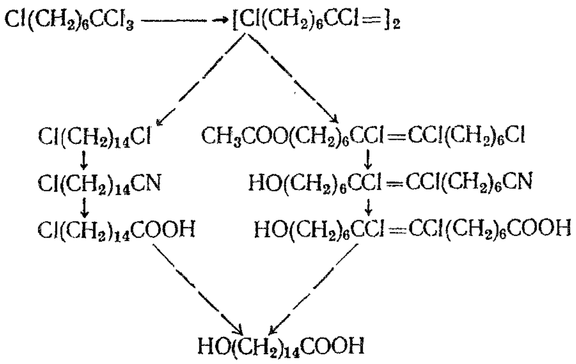
SYNTHESIS OF 15-HYDROXYPENTADECANOIC AND 16-HYDROXYHEXADECANOIC ACIDS

A. N. Nesmeyanov, L. I. Zakharkin, T. A. Kost, and R. Kh. Friedlina

Institute of Heteroorganic Compounds, Academy of Sciences, USSR

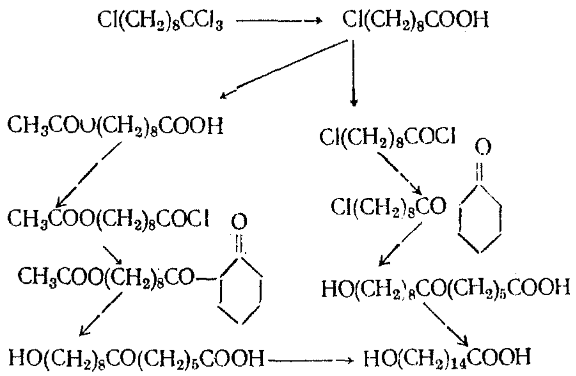
Translated from Izvestiya Akademii Nauk SSSR, Otdelenie Khimicheskikh Nauk No. 2, pp 211-216, February, 1960
Original article submitted June 17, 1958.

$\alpha, \alpha, \alpha, \omega$-Tetrachloroalkanes $CCl_3(CH_2CH_2)_nCl$, which are obtained by the telomerization of ethylene with carbon tetrachloride, present great possibilities for the synthesis of various higher α, ω-bifunctional compounds. We have previously [1] synthesized dodecanedioic and hexadecanedioic acids from 1,1,1,5-tetrachloropentane and 1,1,1,7-tetrachloroheptane respectively. In the present work we investigated several ways of proceeding from 1,1,1,7-tetrachloroheptane and 1,1,1,9-tetrachlorononane to the synthesis of 15-hydroxypentadecanoic and 16-hydroxyhexadecanoic acids, which are of great interest because of the value of their lactones in perfumery (tibettolide, dihydroambrettolide). 15-Hydroxypentadecanoic acid was prepared from 1,1,1,7-tetrachloroheptane in accordance with the schemes:



1,1,1,7-Tetrachloroheptane was hydrogenated in presence of $Pd/BaSO_4$ and ammonia to 1,7,8,14-tetrachloro-7-tetradecene or 1,14-dichlorotetradecane in the way which we have described previously [1]. Treatment of 1,14-dichlorotetradecane with sodium cyanide in 2-ethoxyethanol gave a mixture of the original compound, the mononitrile, and a little of the dinitrile, which was subjected to acid hydrolysis without prior separation. The resulting 15-chloropentadecanoic acid gave 15-hydroxypentadecanoic acid when heated in an autoclave with aqueous alkali. In accordance with the second scheme, 1,7,8,14-tetrachloro-7-tetradecene was converted into the monoacetoxy compound, and alcoholysis of this and treatment with sodium cyanide gave 8,9-dichloro-15-hydroxy-8-pentadecenenitrile. Hydrolysis of the nitrile group and hydrogenation over Raney nickel gave 15-hydroxypentadecanoic acid. By the first method the yield of 15-hydroxypentadecanoic acid was about 45% (on 1,14-dichlorotetradecene), and by the second method it was 36.3% (on 1,7,8,14-tetrachloro-7-tetradecene).

