thesis of the latter from the dimethyl ether of dibromo-*m*-xylohydroquinone.

4. The chemical properties of the coumarin II and many of its derivatives have been described.

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[CONTRIBUTION FROM THE UNIVERSITY OF MARYLAND]

The Structure of Phellonic Acid[1]

BY NATHAN L. DRAKE, HOMER W. CARHART AND RALPH MOZINGO

Work in this Laboratory on material isolable from cork[2] has led to a re-examination of the structure of phellonic acid, one of the saponification products of that portion of cork which is not appreciably soluble in solvents. The present paper is concerned with the degradation of phellonic acid and the synthesis of products identical in every respect with natural phellonic acid and its degradation products.

Previously, phellonic acid had been isolated by Kügler,[3] and its structure investigated in a number of laboratories,[4] with the result that phellonic acid has come to be generally regarded as an α-hydroxy acid[5] containing twenty-two carbon atoms, α-hydroxybehenic acid, $CH_3(CH_2)_{19}CHOHCO_2H$ (I).

However, more recent work in this Laboratory[6] and elsewhere[7] convinced us that phellonic acid is not a twenty-two carbon α-hydroxy acid. We have consequently re-investigated the structure of phellonic acid, and have shown by degradation and synthesis that phellonic acid and 22-hydroxytetracosanoic acid are identical in every respect.

Phellonic acid, purified to constant melting point, was shown by carbon and hydrogen analyses and by determinations of its neutral equivalent to possess the formula $C_{24}H_{48}O_3$. The acid showed no unsaturation with bromine in carbon tetrachloride or with permanganate. Phellonic acid forms an acetate, and, in the "Grignard machine,"[8] liberates methane equivalent to two active hydrogens and consumes four moles of reagent. All of this behavior corroborates the previous conclusion that phellonic acid is a saturated hydroxy acid.

It appeared logical to attempt to oxidize the hydroxyl group to a carbonyl, to prepare the oxime and subject it to Beckmann rearrangement, and to investigate the hydrolysis products of the resultant amide. We were, however, unable to isolate a pure keto acid from the products of oxidation or dehydrogenation of phellonic acid although we used various oxidizing and dehydrogenating agents. Oxidation occurred in most cases, but it either proceeded too far, or produced a mixture which was difficult to separate.

Chromic anhydride in glacial acetic acid oxidized phellonic acid to a dibasic acid, $C_{22}H_{42}O_4$, with loss of two carbon atoms. Reduction of the ester of this acid gave docosamethylene glycol, which possessed the melting point predicted from an extrapolation of the curve given by Chuit[9a] who plotted the melting points of the α,ω-polymethylene glycols up to twenty-one carbon atoms against their carbon contents. These facts, together with analytical data, including neutral equivalent determinations, and the concordance between the melting points of our acid, and its methyl ester and those of 1,20-eicosanedicarboxylic acid and its methyl ester leave no doubt concerning the structure of the acid.

When subjected to a potassium hydroxide fusion, phellonic acid is quickly and quantitatively converted into a dibasic acid. Von Schmidt,[4b] who first isolated this acid, named it "phellogenic acid" and assigned the formula $C_{21}H_{40}O_4$ (m. p. 121°). Zetsche and Bähler repeated the fusion

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(1) In part from the Ph.D. dissertation of Homer W. Carhart, University of Maryland, 1939. The syntheses from sebacic acid were carried out by Ralph Mozingo.

(2) For the latest paper on this subject see Drake and Wolfe, THIS JOURNAL, **62**, 3018 (1940).

(3) Kügler, *Arch. Pharm.*, **22**, 217 (1884); *Ber.*, **17**, 213 (1884).

(4) (a) Gilson, *La Cellule*, **6**, 63 (1890); (b) Schmidt, *Monatsh.*, **25**, 277, 302 (1904); **31**, 347 (1910); (c) Scurti and Tommasi, *Gazz. chim. ital.*, **46**, pt. 2, 159 (1916); *Ann. staz. chim. agrar. sper. Roma*, II, **6**, 40, 53, 67 (1917); *ibid.*, II, **9**, 145 (1920); (d) Zega, Diss. Zürich (1924); (e) Karrer, Peyer and Zega, *Helv. Chim. Acta*, **5**, 856 (1923).

