THE STRUCTURE AND SYNTHESIS OF PHELLOGRIC ACID

BY

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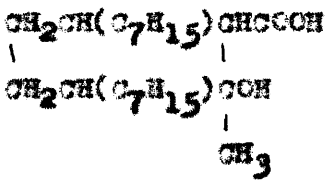
INTRODUCTION

In 1815, Chevreul[1] isolated a product which he called "cerin" by extracting cork first with water and then with alcohol. To the remaining insoluble portion of the cork he gave the name "suberin". Boussingault,[2,3] by treating this "suberin" with alkali, and subsequently acidifying the alkali soluble portion, obtained a brown precipitate which on oxidation with nitric acid gave suberic acid. F. W. Möhnel[4] confirmed this observation and suggested employing the name "suberin" to refer to that part of cork which was saponifiable; he believed that "suberin" was a homogeneous substance. However, Kügler,[5,6] by alcoholic potassium hydroxide saponification of "suberin", isolated, among others, an acid which melted at 96° to which he gave the name "phellonic acid" (from the Greek - phellos = cork), and assigned to it the formula $C_{22}H_{42}O_3$.

Later, Gilson[7] revised the formula of phellonic acid to $C_{22}H_{43}O_3$. M. W. Schmidt,[8,9] however, presented evidence in support of Kügler's original formula, $C_{22}H_{42}O_3$. He believed phellonic acid to be a cyclic saturated hydroxy acid with the following structure:



Scurti and Tommasi[10,11,12] described phellonic acid as a saturated hydroxy acid of formula $C_{22}H_{44}O_3$, whose properties were identical with those of α-hydroxy behenic acid. Their conclusions were supported by Zega.[13,14]

A considerable amount of work has been done on phellonic acid

since its structure was supposedly proven, and until recently this structure has not been doubted. In particular, F. Zetzsche and coworkers[15,16,17,18,19,20,21] have repeatedly isolated phellonic acid, giving methods for its separation from cork, and for the preparation of derivatives, and describing certain of its reactions.

However, recent work in this and other laboratories[22,23] has led to the belief that phellonic acid is neither a twenty-two carbon acid, nor an α-hydroxy acid.

It was the purpose of this research to determine the structure of phellonic acid, and to prove this structure by synthesis.

DISCUSSION

A. Isolation and Purification of Phellonic Acid

The method employed in extracting raw phellonic acid from cork is essentially the same as that used by Zetzsche[17,20]. However, it was found that raw phellonic acid could be purified more readily by recrystallization from several solvents than by using Zetzsche's method[18] of converting the acid to the potassium salt, recrystallising the salt, reconverting it back to the acid and recrystallising the acid, although the yields were about the same. Zetzsche's method of purification is objectionable for other reasons than the greater length of time it requires. In order to convert phellonic acid to its potassium salt, Zetzsche recommended heating the acid in an open dish with 35% aqueous potassium hydroxide. From the filtrates from recrystallization of the potassium salt Zetzsche isolated[18] 1,20-eicosane dicarboxylic acid which he claimed was originally present in the cork. However potassium hydroxide fusion of phellonic acid gives practically quantitative yields of this dibasic acid, so, it is probable that the 1,20-eicosane dicarboxylic acid is formed during the conversion of the raw phellonic acid into its potassium salt; a new substance is thus introduced by what is supposed to be a purification process. Furthermore, Zetzsche used glacial acetic acid as one of his solvents. In this laboratory it was found that recrystallization of phellonic acid from glacial acetic acid considerably lowers the melting point of the product indicating that partial acetylation occurs, since saponification yields a product which melts at the original value.

B. Proof of Structure.

The most important point of attack on the determination of the structure of a compound is to determine its empirical formula as accurately as possible. Therefore, a sample of phellonic acid was purified by repeated crystallization from a variety of solvents until its melting point was constant. Carbon and hydrogen analyses, and neutral equivalents on this sample indicated an empirical formula of $C_{24}H_{48}O_3$ for phellonic acid.

This empirical formula suggests that phellonic acid is either a saturated aliphatic hydroxy acid, or a saturated aliphatic ether acid. That it is a saturated compound is shown by the fact that phellonic acid does not decolorize either bromine in carbon tetrachloride solution or potassium permanganate, nor does it impart color to a carbon tetrachloride solution of tetranitromethane. That phellonic acid is an acid is obvious since it can be titrated to a sharp end point, and forms both salts and esters. Since phellonic acid also forms an acetyl derivative, it is apparently an hydroxy acid rather than an ether acid. Furthermore, a Zerewitinoff determination[24] on phellonic acid showed it to possess two active hydrogens, whereas the whole molecule uses up a total of four moles of Grignard reagent. This further corroborates the conclusion that phellonic acid is an hydroxy acid.

The method which suggested itself as the most plausible in the determination of the structure of phellonic acid was to oxidize the hydroxyl group to a carbonyl, prepare the oxime, and then after a Beckmann rearrangement to cleave the amide thus formed and to isolate and study the fragments. However, it was impossible either to oxidize or to dehydrogenate phellonic acid and isolate a pure keto acid; the reaction did not proceed, the oxidation went too far and cleaved the molecule, or some side reactions occurred.

in spite of the fact that many methods, with varying conditions, were tried. Oxidation with CrO_3 in glacial acetic acid from room temperature to the boiling point of acetic acid, oxidation with potassium permanganate in acetone at room temperature, palladium dehydrogenation at 300°-320° for three hours, cupric oxide oxidation from 150° to 220°, oxidation by lead tetraacetate in glacial acetic acid at 60°, an oxidation-reduction reaction using acetone, or p-benzoquinone, and aluminum tertiary butoxide, and hydrogen peroxide oxidation, in the presence of ferrous sulfate, on both phellonic acid and ethyl phellonate were all studied in an attempt to isolate the expected keto-acid.