From 1,1,1,9-tetrachlorononane, 15-hydroxypentadecanoic acid was synthesized as follows:



By hydrolysis with concentrated sulfuric acid,1,1,1,9-tetrachlorononane was converted into 9-chlorononanoic acid. In accordance with the first scheme this was converted into 9-acetoxynonanoic acid, which was further converted into its acid chloride with thionyl chloride. 9-Acetoxynonanoyl chloride was brought into reaction with 1-(1-cyclohexen-1-yl) piperidine, as described for other acid chlorides [2]. Without being purified, the resulting diketone was subjected to alkaline scission, and without being isolated the keto acid was subjected to Kizhner reduction with hydrazine to 15-hydroxypentadecanoic acid. In accordance with the second scheme, analogous reactions were carried out with 9-chlorononanoyl chloride, but in this case the 15-chloro-7-oxopentadecanoic acid obtained after alkaline scission of the diketone was without isolation, subjected to alkaline hydrolysis to the corresponding hydroxy keto acid, which was then reduced with hydrazine. The yields of 15-hydroxypentadecanoic acid were about 75% (on 9-acetoxynonanoic acid) and about 60% (on 9-chlorononanoyl chloride).

The synthesis of 16-hydroxyhexadecanoic acid from 1,1,1,7-tetrachloroheptane and from 1,1,1,9-tetrachlorononane was carried out as follows:

$$\mathrm{Cl(CH_2)_6CCl_3} \rightarrow \mathrm{Cl(CH_2)_6COOH} \rightarrow \mathrm{I(CH_2)_6COOCH_3} \xrightarrow{\mathrm{Zn}} \mathrm{I\,Zn(CH_2)_6COOCH_3} \xrightarrow{\mathrm{CH_3COO(CH_2)_8COCl}}$$
$$\rightarrow \mathrm{CH_3COO(CH_2)_8CO(CH_2)_6COOCH_3} \rightarrow \mathrm{HO(CH_2)_{15}COOH}$$

and

$$\mathrm{Cl(CH_2)_8CCl_3} \rightarrow \mathrm{Cl(CH_2)_8COOH} \rightarrow \mathrm{I\ (CH_2)_8COOCH_3} \rightarrow$$
$$\xrightarrow{\mathrm{Zn}} \mathrm{I\,Zn(CH_2)_8COOCH_3} \xrightarrow{\mathrm{CH_3COO(CH_2)_6COCl}}$$
$$\rightarrow \mathrm{CH_3COO(CH_2)_6CO(CH_2)_8COOCH_3} \rightarrow \mathrm{HO(CH_2)_{15}COOH}$$

In the first scheme the starting compounds are methyl 7-iodoheptanoate and 9-acetoxynonanoyl chloride; in the second scheme they are methyl 9-iodononanoate and 7-acetoxyheptanoyl chloride. All these are readily prepared from the corresponding ω-chloro carboxylic acids. These ω-iodo carboxylic esters were converted into the corresponding zinc derivatives by the action of zinc in accordance with the method developed previously [3]. By reaction with ω-acetoxy acid chlorides the zinc derivatives gave 16-acetoxy-8(or 10)-oxohexadecanoic esters, whose reduction with hydrazine led directly to 16-hydroxyhexadecanoic acid. The yields of 15-hydroxyhexadecanoic acid were about 50% by the first scheme and about 60% by the second scheme (on the corresponding ω-acetoxy acid chlorides).

EXPERIMENTAL

15-Chloropentadecanoic Acid. A mixture of 29 g of 1,14-dichlorotetradecane and 4.5 g of sodium cyanide in 60 ml of 2-ethoxyethanol was heated with stirring for four hours at 105-108°. The cooled reaction mixture was diluted with water and extracted with chloroform. After removal of solvent a solid residue remained. It was not found possible to separate the mixture of products by vacuum distillation (b.p. 148-200°/1 mm). A solution of the mixture of products in acetic and hydrochloric acids was boiled for 16 hours, diluted with water, and extracted with chloroform. The chloroform extract was washed several times with dilute potassium hydroxide solution. On acidification of the alkaline solution there was a precipitate of mono- and dicarboxylic acids, which was recrystallized from petroleum ether. This gave 8.1 g of 15-chloropentadecanoic acid, m.p. 62-63°, undepressed by admixture of a known sample [4]. From the chloroform solution we recovered 12.5 g of 1,14-dichlorotetradecane.

Alkaline Hydrolysis of 15-Chloropentadecanoic Acid. A solution of 5.3 g of 15-chloropentadecanoic acid and 3.7 g of potassium hydroxide in 100 ml of water was heated in an autoclave at 150° for five hours. Acidification gave a precipitate of 15-hydroxypentadecanoic acid; yield 4.7 g; m.p. 82-83° (from benzene) [5, 6].