(5) (a) Zetsche and Rosenthal, *ibid.*, **10**, 346 (1927); (b) Zetsche, Cholatnikov and Scherz, *ibid.*, **11**, 272 (1928); (c) Zetsche and Sonderegger, *ibid.*, **14**, 632 (1931); (d) Zetsche and Bähler, *ibid.*, **14**, 642 (1931); (e) Zetsche and Bähler, *ibid.*. **14**, 852 (1931).

(6) Drake and Cary, unpublished work.

(7) C. T. Turner, Master's Thesis, Cornell Univ., Ithaca, N. Y., 1931.

(8) Kohler and Richtmyer, THIS JOURNAL, **52**, 3736 (1930).

(9) (a) Chuit, *Helv. Chim. Acta*, **12**, 850 (1937); (b) *ibid.*, **9**, 264 (1926).

and found that one mole of carbon dioxide was liberated per mole of phellonic acid consumed. Since they believed phellonic acid to be α-hydroxybehenic acid (I), and one mole of carbon dioxide was produced during the fusion, they concluded that "phellogenic acid" must be 1,19-nonadecanedicarboxylic acid.[10]

We have repeated the fusion and have compared the product with a sample of synthetic 1,20-eicosanedicarboxylic acid prepared from sebacic acid (see below). The melting point of the acid from the fusion agrees with that of the synthetic acid and a mixture of the two shows no depression.

If, then, phellogenic acid is 1,20-eicosanedicarboxylic acid, it is apparent from the formation of this acid from phellonic acid by both alkaline fusion and oxidation, that there must be in phellonic acid at least twenty carbons in a straight chain separating the carbon holding the hydroxyl from the carboxyl group. The four possible structures, having 24 carbon atoms, which satisfy this condition are

$CH_2OH(CH_2)_{22}COOH$ II $\qquad$ $CH_3CHOH(CH_2)_{21}COOH$ III

$(CH_3)_2COH(CH_2)_{20}COOH$ IV $\qquad$ $CH_3CH_2CHOH(CH_2)_{20}COOH$ V

If phellonic acid possessed structure II, it would be expected to yield an acid of twenty-four carbon atoms when oxidized or subjected to potassium hydroxide fusion.[11] Structure IV should yield acetone (and/or acetic acid and carbon dioxide) and a twenty-one carbon acid on oxidation. Furthermore, phellonic acid can be converted through its iodo derivative into an acid whose methyl and ethyl esters give melting points which are in good agreement with the values listed for corresponding esters of tetracosanoic acid in the literature.[12] Structure IV is, therefore, definitely out of the question.

If structure III represents phellonic acid, it should give a positive iodoform test; both phellonic acid and its methyl ester failed to give iodoform when treated in an alkaline dioxane solution at 60° with iodine in potassium iodide.[13]

Structure V, then, must represent phellonic acid. 22-Hydroxytetracosanoic acid was synthesized. As starting material 1,20-eicosanedicarboxylic acid, prepared by fusion of phellonic acid with potassium hydroxide, was used. The acid was converted, by way of its methyl ester to the half-ester by a method similar to that employed by Ruzicka and Stoll[14] for preparation of half-esters of lower acids. The half-ester was then converted into the half-ester half-acid chloride, and treated with an excess of ethylzinc iodide The complex formed was decomposed with acid and the keto ester isolated. The product, without purification, was hydrogenated (2800 lb. per sq. in. at 150°) using a copper–chromium oxide catalyst.[15] The resulting hydroxy ester was purified and its melting point corresponded to that of methyl phellonate from natural phellonic acid. A mixed melting point showed neither depression nor broadening of the melting range. Saponification of the synthetic ester yielded an acid which melted at the same temperature as phellonic acid and showed no depression in a mixed melting point determination.

Phellonic acid, therefore, is 22-hydroxytetracosanoic acid, and phellogenic acid is 1,20-eicosanedicarboxylic acid.

Experimental

Isolation and Purification of Phellonic Acid.—Crude phellonic acid was isolated from ground cork following the method described by Zetsche and Sonderegger.[5c] The crude product, after two treatments in chloroform solution with decolorizing carbon, was purified by crystallization successively from chloroform, acetone and ethyl acetate. The resulting product was almost white and melted at 90.5–92°. This material was further crystallized from ethyl acetate and finally from chloroform. The acid was practically white and melted at 92–93.5°. Further crystallization did not materially change the melting point, but did slightly shorten the melting range. A sample thus purified for analysis melted at 93–93.5°.

