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THE PREPARATION OF 8-OCTADECENEDIOIC ACID

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Received April 30, 1948

Long-chain unsaturated α,ω-dicarboxylic acids are convenient intermediates for the preparation of macrocyclic ketones of the civetone type. Ruzicka, Plattner, and Widmer (1) were the first to describe the preparation of *cis-* and *trans-*10-eicosenedioic acid and *cis-* and *trans-*9-octadecenedioic acid. Their method consists of doubling a suitably chosen unsaturated ester molecule, as for example ethyl 10-hendecenoate, by means of the acyloin condensation. This reaction is followed by ozonization of the double bonds at the ends of the molecule and elimination of the hydroxyl groups in the center. The transformations are illustrated by the following equations:

$$CH_2{=}CH(CH_2)_8CO_2Et \rightarrow CH_2{=}CH(CH_2)_8COCHOH(CH_2)_8CH{=}CH_2 \rightarrow$$

$$CH_2{=}CH(CH_2)_8CHOHCHOH(CH_2)_8CH{=}CH_2 \rightarrow$$

$$HO_2C(CH_2)_8CHOHCHOH(CH_2)_8CO_2H \rightarrow HO_2C(CH_2)_8CH{=}CH(CH_2)_8CO_2H$$

At about the same time Mitter and Bhattacharyya (2) proposed the use of aleuritic acid, 9,10,16-trihydroxyhexadecanoic acid, for the preparation of unsaturated α,ω-dicarboxylic acids. They recommend the treatment of aleuritic acid or its ethyl ester with phosphorus diiodide, thereby replacing the adjacent hydroxyl groups by a double bond and the third hydroxyl by iodine. This method, however, gives poor yields. Three grams of ethyl 16-iodo-9-hexadecenoate was obtained from 20 g. of the ethyl ester, and the product from free aleuritic acid was obtained only in impure form. Mitter and Bhattacharyya reported unusual difficulties in the further reaction of the ester with sodiomalonic ester or potassium cyanide.

In the present paper we describe some transformations of aleuritic acid which proceed smoothly to form the unsaturated, α,ω-dicarboxylic acids in very good yields. Our procedure consists of reducing the ethyl ester of aleuritic acid (I) to the corresponding alcohol (II), replacing the four hydroxyl groups with bromine (III), and removing the vicinal bromine atoms with zinc dust. The 1,16-dibromo-7-hexadecene so formed (IV) reacts smoothly with potassium cyanide under the usual conditions, and the unsaturated dinitrile (V) can be saponified to 8-octadecenedioic acid (VI).

$$HO(CH_2)_6CHOHCHOH(CH_2)_7CO_2Et \qquad (I)$$

$$HO(CH_2)_6CHOHCHOH(CH_2)_8OH \qquad (II)$$

$$Br(CH_2)_6CHBrCHBr(CH_2)_8Br \qquad (III)$$

$$X(CH_2)_6CH{=}CH(CH_2)_8X \qquad X = Br\ (IV);\ X = CN\ (V);\ X = CO_2H\ (VI).$$

As it was of special interest to ascertain the sterical homogeneity of the unsaturated compounds, considerable effort was devoted to the purification of the 1,16-dibromo compound and the corresponding dioic acid. After purification by high-vacuum distillation, the dibromoalkene showed the expected analytical composition and melted at 16.5–17.5°. This material was repeatedly crystallized from absolute ethanol and petroleum ether (b.p. 45–60°) to give in approximately 40% yield a product with the constant melting point 24.5–25.5° and an unchanged analytical composition. We were unable to isolate a second compound from the mother liquors. The fractions obtained all had melting points ranging between 16.5° and 24.5°. In another attempt, 8-octadecendioic acid was prepared without any purification of the intermediate products. Purification of the end product gave in over 85% yield a compound melting at 110.5–111°, which was not altered by further treatment. We are therefore inclined to assume that the different transformations starting with aleuritic acid yield a sterically homogeneous material. This conclusion is supported by the previous findings of Ruzicka, Plattner, and Widmer (1) that in the reduction of their acyloin compounds two stereoisomeric(m eso and racemic) dihydroxy derivatives are formed, which lead in sequence to the two unsaturated (*cis* and *trans*) acids in sterically homogeneous form.