Attempts to prepare the unsaturated acid, by dehydration of phellonic acid, were also unsuccessful. Heating phellonic acid with iodine in toluene for three hours at the boiling point of toluene left the acid unchanged. The iodo derivative of phellonic acid was prepared by the use of hydroiodic acid in phenol, and this compound was refluxed for two hours with 20% alcoholic potassium hydroxide. The resulting compound gave a negative test for unsaturation using bromine in carbon tetrachloride, or tetranitromethane in carbon tetrachloride. Apparently the iodo derivative had been reduced to a saturated acid; the compound formed gave a negative test for halogen using the Beilstein test, and melted at the same temperature as a compound prepared by treating the iodo derivative with sodium in amyl alcohol. A mixed melting point of these two products showed no depression.

Oxidation of phellonic acid with CrO_3 in glacial acetic acid gives a mixture of a new acid and what appeared to be phellonic acid. These were separated by taking advantage of differences in their solubilities in acetone. This new acid was crystallized repeatedly until its melting

point was constant. Carbon and hydrogen analyses and a determination of its neutral equivalent indicate for this acid an empirical formula of $C_{22}H_{42}O_4$, a dibasic acid. The melting points of this acid and its dimethyl ester are in good agreement with those given in the literature[25,26,27] for 1,20-eicosane dicarboxylic acid and its dimethyl ester. Bouveault-Blanc reduction[27,28] of the dimethyl ester gives the corresponding docosamethylene glycol. A previous preparation of this compound could not be found in the literature. However, Chuit,[23] has prepared the polymethylene glycols up to twenty-one carbon atoms, and gives in his paper the smooth curve resulting when melting points are plotted against the carbon content. Extrapolation of this curve to twenty-two carbon atoms gives a value which is in good agreement with the melting point found for the docosamethylene glycol.

The 1,20-eicosane dicarboxylic acid can be prepared much more readily, and in almost quantitative yields by potassium hydroxide fusion of phellonic acid. This fusion was first attempted by E. Schmidt[3] who isolated a dibasic acid melting at 121° to which he gave the formula $C_{21}H_{40}O_4$. He named this acid "phellogenic acid". Zetzsche[19] repeated this fusion more carefully and found that the fusion liberated one mole of CO_2 for every mole of phellonic acid consumed. He identified phellogenic acid as 1,19-nonadecane dicarboxylic acid. Since Zetzsche believed phellonic acid to be α-hydroxy behenic acid, and since one carbon is lost as CO_2 during the fusion, he concluded that phellogenic acid must have nineteen carbon atoms. The mechanism which Zetzsche suggests for the fusion is improbable, as it involves the oxidation of a terminal methyl group to carboxyl. It is strange that Zetzsche should have assigned this structure to phellogenic acid, particularly since the melting point of the dimethyl

ester is higher than any previously reported, and a mixed melting point of the dimethyl esters of phellogenic acid and 1,20-eicosane dicarboxylic acid showed no depression. Furthermore, Tetzsche's carbon and hydrogen analyses and his determination of methoxyl in the dimethyl ester of phellogenic acid check much better with values calculated for the dimethyl ester of 1,20-eicosane dicarboxylic acid than with those calculated for 1,19-nonadecane dicarboxylic acid.

The phellogenic acid obtained in this laboratory, and its dimethyl ester, are identical with the dibasic acid, and its dimethyl ester, obtained by CrO_3 oxidation of phellonic acid. Therefore, phellogenic acid is 1,20-eicosane dicarboxylic acid and not 1,19-nonadecane dicarboxylic acid as Tetzsche has suggested.

Since 1,20-eicosane dicarboxylic acid is obtained from phellonic acid either by oxidation or potassium hydroxide fusion, it is obvious that there must be at least twenty carbons in a straight chain separating the carbon holding the hydroxyl group from the carboxyl group. The only possible structures which would satisfy this condition are the following:

$CH_2OH(CH_2)_{22}COOH$ (I)

$CH_3CHOH(CH_2)_{21}COOH$ (II)

$(CH_3)_2COH(CH_2)_{20}COOH$ (III)

$CH_3CH_2CHOH(CH_2)_{20}COOH$ (IV)

Structure I is eliminated since a twenty-four carbon dibasic acid would be expected on oxidation or potassium hydroxide fusion[29] of phellonic acid. Structure III is eliminated since on oxidation the expected products would be acetone (and/or acetic acid and carbon dioxide) and a twenty-one carbon dibasic acid.