Anal. Calcd. for $C_{24}H_{48}O_3$: C, 74.93; H, 12.58; neutr. equiv., 384.6; active H (Grignard machine) 2 moles, reagent consumed 4. Found: C, 74.81, 74.85; H, 12.64, 12.69; neutr. equiv., 386.0, 387.3, 387.3; active H, 1.96; moles reagent consumed, 3.94.

Preparation of 1,20-Eicosanedicarboxylic Acid from Phellonic Acid.—Fifty grams of potassium hydroxide was heated in a nickel crucible in a bath of Wood's metal. When the temperature of the bath had been regulated at 250°, 5 g. of phellonic acid was added; the potassium salt of the acid was formed as a gummy mass which did not dissolve in the fused hydroxide. The temperature of the bath was gradually raised to 350° over a period of thirty minutes. As the temperature of the bath rose from 300 to

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[10] The data offered by Zetsche in support of the structure of phellogenic acid are better evidence if used in support of an acid $C_{22}H_{42}O_4$ instead of $C_{21}H_{40}O_4$.

[11] Reid, Worthington and Larchar, THIS JOURNAL, **61**, 99 (1939).

[12] Francis and Piper, *ibid.*, **61**, 577 (1939).

[13] Fuson and Bull, *Chem. Rev.*, **15**, 275 (1934).

[14] Ruzicka and Stoll, *Helv. Chim. Acta*, **16**, 493 (1933).

[15] Connor, Folkers and Adkins, THIS JOURNAL, **53**, 2012 (1931); **54**, 1138 (1932).

320°, there was a vigorous evolution of gas, and the potassium salts became much more granular. After the reaction was over, the cooled melt was dissolved in about 800 ml. of hot water, acidified with an excess of hydrochloric acid, cooled and filtered. The dried product weighed 4.8 g., and melted at 121.5–124°. Recrystallization of this material from acetone yielded a substance which crystallized in very fine, irregularly shaped granules and melted at 122.5–124.5°.

Anal. Calcd. for $C_{22}H_{42}O_4$: C, 71.31; H, 11.43; neutr. equiv., 185.3. Found: C, 71.41, 71.59; H, 11.53, 11.53; neutr. equiv., 182.6, 183.2.

The same acid was produced by oxidation of phellonic acid by chromic anhydride at 70–80°. Melting points recorded in the literature for this acid are 120–122°,[16] 123.5–124.5°[5e] and 123.7°.[17]

Ethyl Octadecanedioate.—A solution of 20 g. of sodium hydroxide in 400 ml. of water was neutralized with ethyl hydrogen sebacate.[18] To the neutral solution was added 30 g. more of the half ester and the solution was electrolyzed in a cell having a 20 sq. cm. platinum anode (both sides) and two platinum wire cathodes. Three to five amperes of current were passed through the cell. When the solution became alkaline, the upper oily layer was removed and more half ester (20–35 g. portions) added until a total of 345 g. had been added. The upper ester layer was removed from time to time during the electrolysis. The resulting oil was dissolved in toluene and washed with sodium bicarbonate solution until neutral and with water. The ester which remained after removal of the toluene weighed 130 g. and was used without purification.

1,18-Octadecanediol.—The crude ester from the electrolysis was reduced with hydrogen at 3000–4000 lb. per sq. in. at 250° for sixteen hours, using 15 g. of copper-chromium oxide catalyst and 300 ml. of purified dioxane as the solvent. The material was removed from the bomb with hot dioxane, filtered, and the solution concentrated. When the solution was cooled a first crop of crystals was removed. Recrystallization of the crude glycol from dioxane gave 10 g. of 1,18-octadecanediol, m. p. 96–97°. The remaining material from the hydrogenation contained lower melting products from impurities in the ester and was therefore discarded.

Octadecamethylene Bromide.—The bromide was prepared by the usual method for decamethylene bromide.[19] Ten grams of the glycol was heated to 135–150° and a current of hydrogen bromide passed through the melt for eight hours. The dibromide was cooled, dissolved in toluene and filtered. The solution was concentrated and 30–60° petroleum ether added. The solution was cooled to −10° and the crystals removed by filtration. The solution was evaporated almost to dryness and petroleum ether (30–60°) added. On cooling the solution, a second crop of crystals formed and was removed. The melting point of the recrystallized material was 60–61°. The yield was 11.6 g. (82%).

