanoate with chromic trioxide in acetic acid at 37° [9], followed by hydrolysis of the ester.

Lower α-keto-esters have generally been prepared via the α-keto-nitrile, via the α-oximino-ester, or by oxalic ester condensation, *cf.* Adickes and Andresen [10] and Vogel and Schinz [11]. None of these methods appears suitable for the synthesis of long chain α-keto-acids, as the yields decrease with increasing chain-length. The highest member so far prepared (C_{15}) was obtained in a yield of 15 per cent by the oxalic ester condensation method [10].

3-Ketooctadecanoic acid was prepared [12] by acid hydrolysis of the methyl ester [13] according to the procedure of Mitz, Axelrod and Hofmann [14].

For the synthesis of keto-acids with the keto group in position 4 to 17 several methods are available, *cf. e.g.* [15, 16]. In the course of the present work, the 4-, 5-, 7-, 11-, 13-, and 17-ketooctadecanoic acids were prepared by alkylation of the appropriate β-keto-esters with esters of ω-iodocarboxylic acids, followed by hydrolysis and ketonic cleavage of the alkylation product. The procedure was that described by Ställberg-Stenhagen and Stenhagen [17]. The β-keto-esters required were synthesized as described by Hunsdiecker [18] and Ställberg-Stenhagen [13].

$$CH_3(CH_2)_nCOCH_2COOCH_3 + I(CH_2)_{14-n}COOCH_3 \xrightarrow[\text{pentanone-2}]{K_2CO_3}$$

$$CH_3(CH_2)_nCOCHCOOCH_3 \xrightarrow[CH_3OH]{KOH,H_2O} CH_3(CH_2)_nCO(CH_2)_{15-n}COOH$$

$$\qquad\qquad\quad |$$

$$\qquad\quad (CH_2)_{14-n}COOCH_3$$

This method gave directly practically pure keto-acids in 60—70 per cent yield.

The 4-, 5-, 6-, 8-, 9-, 10-, 12-, 14-, 15- and 16-ketooctadecanoic acids were prepared by the reaction of the halfester chloride of a dicarboxylic acid with organo-cadmium-compounds according to Gilman and Nelson [19]. For a summary see Cason [20].

$$(CH_3(CH_2)_n)_2Cd + 2\ CH_3OOC(CH_2)_{15-n}COOCl \longrightarrow$$

$$2CH_3(CH_2)_nCO(CH_2)_{15-n}COOCH_3 \xrightarrow[C_2H_5OH]{KOH,H_2O} CH_3(CH_2)_nCO(CH_2)_{15-n}COOH$$

The ketonic reaction products were isolated with Girard's reagent T [21]. The yield of keto-acids was only about 30 per cent of the theoretical. The low yield might at least partly be ascribed to a too short reflux time as in recent work considerably longer reaction times than those initially used have been found necessary [22]; *cf.* also Cason and Winans [23].

THERMAL AND X-RAY INVESTIGATIONS

Ketooctadecanoic acids, cf. Table 1 and Fig 1. This series shows a comparatively simple behaviour. With the exception of the 3-keto-isomer all keto-acids crystallize with vertical (V) chains (double molecules), and acids with the keto group in position 4 up to and including position 15 appear to form an isomorphous series as indicated by the identical side-spacings. The melting point curve of the acids given in Fig. 1 shows that acids with the keto group at even-numbered positions melt slightly higher than the odd-numbered neighbours. However, from the 12-keto-acids on, this behaviour is reversed. When the keto group is near either end, *viz.* in position 2, 16 or 17 respectively, the chains are vertical but the side spacings indicate that different lateral packing of the chains occurs in all these cases. The 3-keto-acid which shows the highest m.p. of the series *cf.* [12] has a structure with tilted double molecules. Polymorphism has only been observed for the 4-, 5- and 7-keto-acids. Specimens of the 7-keto-acid crystallized from light petroleum (b.p. 95°) showed the presence of a small amount of a crystalline modification with a long spacing of 46 Å. The diffraction pattern-temperature diagram (DPT diagram) [24] showed that this form disappeared about 10 degrees below the melting point.

The specimen of 5-keto-acid prepared by the organo-cadmium method melted at 87.1—87.3°, solidified at 86.8° in the form of well developed plates, and remelted at 87.1—87.3°. The specimen prepared by the β-keto-ester method and recrystallized from light petroleum (b.p. 95°) was found to be a mixture of the crystalline modification found for the form of m.p. 87.1—87.3° and a second

Table 1. Ketooctadecanoic acids.

Position of substituent	M.p.° C		Crystal spacings, Å.	
	Present investigation	Literature	Long spacing	Side spacings
2	74.3–74.6 (V)	— —	49.7 P, M	4.15, 3.58
3	99 decomp.[3c]	(64–65[3a]) 102–103 decomp.[3b]	42.0 P	4.45, 4.25, 3.87, 3.65
4	96.3–96.5 (V); 94.2–94.3	97[4a,b,c]	49.7 (V) P, M; 38.4 P, M	4.68, 4. 48, 4.01, 3.63
5	87.1–87.3 (V); 91.4–91.6	— —	49.7 P, M	
6	86.6–86.8 (V)	87[6a,b]; 86–87[6c]; 86[6d]		
7	82.8–83.0 (V)	75[7a]	49.7 P, M; 46 P	
8	83.6–83.8 (V)	— —		
9	81.7–81.9 (V)	83[9a,b]		
10	82.4–82.6 (V)	76[10a]; 74[10b]; 82(corr.)[10c]; 76[10d]; 82–82.8[10e]		
11	81.7–81.9 (V)	(65[11a])		4.10, 3.80, 2.99
12	81.5–81.9 (V)	82[12a]; 81[12b]; 81–81.5[12c]	49.7 P, M	
13	82.1–82.3 (V)	— —		
14	81.7–81.9 (V)	— —		
15	83.0–83.2 (V)	— —		
16	93.1–93.5 (V)	— —		4.50, 3. 76, 3.64
17	87.4–87.7 (V)	— —		4.30, 3.82