In order to eliminate structure III conclusively, an attempt was made to replace the hydroxyl group in phellonic acid by hydrogen. Clemmensen reduction[30] was of no avail, so phellonic acid was treated with hydroiodic acid and red phosphorus in a sealed tube for thirty hours at 150°-170°. The product isolated still gave a positive Beilstein test for halogen. Heating for one-hundred and twenty hours also gave a product which gave a positive Beilstein test. It was found more convenient to prepare this iodo derivative by refluxing phellonic acid with hydroiodic acid in glacial acetic acid or phenol. The iodo compound thus prepared was reduced using sodium and amyl alcohol. The resulting compound gave a negative test for halogen. Repeated crystallization and attempts to purify this acid by means of converting it to the methyl and ethyl esters and crystallizing them gave a product which melted a little below the temperature given in the literature for the melting point of n-tetracosanoic acid.[31] However, the melting points of both the methyl and ethyl esters were in good agreement with the values listed in the literature[31] for the corresponding esters of n-tetracosanoic acid. Hence, the carbon skeleton of phellonic acid contains a straight chain of carbon atoms. Structure III for phellonic acid, therefore, is definitely out of the question.

If the correct structure were II, phellonic acid should give a positive iodoform test, but both phellonic acid and its methyl ester failed to give any iodoform when treated with iodine in potassium iodide in an alkaline dioxan solution at 60°.

Structure IV, then must be the correct structure for phellonic acid, and the acid is 22-hydroxy n-tetracosanoic acid.

C. Synthesis.

In order to prove the structure of phellonic acid definitely, an attempt was made to synthesize it. The first method tried was as follows:

$$HOOC(CH_2)_{20}COOH \xrightarrow[H_2SO_4]{CH_3OH} CH_3OOC(CH_2)_{20}COOCH_3$$

$$CH_3OOC(CH_2)_{20}COOCH_3 + 1 \text{ mole } C_2H_5MgBr \xrightarrow[\text{ether}]{\text{dry}} C_2H_5CO(CH_2)_{20}COOCH_3 \xrightarrow{(H)} C_2H_5CHOH(CH_2)_{20}COOCH_3$$

On treatment of a solution of the dimethyl ester of 1,20-eicosane dicarboxylic acid in dry ether and benzene with one mole of ethyl magnesium bromide, decomposition of the complex yielded a mixture from which a large amount of the dimethyl ester was recovered unchanged. It was obvious therefore that the reaction did not proceed as desired so the low melting product which was also isolated was not investigated further.

The next method of synthesis tried was as follows:

$$HOOC(CH_2)_{20}COOH \xrightarrow[H_2SO_4]{CH_3OH} CH_3OOC(CH_2)_{20}COOCH_3 \xrightarrow{KOH} KOOC(CH_2)_{20}COOCH_3$$

$$\xrightarrow{HCl} HOOC(CH_2)_{20}COOCH_3 \xrightarrow{SOCl_2} ClCO(CH_2)_{20}COOCH_3 \xrightarrow{C_2H_5ZnI}$$

$$C_2H_5CO(CH_2)_{20}COOCH_3 \xrightarrow{(H)} C_2H_5CHOH(CH_2)_{20}COOCH_3$$

The dimethyl ester of 1,20-eicosane dicarboxylic acid was prepared in the usual manner and converted to the half-ester half-acid by a method similar to that employed by Ruzicka[32] for the lower acids. The dimethyl ester was dissolved in a mixture of methanol and benzene at room temperature and partially saponified by adding, over a period of ten hours, with stirring, one-fourth of the necessary amount of a potassium hydroxide (in methanol) to completely saponify the ester. Since the alkali salts of these higher acids are insoluble in petroleum ether, the saponification mixture was evaporated to dryness in vacuo, the residue

ground up and repeatedly leached with boiling petroleum ether to remove the unsaponified dimethyl ester. The residual potassium salts were dissolved in warm water and, with stirring, three-fourths of the necessary amount of hydrochloric acid necessary to completely liberate the organic acids was added; the half-ester was separated by centrifuging. A slurry was made with cold methanol and sucked dry as quickly as possible to prevent hydrolysis. The dried residue which contained some potassium salts, was leached with petroleum ether in order to remove the half-ester half-acid. The half-ester half-acid so obtained was quite pure as neutral equivalents indicated. The acid chloride was next prepared by means of thionyl chloride, and excess thionyl chloride was removed by distillation in vacuo. A small amount of dry toluene was then added and removed by distillation in vacuo. In order to remove the last traces of thionyl chloride, the last operation was repeated. It is necessary to remove the thionyl chloride completely in order that no sulfur compounds be present to poison the catalyst later.

Using a method similar to that employed by Fichter and Lurie,[33] the keto-ester was prepared by adding a considerable excess of a toluene solution of ethyl zinc iodide to a dry toluene solution of the acid chloride. This operation was carried out in an atmosphere of dry nitrogen, as the alkyl zinc iodides react readily with both water and oxygen. The complex first formed was decomposed with dilute acetic acid and the keto-ester isolated. Carbon and hydrogen analyses indicated that the keto-ester was not pure. In the reaction given above, the use of the organo zinc compound is preferred to the use of the Grignard reagent, because the former will react only to the ketone stage and will not affect the ester group appreciably if kept at room temperature, whereas the Grignard reagent will

react readily with both the carbonyl and the ester groups.