7,8,14-Trichloro-7-tetradecen-1-ol Acetic Ester. A mixture of 16.7 g of 1,7,8,14-tetrachloro-7-tetradecene, 19.6 g of anhydrous potassium acetate, and 100 ml of acetic acid was heated for 18 hours. The reaction mixture was treated with three times its volume of water and extracted with chloroform. Removal of solvent left 16.0 g (90%) of 7,8,14-trichloro-7-tetradecen-1-ol acetic ester; b.p. 181-183°/2 mm; n_D^{20} 1.4830; d_4^{20} 1.1132; found MR 91.81; calculated MR 91.88. Found: C 54.00; 53.97; H 7.83; 7.73%. $C_{14}H_{25}Cl_3O$. Calculated: $C_{16}H_{27}Cl_3O_2$. Calculated: C 53.71; H 7.60%.

7,8,14-Trichloro-7-tetradecen-1-ol. A mixture of 20.3 g of the acetic ester of 7,8,14-trichloro-7-tetradecen-1-ol, 50 ml of methanol, and 0.5 ml of concentrated hydrochloric acid was heated for six hours. Methanol and methyl acetate were distilled off, a further 50 ml of methanol and 0.5 ml of concentrated hydrochloric acid was added, and the mixture was heated for five hours. Methanol was distilled off, and the mixture was treated with water and chloroform. The chloroform solution was dried, and removal of chloroform gave 15.0 g (95%) of 7,8,14-trichloro-7-tetradecen-1-ol b.p. 178°/2mm; n_D^{20} 1.4990; d_4^{20} 1.1231; found 82.49; calculated MR 82.51; Found: C53.43; 53.31; H 7.86; 7.57%. $C_{14}H_{25}Cl_3O$. Calculated C 53.26; H 7.98%.

8,9-Dichloro-15-hydroxy-8-pentadecenenitrile. A mixture of 27.3 g of 7,8,14-trichloro-7-tetradecen-1-ol, 126 g of sodium cyanide, 0.5 g of potassium iodide, 25 ml of water, and 100 ml of 2-ethoxyethanol was heated at 100° for six hours. The reaction mixture was treated with water and extracted with chloroform. After drying and removal of solvent we obtained 22 g (83%) of 8,9-dichloro-15-hydroxy-8-pentadecenenitrile; b.p. 205°/2 mm; n_D^{20} 1.4910; d_4^{20} 1.0803; found MR 82.14; $C_{15}H_{25}Cl_2NO$. Calculated MR 82.08.

8,9-Dichloro-15-hydroxy-8-pentadecenoic Acid. A mixture of 22 g of 8,9-dichloro-15-hydroxy-8-pentadecenenitrile, 25 ml of hydrochloric acid, and 25 ml of glacial acetic acid was heated for six hours. The reaction mixture was treated with excess of water and extracted with chloroform. The solution was dried, and removal of chloroform gave 18.4 g (80%) of 8,9-dichloro-15-hydroxy-8-pentadecenoic acid; b.p. 210°/1 mm; n_D^{20} 1.4865; d_4^{20} 1.1074; found MR 84.44; calculated MR 84.48. Found: C 55.32; 55.64; H 7.89; 7.84; Cl 21.61; 21.75%. $C_{15}H_{26}Cl_2O_3$. Calculated: C 55.37; H 8.05; Cl 21.79%.

15-Hydroxypentadecanoic Acid. 8,9-Dichloro-15-hydroxy-8-pentadecenoic acid (9.0 g) was dissolved in aqueous alkali (8.4 g of potassium hydroxide in 300 ml of water) and hydrogenated in the presence of 3g of Ni catalyst for six hours at 100 atm and 100°. The catalyst was filtered off, and the filtrate was acidified with hydrochloric acid. This gave 3.9 g (54.9%) of 15-hydroxypentadecanoic acid, m.p. 78° (from benzene + petroleum ether).

15-Hydroxypentadecanoic Acid from 9-Chlorononanoic Acid. a) A solution of 56 g of 9-chlorononanoic acid and 57 g of potassium hydroxide in 275 ml of water was heated in an autoclave at 150° for five hours. When cool, the solution was acidified with dilute sulfuric acid. The precipitated 9-hydroxynonanoic acid was extracted with ether. The ether solution was dried over magnesium sulfate. Ether was removed, and 35 g of acetic anhydride was added to the residue. Reaction occurred with evolution of heat. The mixture was boiled for ten minutes, and vacuum distillation then gave 43.4 g of 9-acetoxynonanoic acid (b.p. 158-160°/2 mm; n_4^{02} 1.4462; d_4^{20} 1.0518) and 6.7 g of residue, which on hydrolysis with sodium hydroxide solution gave 5.1 g of 9-hydroxynonanoic acid. The 43.4 g of 9-acetoxynonanoic acid was heated with 50 ml of thionyl chloride for four hours. Distillation gave 43 g of 9-acetoxynonanoyl chloride, b.p. 125-126°/2 mm. A solution of this 43 g of acid chloride in 60 ml of chloroform was added over a period of 30 minutes to a stirred solution of 35 g of 1-(1-cyclohexen-1-yl) piperidine* and 24 g of triethylamine in 200 ml of dry chloroform at 35°. The mixture was stirred at this temperature