3 a. Asahina, Y., and Nakayama *J. Pharm. Soc. Japan* no. 526 (1925) 5.
3 b. Mitz, M. A., Axelrod, A. E., and Hofmann, K. *J. Am. Chem. Soc.* **72** (1950) 1231.
3 c. Stenhagen, E. *Arkiv Kemi* **3** (1951) 381.
4 a. Shukoff, A. A., and Schestakoff, P. J. *J. prakt. Chem.* **67** (1903) 418.
4 b. Clutterbuck, P. W. *J. Chem. Soc.* **125** (1924) 2330.
4 c. Clutterbuck, P. W., and Raper, H. S. *Biochem. J.* **19** (1925) 388.
6 a. Bougault, J., and Charaux, C. *Compt. rend.* **153** (1911) 572, 882.
6 b. Robinson, G. M., and Robinson, R. *J. Chem. Soc.* **127** (1925) 179.
6 c. Zellner, J. *Monatsh.* **50** (1928) 214.
6 d. Fieser, L. F., and Szmuszkovicz, J. *J. Am. Chem. Soc.* **70** (1948) 3354.
7 a. Arnaud, A. *Compt. rend.* **134** (1902) 548.
9 a. Behrend, O. *Ber.* **29** (1896) 807.
9 b. Robinson, G. M., and Robinson, R. *J. Chem. Soc.* **1926** 2207.
10 a. Baruch, J. *Ber.* **27** (1894) 174.
10 b. Shukoff, A. A., and Schestakoff, P. J. *J. prakt. Chem.* **67** (1903) 415.
10 c. Robinson, G. M., and Robinson, R. *J. Chem. Soc.* **1926** 2208.
10 d. Myddleton, W. W., Berchem, R. G., and Barrett, A. W. *J. Am. Chem. Soc.* **49** (1927) 2267.
10 e. Fordyce, C. R., and Johnson, J. R. *J. Am. Chem. Soc.* **55** (1933) 3368.
11 a. Shukoff, A. A., and Schestakoff, P. J. *J. prakt. Chem.* **67** (1903) 416.
12 a. Thoms, H., and Deckert, W. *Ber. deut. pharm. Ges.* **31** (1921) 24.
12 b. Perrotte, R. *Compt. rend.* **199** (1934) 358.
12 c. Perrotte, R. *Compt. rend.* **200** (1935) 746.

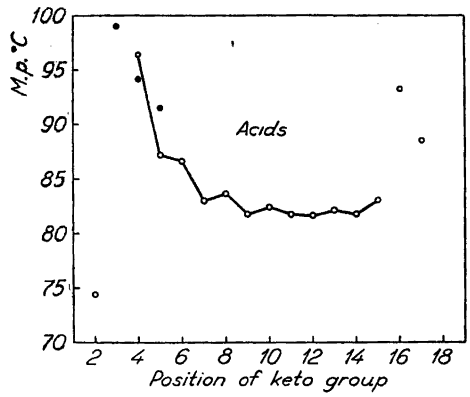

Fig. 1. Melting points of ketooctadecanoic acids. Open circles represent forms with vertically oriented chains. Points representing isomorphic forms are connected with a full drawn line.

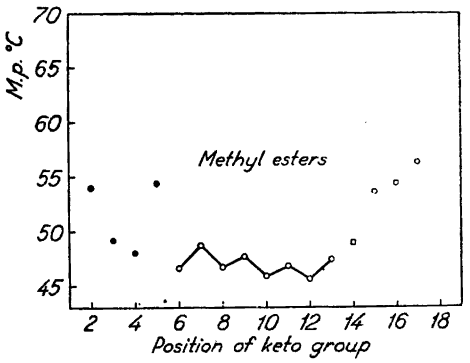

Fig. 2. Melting points of methyl ketooctadecanoates. Open squares represent forms with vertically oriented chains. Open circles represent β form. Tilted forms other than β are marked with filled circles.

form with tilted double molecules. In this case a complete transformation into the latter form took place on heating, followed by melting at 91.4—91.6°. After a second crystallization from the same solvent only the tilted form was present at room temperature. This modification melted at 91.4—91.6° and solidified at about 90° with the formation of long prisms in the melt.

The 4-keto-acid showed a similar behaviour. The specimen prepared by the organo-cadmium method was found to exist in a crystalline modification with

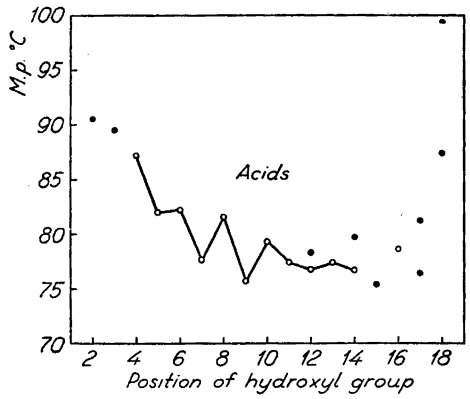

Fig. 3. Melting points of hydroxyoctadecanoic acids. Open circles represent γ form. Crystalline forms other than γ are represented by filled circles.

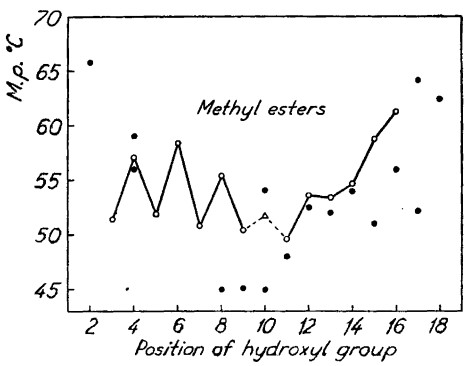

Fig. 4. Melting points of methyl esters of hydroxyoctadecanoic acids. Open circles represent β form. Other forms are represented by filled circles.

Table 2. Methyl esters of ketooctadecanoic acids.

Position of substituent	M.p.° C.		Crystal spacings, Å	
	Present investigation	Literature	Long spacing	Side spacings
2	54.0—54.1	— —	38.7 P, M	3.66, 4.05, 4.56, 4.98
3	49.2 *	49.2[3a]; 49[3b]	38.3 P, M	4.63, 4.40, 3.88, 3.69, 3.55, 3.39
4	47.9—48.0	49.5[4a]	45.6 P, M	4.27, 4.04, 3.90, 3.72, 3.56
5	54.3—54.5	— —	49.6 P, M	4.46, 4.28, 4.05, 3.78
6	46.3—46.8	— —		
7	48.7—48.8	— —		
8	46.4—46.9	42.7—44.3[8a]		
9	47.5—48.0	— —		
10	45.8—46.1	— —	47.6 (β) P, M	β: 3.73, 4.03, 4.27, 4.44
11	46.7—46.9	— —		
12	45.4—45.7	44.5[12a]		
13	47.3—47.7	— —		
14	48.9—49.0	— —	53.5 P, M	4.11, 3.76, 2.99
15	53.5—53.7	— —	47.6(β) P, M; 53 P, M	
16	54.3—54.5	— —	53.5 P, M	4.11, 3.76, 2.99
17	56.1—56.5	— —	47.6(β); 53 P	

* Sample synthesized by S. Ställberg-Stenhagen [13].

3 a. Ställberg-Stenhagen, S. *Arkiv Kemi, Mineral. Geol.* **A 20** (1945) no. 19.
3 b. Mitz, M. A., Axelrod, A. E., and Hofmann, K. *J. Am. Chem. Soc.* **72** (1950) 1231.
4 a. Brown, W. B., and Farmer, E. H. *Biochem. J.* **29** (1935) 631.
8 a. Riley, P. *J. Chem. Soc.* **1951** 1346.
12 a. Perrotte, R. *Compt. rend.* **200** (1935) 746.

tilted double molecules. The DPT diagram showed no transition, and melting occurred at 94.1—94.3°. Solidification took place at 93° with formation of beautiful long prisms extending through the whole mass, and the keto-acid remelted at 94.2—94.3°. The same acid prepared by the β-keto-ester method crystallized with vertical double molecules and melted and remelted at 96.3—96.5° without any transition being observed on heating.