Attempts to hydrogenate the keto-ester using hydrogen and Adams' catalyst[34] (PtO_2) at room temperature and atmospheric pressure, or at sixty pounds per square inch were unavailing. Raney nickel[35] under the same conditions likewise did not catalyze reduction of the keto-ester. The keto-ester was finally hydrogenated in a bomb at a pressure of 2800 lbs./sq. in. and a temperature of 150° using a copper-chromium oxide catalyst.[36] This catalyst was chosen because it has been shown to be active in the hydrogenation of oxygen compounds. The hydroxy-ester was isolated and purified by repeated crystallizations from petroleum ether. The melting point of this synthetic hydroxy-ester was the same as that of methyl phellonate, and a mixed melting point showed no depression. Saponification of the synthetic ester yielded an acid which on purification by crystallization melted at the same temperature as phellonic acid, and a mixed melting point showed no depression.

Phellonic acid, therefore, is 22-hydroxy n-tetracosanoic acid.

EXPERIMENTAL

A. Method of Isolation and Purification of Phellonic Acid.

To a boiling solution of 284 gms. of sodium hydroxide and 738 gms of sodium bisulfite in 20 l. of water was added 1800 gms of cork meal.* The solution was kept boiling for three hours by means of an immersed coil of copper tubing through which steam was passed. The mixture was poured into a cloth sack, and while still hot pressed in a cider press. The cork residue was again subjected to the same treatment. During the boiling, water was added from time to time to replace that which evaporated. The cork was then washed five times with 20 l. portions of boiling water and pressed hot each time; the last filtrate was only a light reddish brown.

The cork, which was now free of most of the tannins, was allowed to stand overnight in 15 l. of ethanol, pressed, and extracted twice by boiling it for three hours with 15 l. portions of ethanol each and pressed hot. The residue was saponified by boiling it with 375 gms. of sodium hydroxide in 9 l. of ethanol for three hours. One half of the cork was added at first; at the end of three hours the other half was added and the whole was then boiled for three hours more. The cork was then drained and pressed hot. The filtrate was saved. The residue was saponified further by boiling it overnight with 225 gms. of sodium hydroxide in 6 l. of ethanol and again pressed hot; the filtrate was added to the one previously obtained. The remaining product was leached thrice by boiling it with 3 l. portions of ethanol. The cork was pressed hot after each treatment. The residue, when dried, was a light brown powder and weighed

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*Courtesy of the Armstrong Cork Co.

750 gms. The filtrates were added to those previously obtained.

The combined alcoholic filtrates were saturated with CO_2 by adding dry ice, heated to boiling and pressed. The sodium carbonate residue was washed thrice with 3-5 l. portions of boiling ethanol; the bulk of the ethanol was removed each time by pressing. The filtrates were combined and evaporated to dryness using vacuum distillation towards the end.

The residue, consisting of the sodium salts of the saponified acids, was taken up in 10 l. of hot water containing 45 gms. of sodium chloride and filtered hot. The filtrate was heated to boiling and saturated with sodium chloride. After cooling to 40° it was filtered through cloth, and the sodium salts were washed with cold saline solution and filtered. The sodium salts were then taken up in 3-4 l. of hot water, an excess of hydrochloric acid added, and the mixture heated until the free acids were completely melted; after cooling, the water was poured off the solidified acids. The product was again melted under dilute hydrochloric acid, cooled, and the water solution poured off. The acids were then washed by melting them under 3-4 l. of water three times. The crude phellonic acid obtained this way was a gummy brown mass weighing about 100 gms.

The raw phellonic acid was next taken up in 3-4 l. of hot chloroform, charcoaled, and filtered. The filtrate was dried with anhydrous sodium sulfate, filtered, the sodium sulfate washed with chloroform and the filtrates heated and charcoaled again. The filtered solution was still brown. The chloroform solution was evaporated to 1 l., cooled in an ice-salt bath and filtered. The product was recrystallized thrice from 1 l. portions of chloroform, once from 1.2 l. of acetone, and once

from 1 l. of ethyl acetate. The product, almost white, melted at 90.5-92°. It was recrystallized from 1.5 l. of ethyl acetate, and then from 1.5 l. of chloroform. The dried product, which was practically white, weighed 54 gms. and melted at 92°-93.5°. During the recrystallizations the solutions were allowed to cool slowly in order that the product might be more easily filtered.

A sample of the above phellonic acid was recrystallized repeatedly from many different solvents without materially changing the melting point; the product melted at 93°-93.5°.

Anal. Calc'd for $C_{24}H_{48}O_3$: C, 74.93; H, 12.58; Neutr. equiv. 384.6. Found: C, 74.81, 74.85; H, 12.64, 12.69; Neutr. equiv. 386.0, 387.3, 387.3.

Determination of Active Hydrogen by Means of a Grignard Machine.*

When 0.0353 gms. of phellonic acid was treated with 1.760 millimoles of methyl magnesium bromide in diamyl ether, 13.25 ml. of methane was collected at 29.4° C. and 764.5 mm. pressure. On adding one ml. of water, a total of 22.85 ml. of methane was collected at the same temperature and pressure.

millimoles of phellonic acid ($C_{24}H_{48}O_3$).....	0.2213
millimoles of Grignard reagent	1.760
millimoles of methane from active hydrogen	0.4320
total millimoles of methane evolved	0.8365
moles of methane per mole of acid	1.96
moles of Grignard reagent used per mole of acid...	3.94

When tested for unsaturation, phellonic acid, as prepared above, did not decolorize bromine in carbon tetrachloride solution, nor potassium permanganate in aqueous solution at once, nor did it alter the color of a

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*Courtesy of P. J. Wingate.

solution of tetranitromethane in carbon tetrachloride.