---

*Hunig and co-workers [2] state that they obtained a yield of 55% in the preparation of 1-(1-cyclohexen-1-yl) piperidine from cyclohexanone and piperidine. We found that the yield could be raised to 70-75% by increase in the reaction time.

for one hour and then left for 12 hours. A solution of 50 g of concentrated sulfuric acid in 70 ml of water was added, and the reaction mixture was boiled with stirring for four hours. The chloroform solution was separated, washed with water, and dried over magnesium sulfate. Removal of chloroform left 53.4 g of residue. The residue was heated to 100° and added with stirring to a solution of 47 g of potassium hydroxide in 33 ml of water at 100°. In the course of this the temperature rose to 123°, and the reaction mixture was stirred for ten minutes at this temperature. A small part of the mixture was dissolved in hot water and acidified with dilute sulfuric acid. The precipitate formed was dissolved in chloroform. The chloroform solution yielded 15-hydroxy-7-oxopentadecanoic acid, m.p. 82-83° (from benzene). Found: C 66.15; 66.00; H 10.16; 10.34%. $C_{15}H_{28}O_4$. Calculated: C 66.17; H 10.29%.

To the hot mass we added 150 ml of diethylene glycol and 70 ml of hydrazine hydrate. The solution was boiled for eight hours, after which 24 g of potassium hydroxide in 100 ml of diethylene glycol was added; water and excess of hydrazine hydrate were distilled from the mixture until the temperature in the liquid reached 195°. The reaction mixture was then boiled for 15 hours. The hot solution was poured into 1 liter of hot water and acidified with dilute sulfuric acid. The precipitated 15-hydroxypentadecanoic acid was filtered off, washed with water, and dried. We obtained 38.5 g of substance, m.p. 84.85° (from benzene).

b) From 26.8 g of 9-chlorononanoyl chloride, 23 g of 1-(1-cyclohexen-1-yl) piperidine, and 15.5 g of triethylamine we obtained, after hydrolysis, 30 g of diketone; b.p. 178-180°/2 mm; n_D^{20} 1.5065. Found: C 66.17; 66.24; H 9.18; 9.32%. $C_{15}H_{25}ClO_2$. Calculated: C 66.06; H 9.17%.

This 30 g of diketone was treated with 26 g of potassium hydroxide in 18 ml of water, as described above, for 20 minutes. The hot mixture was then poured into hot water to make a total volume of 350 ml and was heated in an autoclave at 145-155° for five hours. The cooled solution was extracted with ether and acidified with dilute sulfuric acid. The precipitate formed was extracted with chloroform. We obtained 23.8 g of 15-hydroxy-7-oxopentadecanoic acid, m.p. 82-83° (from benzene), undepressed by admixture of the sample from the preceding experiment. Reduction similar to that described above gave 18.4 g of 15-hydroxypentadecanoic acid.

Methyl 7-Iodoheptanoate. A solution of 44.3 g of methyl 7-chloroheptanoate [4] and 55.8 g of sodium iodide in 300 ml of acetone was boiled for 12 hours. We obtained 58.8 g of the methyl ester; b.p. 107-109°/3 mm; n_D^{20} 1.4958; d_4^{20} 1.4672; found MR 53.74; calculated MR 53.60. Found: C 35.74; 35.70; H 5.71, 5.69%. $C_8H_{15}IO_2$. Calculated: C 35.55; H 5.55%.

Methyl 16-Acetoxy-8-oxohexadecanoate. A mixture of 47.8 g of methyl-7-iodoheptanoate, 19 g of zinc dust (previously treated with copper sulfate solution and dried), 2 ml of ethyl acetate, and 30 ml of dry toluene was boiled with stirring for three hours. The mixture was cooled, and over a period of 30 minutes a solution of 31.2 g of 9-acetoxynonanoyl chloride in 40 ml of toluene was added. On the next day the reaction mixture was heated with stirring for ten minutes in a water bath, cooled, diluted with benzene, and filtered from excess of zinc. The filtrate was washed with dilute sulfuric acid, water, and sodium carbonate solution and was dried over calcium chloride. Solvent was distilled off, and vacuum distillation gave 7.1 g of methyl heptanoate and 23.2 g (51%) of methyl 16-acetoxy-8-oxohexadecanoate; b.p. 209-211°/2 mm; m.p. 52-53° (from petroleum ether). Found: C 66.73; 66.79; H 10.26; 10.28%; $C_{19}H_{34}O_5$. Calculated: C 66.70; H 9.96%.