Methyl ketooctadecanoates, cf. Table 2 and Fig. 2. In this series, the methyl esters with the keto group in position 6 up to and including 13 have similar crystal structures (β) with tilted double molecules, and the corresponding melting point diagram in Fig. 2 shows an alternation of the melting points, the esters with the keto group in an odd-numbered position melting higher than their even-numbered neighbours. The methyl esters of the 15- and 17-keto-acids also possess the same crystal structure but in these two cases minor amounts of a crystalline modification with vertical molecules have also been

Table 3. DL-*Monohydroxyoctadecanoic acids.*

Position of substituent	M.p.° C		Crystal spacings, Å.	
	Present investigation	Literature	Long spacing	Side spacings
2	90.9—91.1	91—92[2a]; 93[2b]; 84—86[2c]	41.9 P, M; 49 M	3.84, 4.33, 4.78 P
3	89.4—89.6 (γ) *)	89[3a]; 90[3b]; 89.4—89.6[3c]	46.5 (β), 44.6 (γ) P, 36.0 (ζ) M[3c]	4.11, 3.89 [3c]
4	87.0—87.4 (γ)	89[4a]; 87[4b]	44.1 P, M	
5	81.9—82.1 (γ)	(54—55[5a])	44.1 P, M	
6	82.0—82.4 (γ)	83[6a]; 84[6b]		
7	77.6—77.8 (γ)	82[7a,b]	44.4 P, M	
8	81.5—81.7 (γ)	— —		
9	75.4—75.9 (γ)	74—75[9a]	44.4 P, M; 47.5 (δ) P	γ: 4.36, 4.08, 3.90
10	79.2—79.5 (γ)	84—86[10a]; 81—81.5[10b]; 83—84[10c]; 84.5[10d]; 81—82[9a]; 85[10e]; 82.5[10f]	44.3 P, M	
11	77.2—77.5 (γ)	84—85[11c]; 76—77[9a]; 84[11a]; 82—85[11b]	44.3; 47.5 P, M	
12	76.6—76.9 (γ); 78.5—78.9	DL: 78—79[9a]; 80[12a]	44.3 P, M	
13	77.2—77.5 (δ)	77—77.5[9a]	47.5 (δ) P, M; 44.3 (γ) P, M	δ: 4.18, 3.85
14	76.6—76.8 (γ); 79.6—79.9 (ε)	— —	44.3 P, M; 42.2 (ε) M	
15	75.3—75.5 (δ)	— —	47.5 (δ) P, M; 44.3 M 42.2 (ε) M	δ: as 13—OH
16	78.4—78.6 (γ)	— —	44.3 P, M	γ: as 12—OH
17	76.4—76.6; 81.0—81.4	— —	40.2 P, M	4.36, 4.11, 3.93, 3.63
18	99.3—99.5; 87—88 (unst.)	96.6—97.2[18a]	46.8 P, M	4.61, 3.78, 3.46

* Sample synthesized by M. Skogh [3c].

2 a. Le Sueur, H. R. *J. Chem. Soc.* **85** (1904) 827.
2 b. Ponzio, G. *Gazz. chim. ital.* **35** II (1905) 570.
2 c. Levene, P. A., and Young, P. S. *J. Biol. Chem.* **102** (1933) 557.
3 a. Ponzio, G. *Gazz. chim. ital.* **35** II (1905) 570.
3 b. Levene, P. A., and Haller, H. L. *J. Biol. Chem.* **63** (1925) 671.
3 c. Skogh, M. *Acta Chem. Scand.* **6** (1952) 809.
4 a. Clutterbuck, P. W. *J. Chem. Soc.* **125** (1924) 2331.
4 b. Kögl, F., and Havinga, E. *Rec. trav. chim.* **59** (1940) 601.
5 a. Jegorow, J. *Chem. Zbl.* **19** I (1915) 934.
6 a. Bougault, J., and Charaux, C. *Compt. rend.* **153** (1911) 573.

6 b. Bougault, J., Cattelain, E., and Chobrier, P. *Compt. rend.* **225** (1947) 876.
7 a. Pigulevskii, G., and Siminova, N., *J. Gen. Chem. (U.S.S.R.)* **9** (1939) 1928.
7 b. Chernoyarova, A. A. *J. Gen. Chem. (U.S.S.R.)* **10** (1940) 146.
9 a. Tomecko, C. G., and Adams, R. *J. Am. Chem. Soc.* **49** (1927) 522.
10 a. Saytzeff, M., C., and A. *J. prakt. Chem.* **35** (1887) 384.
10 b. Geitel, A. C. *J. prakt. Chem.* **37** (1888) 82.
10 c. Arnaud, A., and Posternak, S. *Compt. rend.* **150** (1910) 1527.
10 d. Robinson, G. M., and Robinson, R. *J. Chem. Soc.* **1927** 175.
10 e. Radcliffe, L. G., and Gibson, W. *J. Soc. Dyers Colourists* **39** (1923) 4.
10 f. Pigulevskii, G. V., and Ruboshko, Z. J. *J. Gen. Chem. (U.S.S.R.)* **9** (1939) 829.
11 a. Shukoff, A. A., and Schestakoff, P. J. *J. prakt. Chem.* **67** (1903) 416.
11 b. Saytzeff, M., C., and A. *J. prakt. Chem.* **37** (1888) 277.
11 c. Schreiner, O., and Shorey, E. C. *J. Am. Chem. Soc.* **32** (1910) 1674.
12 a. Reinger, E. *Ber. deut. pharm. Ges.* **32** (1922) 131.
18 a. Chuit, P., and Hausser, J. *Helv. Chim. Acta* **12** (1929) 488.

observed at room temperature. The 14- and 16-keto-esters have the same crystalline structure with vertical double molecules. The 2-, 3-, 4- and 5-keto-esters all crystallize in different tilted forms and no polymorphism has been observed. All keto-esters formed well developed crystals. In the case of the 2- and 4-isomers single crystals of very large size could be obtained.

Hydroxyoctadecanoic acids, cf. Table 3 and Fig. 3. In general, the hydroxy-acids show a more complicated behaviour than the corresponding keto-acids.

The 2-hydroxy-acid melted at 90.9—91.1° and solidified at about 86° with the formation of aggregates of needles. A sample of the original preparation of Le Sueur [2a] (Table 3), obtained through the courtesy of Dr. N. Sheppard, Cambridge, melted at 90.7—91.2° and began to solidify (without nucleus) at 87° in the same manner as our preparation. Remelting took place at 90.6—90.9°. After this specimen had been kept at 92° for 10 hours, the m.p. was about 80°, indicating the formation of lactide. Previously melted specimens of this acid showed the presence of a second crystalline form.