Ethyl 1,1,20,20-Eicosanetetracarboxylate.—To a stirred solution of 37 g. of ethyl malonate (b. p. 60.5–61° (16 mm.)) was added 200 ml. of dry toluene and 2 g. of sodium. The reaction mixture was heated on a steam-bath until the sodium had reacted completely; the solution was then cooled until the sodio-malonic ester began to crystallize. Six and two-tenths grams of octadecamethylene bromide was added and the solution refluxed nine hours and allowed to stand overnight. The reaction mixture was poured over ice containing 10 ml. of hydrochloric acid and the toluene layer removed. The water layer was extracted three times with 20-ml. portions of toluene and the combined extracts dried over "Drierite." The solution was distilled under 20 mm. pressure on a steam-bath until no more distillate came over. The resulting material was diluted with sufficient hot methanol to dissolve the esters. When the solution was cooled the ester crystallized. After two more crystallizations from methanol the ester melted at 37–39° and weighed 7.1 g. (86%). After seven recrystallizations it melted at 43–44°. Further recrystallization did not raise the melting point.

Anal. Calcd. for $C_{32}H_{58}O_8$: C, 67.37; H, 10.18. Found:[20] C, 67.61, 67.87; H, 10.50, 10.57.

Synthetic 1,20-Eicosanedicarboxylic Acid.—A solution of 2 g. of sodium hydroxide and 2.3 g. of the tetracarboxylic ester in 100 ml. of diethylene glycol was heated for thirty minutes on a steam-bath. The resulting solution was diluted with 600 ml. of water and strongly acidified. The mixture was heated until the precipitated acid was coagulated; the acid was removed by filtration. The solid product was heated for sixteen hours with 15% hydrochloric acid to complete the decarboxylation, collected on a filter and recrystallized from acetone. After several recrystallizations the acid melted at 120–122°; its melting point did not change on repeated recrystallization; a mixed melting point with phellogenic acid melted at 121–123°.

The Methyl Ester of 1,20-Eicosanedicarboxylic Acid from Phellonic Acid.—Esterification of 1,20-eicosanedicarboxylic acid from phellonic acid by methanol in the presence of sulfuric acid yielded a product which, when repeatedly recrystallized from petroleum ether (b. p. 50–70°), separated in lustrous flat plates and melted at 67.8–69.0°. Zetsche[10] has reported a melting point of 68–69° for a product prepared in the same manner. He has also recorded a melting point of 72° for the methyl ester of 1,20-eicosanedicarboxylic acid, yet found no depression of melting point when this ester was mixed with the one mentioned above.[5d] Ziegler and Hechelhammer[21] have given the melting point of the methyl ester of 1,20-eicosanedicarboxylic acid as 71–72°. Extrapolation of the curve plotted by Chuit[9b] which shows the melting points of the methyl esters of α,ω-dibasic acids plotted against carbon content, and in which the melting point of the methyl ester of 1,16-hexadecanedicarboxylic acid is given as 60.0°, indicates a melting point of about 71° for the methyl ester of the twenty-two carbon acid.

Anal. Calcd. for $C_{24}H_{46}O_4$: C, 72.31; H, 11.62. Found: C, 72.52, 72.47; H, 11.73, 11.75.

Synthetic Methyl Ester of 1,20-Eicosanedicarboxylic Acid.—The methyl ester of the synthetic acid was pre-

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(16) Ruzicka, Stoll and Schinz, *Helv. Chim. Acta*, **11**, 670, 1174 (1928).

(17) Fairweather, *Proc. Roy. Soc. Edinburgh*, **46**, 71 (1926).

(18) Swann, Oehler and Buswell, "Organic Syntheses," Vol. XIX, 1939, p. 45.

(19) Carothers, Hill, Kirby and Jacobson, THIS JOURNAL, **52**, 5279 (1930).

(20) Microanalyses by Gordon F. Dittmar.

(21) Ziegler and Hechelhammer, *Ann.*, **528**, 114 (1937).

pared in the same manner as the ester directly above. The synthetic ester melted at 68–69°. No depression of melting point was observed when the purely synthetic ester was mixed with the ester obtained indirectly from phellonic acid.

Anal. Calcd. for $C_{24}H_{46}O_4$: C, 72.31; H, 11.62. Found:[20] C, 72.40, 72.30, 72.50; H, 11.41, 11.52, 11.44.