B. Proof of Structure.

Preparation of Methyl Phellonate.

One gram of phellonic acid was dissolved in a mixture of 200 ml. of methanol and 3 ml. of sulfuric acid. The mixture was refluxed for 10 hours then allowed to cool slowly to room temperature. After the solution had been cooled in an ice-salt bath it was filtered and washed with cold methanol. The product was recrystallized from methanol, then twice from petroleum ether (50-70). The dried methyl phellonate melted at 73.4°-75°. Zetzsche[20] reports a melting point of 74.5°.

Anal. Calc'd for $C_{25}H_{50}O_3$: C, 75.32; H, 12.64. Found: C, 75.17, 75.30; H, 12.63, 12.72.

Preparation of Acetyl Phellonic Acid.

One gram of phellonic acid was refluxed for 8 hours with 3 ml. of acetic anhydride and a trace of sulfuric acid. On cooling, the solution was poured upon crushed ice. When the ice melted the crystals were filtered and dried. The product was then taken up in 150 ml. of petroleum ether (50-70), allowed to cool partially, and filtered. The filtrate was cooled in an ice-salt bath and filtered. The second precipitate was recrystallized twice from ethyl acetate. Melting point, 77.5°-80°. Zetzsche[20] reports a value of 79°.

Anal.* Calc'd for $C_{26}H_{50}O_4$: C, 73.19; H, 11.82. Found: C, 73.17, 73.08; H, 12.11, 12.07.

Chromic Anhydride Oxidation of Phellonic Acid.

0.16 gm. of CrO_3 was dissolved in 15 ml. of glacial acetic acid

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*Courtesy of R. C. Cary.

(previously distilled from CrO_3), and then 0.4 gm. of phellonic acid was added. The mixture was kept at a temperature of 70°-80° for 45 minutes. Although the solution still gave a positive test for Cr^{6+} with ether and hydrogen peroxide, it was poured into a mixture of 100 ml. of water and 5 ml. of hydrochloric acid. After digesting this mixture on the steam bath for one hour it was allowed to stand overnight, filtered, and the precipitate washed with water and dried. The precipitate was taken up in 100 ml. of hot acetone (it did not all dissolve), cooled to room temperature and filtered. The precipitate melted slightly above the melting point of phellonic acid. The filtrate was evaporated down to 50 ml., cooled to 0° and filtered. This second precipitate melted at 121°-122.5°. It was taken up in 25 ml. of hot acetone, filtered at room temperature and the filtrate evaporated to 10 ml., cooled to 0° and filtered. The precipitate melted at 122°-124°. It was recrystallized from toluene, and then the operation above was repeated. The precipitate now melted at 122.5°-124.2°. Zetzsche[18] reports the melting point of 1,20-eicosane dicarboxylic acid to be 123.5°-124.5°, Ruzicka[25] reports a value of 120°-122°, Fairweather[26] a value of 123.7°.

Anal. Calc'd 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.

Attempts to oxidize phellonic acid with CrO_3 and stop the oxidation at the ketone stage were unsuccessful, although the reaction was tried at room temperature, at 60° and at the boiling point of acetic acid, for varying lengths of time, and using varying proportions of reagents.

Potassium Permanganate Oxidation of Phellonic Acid.

One-half gram of phellonic acid, 0.152 gm. of potassium permanganate, and 200 ml. of acetone (previously distilled from alkaline

permanganate) were shaken continuously for 24 hours at room temperature. The excess $KMnO_4$ and the MnO_2 were decomposed with oxalic acid and dilute sulfuric acid. The acetone was distilled off, and the residues leached with hot chloroform. The chloroform leachings were evaporated down to 15 ml., cooled, and filtered. The product melted at 95°-103°. By dissolving this product in 100 ml. of acetone and filtering at room temperature, about one-half of it was recovered. It melted at 94.5°-96.5°. Attempts to isolate any sharp melting product from the acetone filtrates was unsuccessful, as was an attempt to prepare a 2,4-dinitrophenylhydrazone.

Palladium Dehydrogenation of Phellonic Acid.

One-half gram of phellonic and 0.25 gm. of Palladium charcoal were heated for 30 hours at 300°-350° in an atmosphere of nitrogen. On cooling there appeared to be an odor of lower fatty acids in the product, so it was leached with water. Attempts to prepare a p-phenyl phenacyl derivative from the leachings were unsuccessful. The water insoluble material was leached with hot chloroform, and the leachings evaporated to dryness. The residue was dissolved in hot acetone, cooled and filtered. The precipitate melted at 79°-81°. The filtrate, on evaporation, yielded a product which was semi-solid at room temperature.

Cupric Oxide Oxidation of Phellonic Acid.

A small sample of phellonic acid was mixed with powdered CuO and heated in an oil bath to 200°. There was a slight evolution of a gas, probably water vapor due to the formation of copper phellonate, since on cooling, the resultant organic portion was colored green. Purification of the product gave a substance which melted at 96°. No noticeable decolorization of the black CuO to red Cu took place.

Lead Tetraacetate Oxidation of Phellonic Acid.