The crystal behaviour of 3-hydroxyoctadecanoic acid has been investigated by Skogh [25]. Three different crystalline modifications were found, which were called β, γ and ζ respectively.

A crystalline form corresponding to the γ form of the 3-hydroxy-acid has also been found for the 4- up to and including the 16-hydroxy-acid. It is the only form found for the 4-, 5-, 6-, 7-, 8-, 10- and 16-hydroxy-acids.

The 4- and 5-hydroxy-acids are on melting partly converted into the corresponding lactones, indicated by the successively lowered remelting points.

A form with a long spacing of 47.5 Å, which we have called δ, has been observed for the 9-, 11-, 13- and 15-hydroxy-acids. The DPT diagrams showed that in the case of the 9-hydroxy-isomer the δ form disappeared on heating,

and that the m.p. is that of the γ form. This was also usually the case with the 11-hydroxy-isomer but on one occasion a specimen melting at 76.6—76.9° was obtained in which the γ and δ forms coexisted up to the m.p. The 13- and 15-isomers both existed in the δ form close to the m.p.

The 12-hydroxy-acid exists in the γ form at room temperature. The acid melts at 76.6—76.9°, but on reheating immediately after solidification melting takes place at 78.5—78.9°. It is possible that the form with the higher m.p. corresponds to the ε form described below for the 14-hydroxy-acid.

The crystalline form with the long spacing 42.2 Å that we have called ε has been observed for previously melted specimens of 14- and 15-hydroxy-acids. In the case of the 14-hydroxy-acid previously melted specimens existed in the γ form at room temperature. On heating, transition to the ε modification began at 70° and this form melted at 79.6—79.9°.

The DPT diagram of the 15-hydroxy-acid showed that previously melted samples existing in the γ form at room temperature underwent a transition to a mixture of the δ and ε forms at about 60°.

The 17-hydroxy-acid melted at 76.4—76.6° but after solidification part of the specimen did not melt until 81.0—81.4°. The X-ray data refer to the low-melting form.

Two crystalline forms were also observed for the 18-isomer. The melt did not solidify until about 87° and on immediate reheating part of the sample melted at 87—88° but complete melting did not occur until 99.5°. The X-ray data refer to the higher-melting form.

The melting point diagram (Fig. 3) shows that for acids with the hydroxyl group in position from 5 to 11 the m.p.'s of the γ forms alternate, the even-numbered isomers having higher m.p.'s than their odd-numbered neighbours.

Methyl esters of monohydroxy octadecanoic acids, cf. Table 4 and Fig. 4. Only one crystalline form has been observed for the 2-hydroxy-ester. All hydroxy-esters from 3- up to the 16-isomer possess the same crystalline modification (β) with a long spacing of 47.5 Å. This is the only form observed for the 3-, 5-, 6- and 7-hydroxy-esters. All other esters show additional crystalline modifications.

Three different melting points have been observed for the 4-hydroxy-isomer. The β modification melts at 57.2—57.4°. The solidified melt on immediate reheating remelts at 58.6—59.1° but if the solidified melt is kept for 24 hours at room temperature the m.p. is again that of the β form. After rapid cooling of the melt the ester remelts at 56.2°.

The 8-, 9- and 10-isomers have a low-melting modification of m.p. 45°. For the 8- and 10-isomers this form is very unstable and has only been observed

Table 4. Methyl esters of DL*-monohydroxyoctadecanoic acids.*

Position of substituent	M.p.° C.		Crystal spacings, Å.	
	Present investigation	Literature	Long spacing	Side spacings
2	65.7—65.9	64—66[2a]	26.4 P	4.18, 3.64 P
3	51.1—51.4 (β)	— —	(β) 47.5 P, M	
4	56.1—56.4; 57.2—57.4; 58.6—59.3	— —		
5	51.7—52.1 (β)	— —		
6	58.2—58.5 (β)	— —		
7	50.7—51.0 (β)	— —		
8	55.3—55.6 (β); 45	— —		
9	50.3—50.6(β);45.0—45.3	45—46[9a]	~52 M	
10	45 (unst.); 51.5—52 (trans.); 54.1—54.2	46[10a]; 53—54[9a]	(β) 47.5 P	4.34, 4.11, 3.89 P, M
11	49.6—49.8 (β); 48 (unst.)	49—50[9a]		
12	53.4—53.6 (β); 52.3—52.7 (unst.)	50—51[9a]		
13	53.3—53.5(β);52.0—52.4	52—52.5[9a]		
14	54.5—54.8 (β); 54 (unst.)	— —		
15	58.7—58.9 (β); 51 (unst.)	— —		
16	61.2—61.5; 56 (unst.)	— —	40.6 (β) P, 40.6, 47.8 M	
17	64.1—64.3; 52—52.5 (unst.)	— —	47.5 P	4.64, 4.29, 4.07, 3.72
18	62.4—62.6 (38.5 Å-form)	61.5—62[18a]	38.5 P, 48 M	

2 a. Levene, P. A., and Young, P. S. *J. Biol. Chem.* **102** (1933) 557.
9 a. Tomecko, C. G., and Adams, R. *J. Am. Chem. Soc.* **49** (1927) 522.
10 a. Radcliffe, L. G., and Gibson, W. *J. Soc. Dyers Colourists* **39** (1923) 4.
18 a. Chuit, P., and Hausser, J. *Helv. Chim. Acta* **12** (1929) 488.

after very rapid solidification by cooling the m.p. tube in cold water. Immediately after melting the higher-melting β form crystallizes out.

On slow cooling the melt of the 9-isomer the low-melting modification of m.p. 45.0—45.3° crystallized in the form of long prisms.

In the case of the 10-hydroxy-isomer a transition point has been observed at 51.5—52°. The β form is transformed into another modification of m.p. 54.1—54.2°. The diffraction pattern is similar to that of the β form but additional lines appear.