1,22-Docosamethylene Glycol.—A few grams of sodium ribbon were pressed into 200 ml. of dry benzene, and 1 g. of the methyl ester of 1,20-eicosanedicarboxylic acid was added. The mixture was heated to gentle boiling, and 25 ml. of dry butanol was added over a period of three hours. After removal of alkali by repeated washing with water, the benzene layer with suspended solids was evaporated to dryness, and the residue leached with boiling petroleum ether (90–100°), and filtered hot. The leachings were evaporated and small flat plates separated. After several recrystallizations the product melted at 105.7–106.2°. Extrapolation of the curve given by Chuit[9a] would lead one to predict a melting point of 106.5° for this glycol.

Anal. Calcd. for $C_{22}H_{46}O_2$: C, 77.12; H, 13.54. Found: C, 77.12, 76.99; H, 13.68, 13.72.

The Monomethyl Ester of 1,20-Eicosanedicarboxylic Acid.—The methyl ester of 1,20-eicosanedicarboxylic acid (10 g.) was dissolved in 600 ml. of methanol–benzene (2:1). A 1% solution of potassium hydroxide (67.2 ml.) was then added over a period of ten hours to the well-stirred solution of the ester. The solvents were removed by distillation under reduced pressure, and the residue pulverized and extracted with four 300 to 400-ml. portions of boiling petroleum ether (60–75°) to remove unsaponified methyl ester. The residual potassium salts were dissolved in 1.5 liter of warm water and acidified slowly, while stirred, with three-fourths of the calculated amount of hydrochloric acid. The precipitated acids were separated by centrifugation, washed with a little cold methanol, and sucked dry on a Büchner funnel. The dried product which contained some potassium salts was leached with boiling petroleum ether (60–75°) and the leachings evaporated to a small volume. The half-ester separated in flat plates which melted at 82.5–84.0°. Analyses indicated that the product was not entirely pure, but it was used in subsequent reactions without further purification.

Anal. Calcd. for $C_{23}H_{44}O_4$: neutr. equiv., 384.6. Found: neutr. equiv., 379, 375.

Synthesis of Methyl Phellonate and Phellonic Acid.—The half-ester of 1,20-eicosanedicarboxylic acid was heated for one-half hour under reflux with 5 ml. of thionyl chloride. Excess thionyl chloride was removed under reduced pressure. In order to remove the last traces of thionyl chloride 10 ml. of dry toluene was then added and removed *in vacuo*. This process was repeated and the resultant product taken up in 30 ml. of dry toluene. A considerable excess of ethylzinc iodide reagent in toluene (about 0.9 *N*) was then added, and the mixture allowed to stand for one hour at room temperature. Excess ethylzinc iodide was destroyed by a few milliliters of dilute acetic acid. Ether was added and the solution washed several times with water. The ethereal solution was dried over sodium sulfate and evaporated to dryness *in vacuo*. The residue was dissolved in methanol, exactly neutralized with sodium hydroxide in methanol and evaporated to dryness *in vacuo*. The residue was leached with hot petroleum ether (60–75°), the leachings were evaporated to dryness, and the residue was recrystallized from methanol. The product melted at 58–59°, and analyses indicated it to be impure. Without further purification the impure keto ester was hydrogenated by heating it at 150° for four hours in methanol solution under 2800 lb. per sq. in. hydrogen pressure in the presence of copper–chromium oxide catalyst. Fractional crystallization of the hydrogenated material from petroleum ether (60–75°) gave two products, one of which melted at 93.5–99°. The second product melted at 73.8–74.8° after repeated crystallization from petroleum ether, and showed no depression of melting point when mixed with methyl phellonate prepared from natural phellonic acid.

Anal. Calcd. for $C_{25}H_{50}O_3$: C, 75.32; H, 12.64. Found: C, 75.23, 75.19; H, 12.70, 12.78.

Saponification of the hydrogenated material yielded an acid which, after purification by repeated crystallization from petroleum ether, chloroform, and acetone, melted at 92.8–94.3° and showed no depression of melting point when mixed with natural phellonic acid.

Anal. Calcd. for $C_{24}H_{48}O_3$: C, 74.94; H, 12.58. Found: C, 74.83; H, 12.72.

Summary

1. Phellonic acid has been shown by degradation and synthesis to be 22-hydroxytetracosanoic acid.
2. Phellogenic acid has been shown to be 1,20-eicosanedicarboxylic acid.

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