0.2 gm. of phellonic acid was dissolved in a mixture of 50 ml. of glacial acetic acid (previously distilled from CrO_3), 20 ml. of chloroform, and a few ml. of acetic anhydride. At 60°, with stirring, 0.36 gm. of Pb_3O_4 was added in small portions over a period of about one hour. The temperature was raised to 80°-85° and stirring continued for 2 hours. The reaction mixture was then heated for 12 hours on the steam bath, the solvents evaporated down to 10 ml., the lead salts decomposed with dilute hydrochloric acid, and the organic material extracted with ether. Attempts to purify the ether extracts by crystallization from different solvents were unavailing, as the melting point of the product would be either raised or lowered depending on the solvent used. Fractional crystallization yielded as one of the products a substance melting at 74°-75°. Since this suggested that possibly acetylation had occurred, this product was saponified to yield an acid which melted at 94°-95°, phellonic acid. Attempts to prepare a 2,4-dinitrophenylhydrazone from the other fractions were unsuccessful.

Oxidation of Phellonic Acid by Oppenauer's Method.[37]

Preparation of Reagents: Aluminum tert.-Butoxide. A small amount of granular aluminum metal (Mallinckrodt) was treated with dilute sodium hydroxide until a vigorous evolution of hydrogen occurred. The alkali was decanted, the aluminum washed several times with water, and then shaken for 1-2 minutes with a 1% solution of $HgCl_2$. The $HgCl_2$ solution was poured off, the aluminum washed several times with water, then with ether, and finally with propanol-2 (previously distilled twice from CaO and once from metallic sodium). The aluminum was immediately covered with dry propanol-2, a crystal of iodine was added, and the mixture heated under reflux (condenser protected by a $CaCl_2$ tube). The reaction began promptly and was proceeding briskly until it was stopped after about 15 minutes.

The propanol-2 was poured off, the activated aluminum washed twice with tert.-butyl alcohol (previously distilled from metallic sodium, m. p. 25°), then quickly covered with dry tert.-butyl alcohol and heated under reflux (condenser protected by a $CaCl_2$ tube). The reaction began promptly and proceeded fairly briskly for about 30 minutes.

A sample of 40 gms. of aluminum was amalgamated, as described above, and covered with 200 gms. of dry tert.-butyl alcohol. The butoxide (including unreacted aluminum) already prepared was added quickly, then the mixture was heated under reflux, the condenser being protected with a $CaCl_2$ tube which led to a bubble counter. The evolution of hydrogen was fairly brisk. After 2 hours of refluxing, 500 ml. of dry benzene (previously distilled from sodium) was added and the mixture refluxed for 20 hours until no more hydrogen was given off. The mixture was centrifuged hot, and the supernatant liquid, which was clear but a dark brown, was decanted. The residue was washed with 400 ml. of hot dry benzene and centrifuged. The benzene solutions were combined and evaporated to dryness under reduced pressure. A yield of 156 gms. of a grayish granular material was obtained.

Acetone. Ordinary acetone was distilled twice from alkaline permanganate, once from aluminum tert.-butoxide, once from freshly fused potassium hydroxide, and again from aluminum tert.-butoxide.

Method. One gram of methyl phellonate was dissolved in a mixture of 15 ml. of the specially purified acetone and 20 ml. of dry benzene (previously distilled from metallic sodium). This solution was heated to boiling and one gram of aluminum tert.-butoxide in 10 ml. of dry boiling benzene was added. The mixture was refluxed (condenser protected by a $CaCl_2$ tube) for 3 hours. On cooling, 4 ml. of water, then 10 ml. of 10% sulfuric acid (acid to congo red) was added. A bad emulsion formed on shaking, so a

large volume of both water and benzene were added and the mixture centrifuged to break the emulsion. The benzene layer was washed with water until free of acid and evaporated to dryness. The residue was recrystallized from petroleum ether (90-100) to give a product which melted at 73°-74°. A mixed melting point with methyl phellonate showed no depression.

Oxidation Using p-Benzoquinone. A boiling solution of one gram of aluminum tert.-butoxide in 10 ml. of dry benzene was added to a boiling solution of 3 gms. of dry p-benzoquinone and one gram of methyl phellonate in 30 ml. of dry benzene, and refluxed (condenser protected by a $CaCl_2$ tube) for 3 hours. In about 5 minutes the solution had turned a light purple which kept getting deeper in color. After about 2 hours a very dark purple (?) precipitate had formed, which kept getting more and more voluminous. Addition of 25 ml. of dry benzene did not dissolve it.*

Four ml. of water and then 10 ml. of 10% sulfuric acid was added and shaken. A bad emulsion formed so a large volume of both water and benzene was added and the mixture centrifuged. The benzene layer was washed repeatedly with dilute ammonia then with water, and the benzene evaporated to dryness. On attempting to crystallize the residue from petroleum ether the material could not be induced to crystallize, so it was saponified to give an acid which melted at 89°-93°. A mixed melting point with phellonic acid gave no depression. Since this was only a part of the total starting material, the solids which separated in the centrifugation were worked up to give an acid which melted at 83.5°-91°. A

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*It is interesting to note that p-benzoquinone and aluminum tert.-butoxide in dry benzene will not change color appreciably even after refluxing for 30 minutes. However, when a few drops of dry propanol-2 are added, the solution turns a dark purple in a few minutes.

mixed melting point with phellonic acid showed no depression.

When the experiment was repeated using 0.3 gm. of ethyl phellonate and 0.25 gm. of p-benzoquinone, an acid was isolated which melted at 86°-89°.

Hydrogen Peroxide Oxidation.