A perusal of Tables 1—4 and Figs. 1—4 will show that a keto- or hydroxy-octadecanoic acid with unknown position of the substituent can be identified by

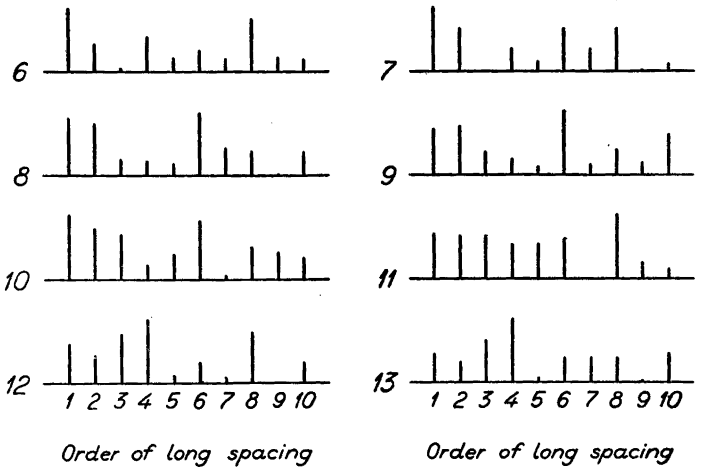

Fig. 5. Intensity distribution among the 00l reflexions of methyl esters of monoketooctadecanoic acids.

the thermal and X-ray spacing data, provided that the substituent is in a position near either end of the chain. However, in a hydroxy-acid or methyl ester with the hydroxyl group in position 5 to 14, the data in the tables will not be sufficient to distinguish clearly between the isomers. Conversion of the hydroxy-compound into the corresponding keto-compound decreases the uncertain region to position 6 to 13. In the case of an acid with the substituent in this region the identification may be achieved with the aid of the intensity distribution among the 00*l* reflexions in the X-ray diffraction patterns, which varies in a characteristic manner with the position of the substituent. The method was first employed by Shearer [26] for long chain keto-acids.

In the present case the identification is best performed on the methyl esters of the keto-acids, as the esters of acids with the ketogroup in position 6 to 13 do not exhibit polymorphism, which complicates the matter for the hydroxy-compounds and for the keto-acids. The visually estimated intensity distribution data for the 00*l* reflexions (up to *0010*) for the methyl ketooctadecanoates (β form) are given in Fig. 5.

EXPERIMENTAL

Due to the great difficulty in obtaining chemicals at the time when a large part of this work was done (1944—45), the availability of suitable starting material has in many cases determined the choice of the method used. The starting material was in every case purified with great care to ensure the absence of homologous impurities, generally by distillation through efficient columns or by crystallization. The final products have

been crystallized from different solvents until further crystallization brought about no further change in the properties of the compound. The acids were crystallized from methanol and acetone (in some cases with the addition of a small amount of water), or from light petroleum (b.p. 80—100°). The methyl esters were crystallized from methanol-water and from low-boiling light petroleum (b.p. below 40°).

As the procedures were identical in many cases, experimental details are given only for the 2-, 15-, 16- and 17-ketooctadecanoic acids, and the 4-, 5-, 17- and 18-hydroxyoctadecanoic acids. The 4-, 5-, 6-, 8-, 9-, 10-, 12- and 14-keto-acids were prepared by the general procedure described for the 15-keto-acid, and the 4-, 5-, 7-, 11- and 13-keto-acids by the procedure given for 17-ketooctadecanoic acid.

The melting points of the acids and their methyl esters are collected in Tables 1—4. The analyses given in Table 5 have been performed in the Microanalytical laboratory at the Institute of Medical Chemistry, Uppsala.

2-Hydroxyoctadecanoic acid. A pure specimen of stearic acid was converted into the α-bromo-acid, using the standard procedure. The α-bromo-acid was then treated with alkali, *cf.* Le Sueur [27].

2-Ketooctadecanoic acid. Methyl 2-hydroxyoctadecanoate (501 mg), obtained by esterification of the acid by means of diazomethane, was dissolved in 50 ml of glacial acetic acid at 37°. A solution of 169.6 mg of chromic trioxide in 50 ml 95 per cent acetic acid was added and the mixture kept at 37° for 60 minutes. The course of the reaction is shown in Fig. 6. One ml of methanol was then added and the solution taken to dryness *in vacuo*. The residue was dissolved in 80 ml of ether and a little water. The ether solution was washed twice with water, dilute sodium carbonate solution and water, dried over sodium sulphate and evaporated to dryness. The keto-ester was crystallized from methanol. The ester was saponified in methanolic potassium hydroxide at room temperature and the acid recrystallized from light petroleum (40—60° and 95°). Yield, 80 % of the theoretical.

3-Ketooctadecanoic acid and methyl ester. The specimens used were those previously described by Stenhagen [12] and Ställberg-Stenhagen [13] respectively.

3-Hydroxyoctadecanoic acid. A sample was kindly supplied by M. Skogh [25]. The methyl ester was prepared from this specimen by means of diazomethane.

4-Ketooctadecanoic acid. Specimens of this keto-acid were prepared both by the organo-cadmium and by the long chain β-keto-ester method. The initial materials in the former case were methyl hydrogen succinate and 1-iodotetradecane; in the latter case ethyl chloroacetate and methyl 3-ketoheptadecanoate [13] were employed.

5-Ketooctadecanoic acid. This acid was also prepared along both routes, starting in one case from methyl hydrogen glutarate and 1-iodotridecane, and in the other case from ethyl β-iodopropionate (obtained via the bromo-ester [28]) and methyl 3-ketohexadecanoate [13].

4- and 5-Hydroxyoctadecanoic acids. Methyl 4- and 5-ketooctadecanoate were hydrogenated at ordinary pressure and temperature over Raney Nickel W—6 in methanolic solution. The reductions were completed in one hour.

The crude 4- and 5-hydroxyoctadecanoic esters obtained after reduction of the corresponding keto-esters were hydrolyzed by excess alkali in refluxing ethanol. After cooling, diluting with water and acidification with the calculated amount of dilute acid, the hydroxy-acids crystallized. They were recrystallized from acetone at −25°. Both acids were obtained as well developed rhombic plates.

6-Ketooctadecanoic acid. Methyl hydrogen adipate and 1-iodododecane were used as in the organo-cadmium procedure.

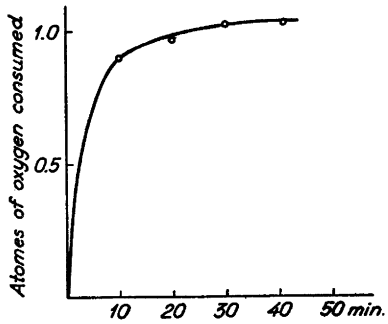

Fig. 6. *Oxidation of methyl 2-hydroxyoctadecanoate with chromic trioxide in 97.5 % acetic acid at 37° as followed by iodometric titration.*

7-Ketooctadecanoic acid. Ethyl 5-bromopentanoate was prepared from adipic acid by the method of Hunsdiecker and Hunsdiecker [29]. Ethyl 5-iodopentanoate, obtained from the bromo-ester by means of sodium iodide in acetone solution, was used for the alkylation of methyl 3-ketotetradecanoate [13].

8-Ketooctadecanoic acid was prepared from methyl hydrogen suberate and 1-bromodecane.

9-Ketooctadecanoic acid. This compound was prepared from methyl hydrogen azelate and 1-bromononane.

10-Ketooctadecanoic acid. Methyl hydrogen sebacate and 1-bromooctane were used.