16-Hydroxyhexadecanoic Acid. A solution of 7.1 g of methyl 16-acetoxy-8-oxohexadecanoate in 15 ml of diethylene glycol was added to a solution of 2.9 g of potassium hydroxide in 20 ml of diethylene glycol. The mixture was heated at 120-130° without a condenser for 20 minutes, 8 ml of hydrazine was added, and the reaction mixture was boiled for eight hours. Addition was made of 7.5 g of potassium hydroxide in 20 ml of diethylene glycol. Water and excess of hydrazine hydrate were distilled off until the temperature in the liquid reached 195°. The solution was boiled for 15 hours and then poured into hot water and acidified with dilute sulfuric acid. We obtained 5.3 g of 16-hydroxyhexadecanoic acid, m.p. 93-94° (from benzene).

7-Acetoxyheptanoyl Chloride. A solution of 45 g of 7-chloroheptanoic acid and 35 g of sodium hydroxide in 250 ml of water was heated in an autoclave at 150° for four hours. The solution was acidified with dilute sulfuric acid, and the 7-hydroxyheptanoic acid was extracted with ether and dried over magnesium sulfate. Ether was removed, and 34 g of acetic anhydride was added to the residue. Reaction occurred with evolution of heat. The solution was boiled for ten minutes and vacuum-distilled. We obtained 39.1 g of 7-acetoxyheptanoic acid;

b.p. 142-143°/ 2 mm; n_D^{20} 1.4420; d_4^{20} 1.0570; found MR 47.06; calculated MR 46.95. On alkaline hydrolysis the residue gave 5.1 g of 7-hydroxyheptanoic acid. A mixture of 32 g of 7-acetoxyheptanoic acid and 40 ml of thionyl chloride was heated for four hours. We obtained 31.3 g of 7-acetoxyheptanoylchloride. b.p. 106-107°/ 2 mm.

Methyl 9-Iodononanoate. A solution of 35.2 g of methyl 9-chlorononanoate [4] and 49 g of sodium iodide in 260 ml of acetone was heated in a water bath for 16 hours. We obtained 43.2 g (87%) of methyl 9-iodononanoate; b.p. 124-127°/ 2 mm; n_D^{20} 1.4911; d_4^{20} 1.3730; found MR 63.09; calculated MR 62.84. Found: C 40.44; 40.51; H 6.50; 6.42%. $C_{10}H_{19}IO_2$. Calculated: C 40.26; H 6.37%.

Methyl 16-Acetoxy-10-oxohexadecanoate. The procedure was analogous to that of the experiment with methyl 7-iodoheptanoate: From 41 g of methyl 9-iodononanoate, 14 g of zinc, and 21.5 g of 7-acetoxyheptanoyl chloride we obtained 5.1 g of methyl nonanoate and 22.4 g (62.5%) of methyl 16-acetoxy-10-oxodecanoate; b.p. 205-207°/2 mm; m.p. 40.41° (from petroleum ether). Found: C 66.40; 66.53; H 10.14; 10.05%. $C_{19}H_{34}O_5$. Calculated: C 66.70; H 9.96%.

Reduction of this keto ester with hydrazine hydrate gave 16-hydroxyhexadecanoic acid in 92.4% yield.

SUMMARY

1. 15-Hydroxypentadecanoic acid was synthesized by several routes from 1,1,1,7-tetrachloroheptane and 1,1,1,9-tetrachlorononane.

2. 16-Hydroxyhexadecanoic acid was synthesized from 1,1,1,7-tetrachloroheptane and 1,1,1,9-tetrachlorononane via the corresponding ω-chloro carboxylic acids.

LITERATURE CITED

1. A. N. Nesmeyanov, L. I. Zakharkin, and T. A. Kost, Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk, 657 (1955).*
2. S. Hünig, E. Lücke, and E. Benzing, Chem. Ber. 91, 129 (1958).
3. H. Hunsdiecker and H. Erlbach, Chem. Ber. 80, 129 (1947).
4. A. N. Nesmeyanov and L. I. Zakharkin, Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk, 224 (1955).*
5. L. Ruzicka and M. Stoll, Helv. chim. acta 11, 1167 (1928).
6. T. É. Svadkovskaya, S. A. Voitkevich, E. K. Smol'yaninova, and V. N. Belov, Zhur. Obshchei Khim 27, 2146 (1957).*

---

*Original Russian pagination. See C. B. translation.