An interesting observation was made regarding 1,7,8,16-tetrahydroxyhexadecanealeurityl alcohol. This compound was analyzed and described by Mitter and Mukherjee (3), who reported the melting point 56°. Starting with aleuritic acid melting at 100–101°, in agreement with these authors, we obtained the tetrahydric alcohol melting at the constant temperature 90–90.5° to a cloudy liquid, with meniscus, which clears sharply at 95°. (We presume the formation of liquid crystals.) We are at present unable to explain this divergence, since the high-melting product was the only one obtained by us in oft-repeated reductions and no other material was present in the mother liquors.

EXPERIMENTAL PART

For all melting points and analyses, the materials were dried over P_2O_5 at 60° and 1–2 mm. pressure. The melting points are uncorrected.

1,7,8,16-Tetrahydroxyhexadecane (II). Uniformly high yields were obtained by the modified Bouveault-Blanc procedure described below. In conformity with the experiences of Chuit (4) and Ziegler (5), satisfactory results required the painstaking exclusion of all traces of water, but contrary to the recommendation of Ziegler, addition of the sodium to the boiling ester solution rather than the reverse procedure gave better results in our hands.

Forty grams of the ethyl ester of aleuritic acid, melting at 59–59.5°, [Mitter and Bhattacharyya (2), m.p. 50–55°], dried over P_2O_5 at 70° *in vacuo*, was dissolved in 500 ml. of absolute 1-butanol (dried with magnesium), and heated to boiling. Thirty-five grams of metallic sodium cut in large lumps was introduced in two to three lots. After the violent reaction had subsided the mixture was heated in an oil-bath at 150–160° for a further 2½ hours. The contents of the flask were cooled to approximately 70°, decomposed with water, and heated for one-half hour. The warm alcohol layer was separated, washed with warm water, and steam distilled to remove solvent. The remaining yellowish oil solidified on cooling to room temperature. After being filtered and washed, the already pure material was recrystallized from dilute alcohol and benzene. As mentioned above, it showed a constant double transition point: at 90–90.5° it melted to a cloudy liquid, with a meniscus, which turned clear at 95° (sharp); yield 80–85%.

Anal. Calc'd for $C_{16}H_{34}O_4$: C, 66.2; H, 11.7.
Found: C, 65.9, 66.0; H, 11.7, 11.6.

1,7,8,16-Tetrabromohexadecane (*III*). Thirty grams of the tetrahydroxy compound was treated with 300 ml. of a solution of HBr in glacial acetic acid (sp. gr. 1.25 = 22.5% HBr by wt.). On gentle warming in an oil-bath the solid disappeared into the solution. The bath was brought slowly (two hours) to 80–85° and kept for two hours at 85–95° and for four hours at 100–105°. After cooling to approximately 40°, the excess HBr and acetic acid were removed under reduced pressure. The oily, dark-brown residue was taken up with ether and the ethereal solution washed with water and bicarbonate solution. The dried ethereal solution was repeatedly decolorized with charcoal and the ether was removed. A pale yellow, heavy oil remained which turned to a waxy, non-crystalline solid on cooling to −10°. The yield (55 g.) was almost quantitative. The bromine content was found to be 58.53% whereas $C_{16}H_{30}Br_4$ requires 58.95% Br.

In an attempt to purify the crude material, 2 g. was subjected to a short-path distillation at 0.01 mm. and an oil-bath temperature of 180–200°. The resulting pale yellow oil had the same physical properties and the bromine content was found to be 58.6%.

1,16-Dibromo-7-hexadecene (*IV*). For the debromination of the tetrabromide, 32 g. of zinc powder was activated under 100 ml. of 98% alcohol by boiling 3–5 minutes with 1 ml. of concentrated hydrogen bromide solution. The mixture was cooled to room temperature and a solution of 52 g. of the crude tetrabromide in 70 ml. of benzene was added in three to four portions with constant shaking. The temperature rose with each addition and was kept near the boiling point for approximately 15 minutes with constant mixing. The boiling solution was filtered from the excess zinc powder and the filtrate was washed with water, dilute sulfuric acid, and bicarbonate solution. After drying over Na_2SO_4, the solvent was removed under reduced pressure. The remaining oil, which melted at 16–17°, could be purified by high-vacuum distillation, but crystallization was more convenient. The material was dissolved at 35–40° in 5–6 times its weight of 98% alcohol and filtered from a small insoluble residue. The filtrate, which should remain clear at 25–30°, was cooled slowly to −10°, the dibromo compound separating in the form of beautiful silky needles which turned the solution into a solid paste. After standing 12 hours in a refrigerator the crystalline precipitate was filtered through a cooled Büchner funnel and washed with small portions of cold alcohol. The melting point of the purified material after repeated crystallizations from alcohol, petroleum ether, and acetone was constant at 25–25.5°.