11-Ketooctadecanoic acid was prepared by the β-keto-ester procedure, starting from ethyl 9-iodononanoate (obtained via the bromo-ester prepared from sebacic acid by the method of Hunsdiecker and Hunsdiecker [29]) and methyl 3-ketodecanoate [13].

12-Ketooctadecanoic acid. Methyl hydrogen dodecane-1,12-dioate and 1-bromohexane were used as initial materials.

13-Ketooctadecanoic acid. Ethyl 11-iodohendecanoate, obtained from undecylenic acid by the procedure of Ashton and Smith [30], was used in the alkylation of methyl 3-ketooctanoate [13].

14-Ketooctadecanoic acid was prepared from methyl hydrogen tetradecane-1,14-dioate and 1-bromobutane.

15-Ketooctadecanoic acid. 13.9 Grams of methyl hydrogen pentadecane-1,15-dioate were dissolved in dry benzene, an excess of thionyl chloride was added, and the mixture was left overnight at room temperature. The acid chloride was taken to dryness *in vacuo* two times after the addition of fresh benzene, and finally dissolved in 25 ml of dry benzene. A Grignard reagent was prepared from 9.26 g of 1-bromopropane and 1.8 g of magnesium turnings under dry nitrogen in a three-neck flask. 7.3 Grams of powdered dry cadmium chloride were added to the ice-cold, well stirred Grignard reagent. After five minutes the ether was distilled off by heating on a steam cone, and subsequently 45 ml of dry benzene were added and distilled off. The sticky reaction product was then stirred under reflux with 45 ml of fresh benzene and the solution of the acid chloride was added gradually during 10 minutes whereafter the mixture was refluxed for one hour. The mixture was then poured onto ice and sulphuric acid. Extraction with ether

yielded 13.5 g of crude reaction product. The ketonic part was isolated with Girard's reagent T according to Ruzicka and Prelog [31] in the following way:

The product was dried *in vacuo* over phosphorous pentoxide and dissolved in a mixture of 225 ml of dry methanol and 13.5 ml of glacial acetic acid. After addition of 12.5 g of "Girard T" the solution was refluxed for two hours. After cooling, about 250 g of ice and 225 ml of 5 per cent sodium carbonate were added and the mixture was extracted four times with ether. The aqueous phase was acidified and the ketones were isolated as usual. Yield 6.6 g of m.p. 48—50°. Saponification and separation of a small amount of neutral products yielded after recrystallization from ethanol or acetone 15-ketooctadecanoic acid. Eq. weight 298.5, Calc. 298.3. The methyl ester was prepared with diazomethane and recrystallized from aqueous methanol and from benzene-light petroleum (b.p. 60—80°).

15-Ketooctadecanoic acid. Ethyl 6-iodohexanoate was prepared from the ω-bromo-compound [32,33] by refluxing with sodium iodide in 2-butanone. *8-Ketopentadecane-1,15-dioic acid.* The methods described by v. Pechmann and Sidgwick [34] and English [35] for a lower homologue were followed. Equimolecular amounts of ethyl 3-ketopentanedioate and ethyl 6-iodohexanoate were heated together on the steam bath and 1 mole of sodium in ethanol was slowly added. When the solution had become neutral (10 hours) one mole iodo-ester was again added followed by sodium ethoxide as before. After the reaction mixture was neutral again the product was isolated in ether, saponified and decarboxylated with hydrochloric acid. Recrystallization from aqueous acetone yielded 8-ketopentadecane-1,15-dioic acid, m.p. 116—117° (m.p. 114° [36]). Yield 40 % of the theoretical.

$C_{15}H_{26}O_5$ (286.4)	Calc.	C 62.89	H 9.15
	Found	» 63.12	» 9.12

Pentadecane-1,15-dioic acid was prepared from the keto-acid by Clemmensen reduction using the conditions described by G. M. Robinson [37] and Stenhagen *et al.* [38]. 59.3 Grams of keto-acid were heated with 400 g of amalgamated zinc, 1 200 ml of conc. hydrochloric acid and 240 ml of acetic acid. The solvents were changed every day for 7 days. After saponification, 50 g of crude *n*-pentadecanedioic acid (m.p. 112—117°) were obtained. The dimethyl ester was purified by distillation, b.p. 199—203°, 11 mm, m.p. 40—43°. (Lit.: m.p. 42° [39], 43° [40], b.p. 203—205°, 11 mm [21]).

$C_{17}H_{32}O_4$ (300.4)	Calc.	C 67.94	H 10.74
	Found	» 68.18	» 10.77

Partial saponification yielded the mono-ester, m.p. 62—63°, after recrystallization from light petroleum (b.p. 60—80°). The acid chloride of this mono-ester and dipropylcadmium gave 15-ketooctadecanoic acid.

16-Ketooctadecanoic acid. Diethyl tetradecane-1,14-dioate was prepared from 1,10-diiododecane through a double malonic ester synthesis [41]. The crude ester had m.p. 24—29° and the yield was 60 per cent of the theoretical. The ester was reduced over copper chromite according to Adkins [42], yielding 1,14-dihydroxytetradecane. *1,14-Diiodotetradecane* was prepared in 94 per cent yield with iodine and read phosphorous [43] from the crude diol, and recrystallized from ethanol, m.p. 48—50°.

$C_{14}H_{28}I_2$ (450.2)	Calc.	C 37.35	H 6.27	I 56.38
	Found	» 37.42	» 6.08	» 55.90

To 58.4 g of diiodide in 250 ml ethanol were added 39 g of potassium cyanide in 65 ml of water and the mixture was left for 20 hours in the steam bath. A small sample of the dinitrile was distilled, b.p. 216—220°, 4 mm. M.p. 47—49°.

Table 5. Analyses.

Position of substituent	Ketooctadecanoic acids		Methyl ketooctadecanoates		DL-Hydroxyoctadecanoic acids		Methyl DL-hydroxyoctadecanoates	
	% C	% H	% C	% H	% C	% H	% C	% H
2	72.51	11.43	73.05	11.63	71.85	12.03	72.52	12.19
3	72.88	11.65[12]	72.50	11.52[13]	71.90	12.12[25]	72.47	12.15
4	72.74	11.45	72.97	11.60	72.10	12.06	72.71	12.14
5	72.48	11.47	72.96	11.50	71.86	12.05	72.77	12.20
6	72.32	11.53	73.07	11.60	71.85	12.11	72.63	12.16
7	72.37	11.46	73.10	11.68	71.86	12.04	72.39	12.12
8	72.56	11.45	72.90	11.64	71.64	12.03	72.82	12.26
9	72.71	11.48	72.76	11.56	71.92	12.08	72.58	12.25
10	72.73	11.49	73.05	11.61	72.09	12.04	72.67	12.18
11	72.29	11.41	73.16	11.67	71.84	12.17	72.90	12.27
12	72.48	11.41	72.75	11.57	71.90	12.06	72.52	12.09
13	72.47	11.43	73.04	11.58	71.94	12.04	72.60	12.22
14	72.17	11.43	72.58	11.47	72.05	12.14	72.77	12.16
15	72.75	11.49	73.07	11.63	72.10	12.07	72.57	12.19
16	72.37	11.46	73.07	11.57	71.65	12.00	72.58	12.17
17	72.25	11.42	72.77	11.60	71.36	11.97	72.57	12.19
18					71.99	12.18	72.28	12.14
Calc.	72.43	11.48	73.03	11.61	71.95	12.08	72.56	12.18

$C_{16}H_{28}N_2$ (248.4) Calc. C 77.36 H 11.36 N 11.28
Found » 77.09 » 11.44 » 11.40

The crude dinitrile was refluxed with ethanolic potassium hydroxide for 22 hours and the crude acid esterified with ethanol-sulphuric acid and distilled, b.p. 205—207°, 3 mm.