One gram of phellonic acid was dissolved in 200 ml. of glacial acetic acid, a small amount of $FeSO_4 \cdot 7H_2O$ was added, and at 20° one ml. of 30% H_2O_2 added. The mixture was heated to boiling, dilute hydrochloric acid was added, then the mixture cooled and filtered. Recrystallization of the solid from benzene gave a product which melted at 86°-89°.

The experiment was repeated, adding a large excess of hydrogen peroxide and heating for a longer period of time. Two products were isolated, one of which melted at 70°-72.5° and which gave no depression when a mixed melting point with acetyl phellonic acid was taken; the other product melted at 89°-91°. Saponification of the first product gave an acid which melted at 90.5°-97°.

Potassium Hydroxide Fusion of Phellonic Acid. 1,20-eicosane Dicarboxylic Acid.

Fifty grams of potassium hydroxide was fused in a Ni crucible (clamped in a Wood's metal bath) at 280°, let cool to 250° and 5 gms. of phellonic acid added. The potassium salt formed a gummy solid which did not dissolve. The temperature was gradually raised to 350° over a period of 30 minutes. Between 300°-320° there was a vigorous evolution of a gas, and the potassium salts became more granular. On cooling, the solidified mass was dissolved in about 800 ml. of hot water and then an excess of hydrochloric acid was added and the mixture cooled and filtered. The dried product weighed 4.8 gms. and melted at 121.5°-124°. Recrystallization from acetone gave a product which melted at 122.5°-124.5°.

Preparation of the Dimethyl Ester of 1,20-eicosane Dicarboxylic Acid.

9.5 gms. of 1,20-eicosane dicarboxylic acid was dissolved in a mixture of 1 l. of dry methanol and 5 ml. of sulfuric acid. The mixture was refluxed overnight, evaporated down to 300 ml., cooled, filtered and washed with cold methanol. Recrystallization of the product from 100 ml. of petroleum ether (50-70) gave 9.3 gms. of ester melting at 66.5°-68.5°. Purification of a small amount gave a product which melted at 67.5°-69.0°. Zetzsche[19] reports a value of 68°-69° for the product prepared in the same manner, although he calls it 1,19-nonadecane dicarboxylic acid dimethyl ester. He lists[18,20] a melting point of 72° for 1,20-eicosane dicarboxylic acid dimethyl ester, yet finds no depression on a mixed melting point of the two. Ziegler and Hechelhammer[27] give a value of 71°-72°. Chuit[28] lists a melting point of 65.5° for 1, 19-nonadecane dicarboxylic acid dimethyl ester, and extrapolation of the curve plotted from the lower dimethyl esters gives a value of about 69° for the dimethyl ester of the twenty-two carbon dibasic acid.

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

Bouveault-Blanc[27,28] Reduction of the Dimethyl Ester. Docosamethylene Glycol.

2-3 gms. of sodium ribbon were pressed into 200 ml. of dry benzene and one gram of 1,20-eicosane dicarboxylic acid dimethyl ester was added. The reaction flask was connected to a condenser protected by a $CaCl_2$ tube and a dropping funnel containing 25 ml. of dry butanol. The reaction mixture was heated to gentle boiling and the butanol added over a period of 3 hours. After standing overnight 50 ml. of 95% ethanol were added and the mixture was refluxed for 30 minutes. The solution was

washed repeatedly with water; it was necessary to centrifuge the mixture to break the emulsion formed. The benzene layer plus the centrifuged solids was evaporated to dryness, and the residue was leached with 100 ml. of boiling petroleum ether (90-100) and filtered hot. The leachings were evaporated to a volume of 10 ml. and cooled slowly. Filtration and purification of the precipitate gave a product which melted at 105.7°-106.2° which is approximately the value obtained for the docosamethylene glycol when the curve plotted by Chuit[28] is extrapolated to twenty-two carbon atoms.

Anal. Calc'd for $C_{22}H_{46}O_2$: C, 77.12; H, 13.54. Found: C, 77.12, 76.99; H, 13.63, 13.72.

Iodoform Reaction.

0.2 gm. of methyl phellonate was dissolved in 5 ml. of dioxane at 60°. A solution of 2 ml. of 10% NaOH and enough I_2 in KI to color it yellow in 5 ml. of dioxane at 60° was added slowly. The first few drops lost their yellow color, but the main bulk of the solution did not. The mixture was then diluted with a large amount of water and steam distilled. No iodoform was found present in the distillate, so the residue was extracted with chloroform. Distillation of the chloroform left no residue. The sodium salts were then converted to the free acids which when recrystallized from acetone melted at 96°-100° and gave a positive Beilstein test for halogen.

Similarly, phellonic acid itself gave no iodoform when tested in the same manner.

Attempt to Prepare the Unsaturated Acid.

One gram of phellonic acid and 0.05 gm. of I_2 were refluxed for three hours in 10 ml. of toluene. Isolation and purification of the product gave 0.95 gm. of a substance which melted at 92° and gave no test for

unsaturation with tetranitromethane.

Reduction of Phellonic Acid.

By means of HI and red P in a sealed tube at 150° for 24 hours, Cary[22] was able to replace the hydroxyl group of phellonic acid by hydrogen. He thus obtained a fatty acid which, on purification, melted at 80.5°. Francis and Piper[31] report a melting point of 84.1° for n-tetracosanoic acid.