Anal. Calc'd for $C_{16}H_{30}Br_2$: C, 50.25; H, 7.9; Br, 41.8.
Found: C, 50.6; H, 8.0; Br, 42.0.

A material purified by distillation only, melted at 16.5–17.5° and contained 42.1% bromine.

8-Octadecenedinitrile (*V*). To 25 g. of 1,16-dibromo-7-hexadecene in 150 ml. of alcohol was added a solution of 14 g. of potassium cyanide and 0.75 g. of potassium iodide in 30 ml. of water. This mixture was boiled 15 hours under reflux with good stirring. An additional 7 g. of potassium cyanide in 15 ml. of water was added and refluxing was continued for 15–20 hours. After cooling, the reaction mixture was taken up in water and ether. The ethereal solution was washed with bicarbonate solution and water and dried with sodium sulfate. After removal of the solvent, the sludge of pale yellow crystals which remained was purified by high-vacuum distillation. After a small forerun the main fraction distilled at 182–185°/0.5 mm. The distillate solidified to a sludge of white waxy crystals which sintered at 35–38° and melted at 45–47°; yield 85–90%.

A material free of all traces of halogen and distilling with a very small forerun can be obtained if after the first reaction period with potassium cyanide the crude dinitrile is separated by partition between ether and water, freed from solvent, and treated in a water-alcohol solution with a fresh portion of 10 g. of potassium cyanide and 0.75 g. of potassium iodide.

Anal. Calc'd for $C_{18}H_{30}N_2$: C, 78.8; H, 11.0; N, 10.2.
Found: C, 78.5; H, 11.3; N, 9.8.

8-Octadecenedioic acid (*VI*). The 8-octadecenedinitrile was saponified by dissolving 2.5

g. in 20 ml. of alcohol, adding 4 g. of potassium hydroxide dissolved in 10 ml. of water, and refluxing the homogeneous solution strongly for 30 hours. The alcohol was removed by evaporation and replaced with water, and the hot alkaline solution was filtered from impurities. Upon acidification of the filtrate there was obtained a white fluffy precipitate of the crude acid melting at 102–106°; yield 2.55 g. (90%). After repeated crystallization from dilute alcohol and benzene the material attained the constant melting point 110.5–111°.

Anal. Calc'd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.34; Eq. wt., 156.2.
Found: C, 69.0; H, 10.5; Eq. wt., 156, 156.2.

Dimethyl 8-octadecenedioate. The ester was prepared by boiling 0.3 g. of the acid for 3 hours with 4 ml. of methanol and a trace of sulfuric acid. After the usual purification, a solid material was obtained which after rubbing with a few drops of ice-cold petroleum ether and recrystallization from 90% methanol sintered at 32° and melted at 36–37°.

Anal. Calc'd for $C_{20}H_{36}O_4$: C, 70.5; H, 10.6.
Found: C, 70.6; H, 10.7.

Octadecanedioic acid. For the purpose of further characterization, the unsaturated acid was hydrogenated to the saturated compound, whose properties have been described by Chuit (4). A sample (0.6 g.) of the acid recrystallized from thiophene-free benzene was hydrogenated in 15 ml. of purified alcohol with 0.25 g. of palladium charcoal (6). The calculated amount of hydrogen (55 ml.) was taken up in the course of half an hour. After separation from the catalyst, the filtrate was saponified by heating two hours on a water-bath with 10 ml. of 2 *N* sodium hydroxide solution. The alcohol was removed by evaporation and the acid precipitated with dilute hydrochloric acid. The crude octadecanedioic acid showed the expected melting point 124.5°, which after repeated recrystallization from benzene remained at 124.5–125°.

Anal. Calc'd for $C_{18}H_{34}O_4$: Eq. wt., 157.2.
Found: Eq. wt., 156.2, 157.

The yield was nearly quantitative.

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