Methyl hydrogen hexadecane-1,16-dioate was prepared by partial saponification of the diester [29] and 16-ketooctadecanoic acid prepared from the acid chloride of this monoester and diethylcadmium.

17-Ketooctadecanoic acid. Methyl 15-bromopentadecanoate: 25 Grams of methyl hydrogen hexadecane-1,16-dioate (see above) were dissolved in 100 ml of hot methanol and one mole of potassium hydroxide in aqueous solution was added — the volume was increased to about 600 ml with water to give a clear solution of the potassium salt. This was poured into 500 ml of hot water that was vigorously stirred, simultaneously with the addition of 13.6 g of silver nitrate in 50 ml water. The precipitate was filtered, washed and dried over phosphorous pentoxide *in vacuo*. Yield 33.7 g. The dry silver salt (33.7 g) was suspended in 300 ml of dry carbon tetrachloride, about 100 ml of the solvent distilled off and 12.6 g of dry bromine slowly added [44,45]. When the reaction was complete, water was added and the carbon tetrachloride phase washed wi th alkali

and evaporated to dryness. Crystallization from methanol yielded 22.8 g of methy 15-bromopentadecanoate, m.p. 37.6—38.0°.

$C_{16}H_{31}O_2Br$ (335.3)	Calc.	C 57.30	H 9.32	Br 23.65
	Found	» 57.33	» 9.23	» 23.48

Methyl 15-iodopentadecanoate was prepared by refluxing 21.8 g of the bromo-ester with 40 g sodium iodide in 150 ml acetone for 4 hours. Crystallization from ethanol yielded 22 g of iodo-ester, m.p. 45.2—45.8°.

$C_{16}H_{31}O_2I$ (382.3)	Calc.	C 50.26	H 8.17	I 33.20
	Found	» 50.67	» 8.11	» 32.19

17-Ketooctadecanoic acid was prepared according to the general conditions used by Ställberg-Stenhagen and Stenhagen [17]. 13.87 Grams of the iodo-ester, 4.55 g ethyl acetoacetate and 15 g pulverized, dry potassium carbonate were refluxed in 100 ml of freshly distilled 2-pentanone for 24 hours; water and ether were added and the ether layer was washed with dilute acid, alkali and water. The ether solution was taken to dryness and the residue dissolved in 300 ml of methanol to which 30 g of potassium hydroxide in 30 ml of water were added. The solution was kept at 50° for 20 hours. The acid was isolated and crystallized from aqueous acetone yielding 7.7 g 17-ketooctadecanoic acid, m.p. 87.4—87.7°. The methyl ester was prepared with methanol-sulphuric acid and recrystallized from aqueous methanol, m.p. 56.1—56.5°.

17-Hydroxyoctadecanoic acid. The keto-ester was hydrogenated in methanol (150°, 150 atm., Raney nickel) and the hydroxy-ester was isolated with succinic anhydride as described by Dutcher and Wintersteiner [46]. The acid was recrystallized from aqueous acetone, m.p. 76.4—76.6° and 81.0—81.4°. Methyl 17-hydroxyoctadecanoate was obtained with diazomethane and recrystallized from aqueous methanol and from benzene-light petroleum (b.p. 60—80°).

18-Hydroxyoctadecanoic acid. The monomethyl ester of octadecane-1,18-dioic acid [47] was prepared according to Hunsdiecker *et al.*[29]. M.p. 76.5—77.5°. *Ethyl 17-carbomethoxythiolheptadecanoate.* $CH_3OOC(CH_2)_{16}COSC_2H_5$. 6 Grams of the monomethyl ester were dissolved in 25 ml of dry benzene with slight warming, 10 ml of thionyl chloride were added and the solution was left overnight at room temperature. It was then taken to dryness *in vacuo* and dissolved in fresh benzene to which 1.6 ml of pyridine and 5 ml of ethanethiol were added [48,49,50]. After 24 hours at room temperature, water and ether were added. The ether phase was washed with sodium hydroxide, hydrochloric acid and water, dried over sodium sulphate and evaporated to dryness. The yellow solid obtained (6.9 g) was dissolved in 100 ml of light petroleum (b.p. 40—60°) and filtered through a column of 20 g alumina that was then washed with 200 ml of the same solvent. All colour was retained on the alumina and 4.4 g of a crystalline solid of m.p. 44—47° were obtained. Two recrystallizations raised the m.p. to 48—49°.

$C_{21}H_{40}O_3S$	Calc.	C 67.69	H 10.82	S 8.60
	Found	» 67.89	» 10.95	» 8.33

Methyl 18-hydroxyoctadecanoate. One gram of the above thiol ester was refluxed 5 hours with approximately 10 g of Raney nickel [51] in 80 per cent ethanol. The reaction product was recrystallized 3 times from light petroleum (b.p. 40—60°) yielding very long needles of methyl 18-hydroxyoctadecanoate, m.p. 62.4—62.6°. Saponification yielded 18-hydroxyoctadecanoic acid, m.p. 99.3—99.5°. Chuit and Hausser [52] have isolated the hydroxy-acid, m.p. 96.6—97.2° (methyl ester m.p. 61.4—62°), as a by-product in the reduction of the dimethyl ester of octadecane-1,18-dioic acid with sodium and ethanol.

X-ray and thermal investigations

The X-ray work was carried out with powder methods, using copper Kα radiation (λ = 1.5418 Å, *cf.* ref.[53]). The technique was the same as that used previously in similar work [54]. The long crystal spacings were calculated from the 00*l* reflexions of diffraction patterns given by specimens deposited on glass plates by means of pressing or melting. Side spacings were calculated from diffraction patterns given by specimens contained in very thin-walled glass capillaries (Keesom-capillaries).

The crystal form found in a sample crystallized from solvents was in most cases independant of the solvent used (polar solvents such as methanol and acetone and non-polar solvents such as light petroleum of different boiling ranges were employed).

Apart from the general survey carried out at room temperature, the behaviour of all hydroxy-acids and several of the other compounds from room temperature up to the melting point has been studied by means of a continuously recording X-ray camera described by Stenhagen [24].

The melting points were taken in capillary tubes using the technique described previously [54].

We are indebted to Mrs B. Sjöbeck and Miss K. Pääbo for technical assistance and to Mrs S. Ställberg-Stenhagen for supplying several compounds used as intermediates.

This work was begun when three of the authors (S. B., G. A. E. and B. R.) worked at the Nobel Institute for Biochemistry in Stockholm and has been completed in the laboratories in Lund and Uppsala.

The work has been supported by grants from *Statens Tekniska Forskningsråd* and *Statens Naturvetenskapliga Forskningsråd.*

SUMMARY

The complete series of monoketo- and DL-monohydroxyoctadecanoic acids and their methyl esters has been synthesized. Great care has been taken to get homologue-free and pure compounds.

The polymorphism of the compounds has been studied by thermal and X-ray methods. The hydroxy-compounds are more complicated with regard to polymorphic behaviour than the keto-compounds.

The work described was originally undertaken in order to get synthetic material for the identification of hydroxy-acids derived from unsaturated fatty acids. The thermal and X-ray data given should permit the identification of any monohydroxyoctadecanoic acid, using a minimum amount of material.

REFERENCES

1. Bergström, S. *Arkiv Kemi, Mineral. Geol.* **A 21** (1946) no. 14.
2. Bergström, S. *Arkiv Kemi. Mineral. Geol.* **A 21** (1946) no. 15.
3. Bergström, S. *Nature* **156** (1945) 717.
4. Windaus, A., and van Schoor, A. *Z. physiol. Chem.* **161** (1926) 145.
5. Ruttan, R. F., and Marshall, M. J. *J. Biol. Chem.* **29** (1917) 323.
6. Kon, S., and Funk, C. *Biochem. J.* **18** (1924) 1238.

7. Scurti, F., and Tommasi, G. *Gazz. chim. ital.* **46** II (1916) 166.
8. Adkins, H., and Billica, H. R. *J. Am. Chem. Soc.* **70** (1948) 695.
9. Bergström, S., Theorell, H., and Davide, H. *Arkiv Kemi, Mineral. Geol.* **A 23** (1947) no. 13.
10. Adickes, F., and Andresen, G. *Ann.* **555** (1944) 41.
11. Vogel, E., and Schinz, H. *Helv. Chim. Acta* **33** (1950) 116.
12. Stenhagen, E. *Arkiv. Kemi* **3** (1951) 381.
13. Ställberg-Stenhagen, S. *Arkiv Kemi, Mineral. Geol.* **A 20** (1945) no. 19.
14. Mitz, M. A., Axelrod, A. E., and Hofmann, K. *J. Am. Chem. Soc.* **72** (1950) 1231.
15. Smith, J. C. *Ann. Reports* **35** (1938) 251.
16. Bowman, R. E. *Ann. Reports* **46** (1949) 156.
17. Ställberg-Stenhagen, S., and Stenhagen, E. *Arkiv Kemi, Mineral. Geol.* **A 19** (1945) no. 1.
18. Hunsdiecker, H. *Ber.* **75** (1942) 447.
19. Gilman, H., and Nelson, J. F. *Rec. trav. chim.* **55** (1936) 518.
20. Cason, J. *Chem. Revs.* **40** (1947) 15.
21. Girard, A., and Sandulesco, G. *Helv. Chim. Acta* **19** (1936) 1095.
22. Dauben, W. G. *J. Am. Chem. Soc.* **70** (1948) 1376.
23. Cason, J., and Winans, W. R. *J. Org. Chem.* **15** (1950) 139.
24. Stenhagen, E. *Acta Chem. Scand.* **5** (1951) 805.
25. Skogh, M. *Acta Chem. Scand.* **6** (1952) 809.
26. Shearer, G. *Proc. Roy. Soc. (London)* **A 108** (1925) 655.
27. Le Sueur, H. R. *J. Chem. Soc.* **85** (1904) 827.
28. Kendall, E. C., and McKenzie, B. *Org. Syntheses Coll. Vol. I*, 246.
29. Hunsdiecker, H., and Hunsdiecker, C. *Ber.* **75** (1942) 297.
30. Ashton, R., and Smith, J. C. *J. Chem. Soc.* **1934** 435, 1308.
31. Ruzicka, L., and Prelog, V. *Helv. Chim. Acta* **26** (1943) 975.
32. Brown, G. B., and Partridge, C. W. H. *J. Am. Chem. Soc.* **66** (1944) 839.
33. Robinson, R., and Smith, L. H. *J. Chem. Soc.* **1937** 373.
34. v. Pechmann, H., and Sidgwick, N. V. *Ber.* **37** (1904) 3816.
35. English, J. Jr. *J. Am. Chem. Soc.* **63** (1941) 943.
36. Kenner, J., and Morton, F. *Ber.* **72** (1939) 455.
37. Robinson, G. M. *J. Chem. Soc.* **1934** 1543.
38. Stenhagen, E., and Tägtström-Eketorp, B. *Arkiv Kemi, Mineral. Geol.* **A 19** (1945) no. 8.
39. Ruzicka, L., Stoll, M., and Schinz, H. *Helv. Chim. Acta* **9** (1926) 261.
40. Chuit, P. *Helv. Chim. Acta* **9** (1926) 273.
41. Adams, R., and Kamm, R. M. *Org. Syntheses Coll. Vol. I*, 250.
42. Adkins, H. *Reactions of Hydrogen.* (1937). University of Wisconsin Press, Madison.
43. Hartman, W. W., Byers, J. R., and Dickey, J. B. *Org. Syntheses Coll. Vol. II*, 322.
44. Lüttringhaus, A., and Schade, D. *Ber.* **74** (1941) 1565.
45. Kleinberg, J. *Chem. Revs.* **40** (1947) 381.
46. Dutcher, J. D., and Wintersteiner, O. *J. Am. Chem. Soc.* **61** (1939) 1992.
47. Swann, S., Oehler, R., and Pinkney, P. S. *Org. Syntheses* **21** (1941) 48.
48. Prelog, V., Norymberski, J., and Jeger, O. *Helv. Chim. Acta* **29** (1946) 360.
49. Jeger, O., Norymberski, J., Szpilfogel, S., and Prelog, V. *Helv. Chim. Acta* **29** (1946) 684.
50. Ruzicka, L., Szpilfogel, S., and Jeger, O. *Helv. Chim. Acta* **29** (1946) 1520.
51. Mozingo, R. *Org. Syntheses* **21** (1941) 15.
52. Chuit, P., and Hausser, J. *Helv. Chim. Acta* **12** (1929) 463.
53. Bragg, W. L., and Armstrong Wood, E. *J. Am. Chem. Soc.* **69** (1947) 2919.
54. Ställberg-Stenhagen, S., and Stenhagen, E. *J. Biol. Chem.* **173** (1948) 383.

Received September 24, 1951.