Anal.* Calc'd for $C_{24}H_{48}O_2$: C, 78.19; H, 13.13. Found: C, 78.17, 78.21; H, 13.14, 13.19.

When one gram of phellonic acid was refluxed for 5-8 hours with 5 ml. of HI and 10 ml. of phenol or 20 ml. of acetic acid an iodo derivative melting at 86° was obtained. When this product was refluxed for 2 hours with 20% alcoholic KOH a product melting at 71° was obtained which gave a negative test for unsaturation with bromine in CCl_4 or with tetranitromethane. When the iodo derivative was reduced by dissolving it in dry amyl alcohol and adding sodium, a product was isolated which also melted at 71°. A mixed melting point of the two showed no depression.

Purification of this product and conversion to the methyl ester by means of methanol and sulfuric acid, gave a product melting at 55°-58°. Conversion to the ethyl ester by means of ethanol and sulfuric acid, gave a product melting at 51.4°-52°. Francis and Piper[31] report a melting point of 58.4° for methyl n-tetracosanoate, and 54.8° for ethyl n-tetracosanoate. These products are apparently impure, although the melting points were not changed on recrystallization.

C. Synthesis of Phellonic Acid.

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*Analyses by R. C. Cary.

Attempted Synthesis by Means of the Grignard Reagent.

5.3 gms. of 1,20-eicosane dicarboxylic acid dimethyl ester was dissolved in 200 ml. of dry benzene (previously distilled from sodium). To this was added, slowly, with stirring, the same number of moles of ethyl magnesium bromide in absolute ether. A considerable amount of heat was evolved. Towards the end of the addition, a gummy material collected on the sides of the flask. After standing overnight, some wet ether was added and the solution filtered. The filtrate, on evaporation to dryness, gave a product melting at 60.5°-62°. Fractional crystallization of the product from acetone and petroleum ether (60-75) gave, as the more soluble part, a product melting at 53°-55.5°. Saponification of this fraction gave an acid mixture melting at 104°-119°. Recrystallization of this acid from acetone, three times, gave 1.2 gms. of a product melting at 119.5°-123.5°. The less soluble fraction melted at 67°-68.5° and saponification gave an acid melting at 123°-125°. The investigation was not carried further, since the product was apparently 1,20-eicosane dicarboxylic acid.

Synthesis Through the Use of Ethyl Zinc Iodide.

Preparation of 1,20-eicosane dicarboxylic acid monomethyl ester.

10 gms. of 1,20-eicosane dimethyl ester were dissolved in 600 ml. of methanol-benzene (2:1). With stirring, over a period of 10 hours, 67.2 ml. of a 1% solution of potassium hydroxide in methanol was added. The solvents were distilled off in vacuum and the residue pulverized and leached four times with 300-400 ml. of boiling petroleum ether (60-75) in order to remove the unsaponified dimethyl ester. The potassium salts were dissolved in 1.5 l. of warm water and slowly, with stirring, three-fourths of the necessary amount of dilute hydrochloric acid to liberate the organic acids was added. The mixture was centrifuged and the precipitate washed with a little cold methanol and sucked dry on a filter. The dried product, containing some potassium salts was leached with boiling petroleum ether

(60-75), the leachings evaporated to 75 ml., cooled and filtered. Yield 1.9 gms. of product melting at 32.5°-34.0°.

Anal.* Calc'd for $C_{23}H_{44}O_4$: Neutr. equiv., 384.6. Found: Neutr. equiv., 379, 375. 192.3 189.5

Preparation of Ethyl Zinc Iodide Reagent.

57 gms. of zinc dust and 5 gms. of powdered cupric oxide were heated just below fusion in an atmosphere of hydrogen. To this was added a solution of 66 gms. of ethyl iodide, 50 ml. of dry toluene, and 15 ml. of ethyl acetate. The mixture was heated (with a reflux condenser protected by a $CaCl_2$ tube) to 100° when a vigorous reaction started. Heating was discontinued until the reaction had subsided and then heated again at 110° for 30 minutes. The reaction mixture was poured into 400 ml. of dry toluene and allowed to stand overnight to settle. The clear liquid was transferred to the reservoir of an automatic burette. The solution was found to be 0.90 N by titration with standard hydrochloric acid.

The ethyl zinc iodide reagent was prepared, kept, and used entirely in an atmosphere of dry nitrogen.

Preparation of 22-keto tetratriacontoic acid.

The half-ester half-acid was refluxed for one hour with 5 ml. of thionyl chloride (previously distilled from linseed oil). The thionyl chloride was then distilled off in vacuo, 10 ml. of dry toluene was added, removed by distillation in vacuo, and the last operation repeated. To the product was added 30 ml. of dry toluene and then an excess of ethyl zinc iodide reagent. The mixture was allowed to stand at room temperature for one hour, and then a few ml. of water and dilute acetic acid to dissolve the Zn(OH)I were added. 100 ml. of ether was added and the mixture was then

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*Courtesy of J. B. Lamm

washed four times with cold water. The ether layer was dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuo. The residue was dissolved in methanol and exactly neutralized with sodium hydroxide in methanol, evaporated to dryness, and leached with hot petroleum ether (60-75). The leachings were evaporated to dryness and the residue recrystallized from 30 ml. of methanol to give a product melting at 58°-59°. Analyses showed the sample to be impure.

Reduction of the Keto-ester.

Attempts to hydrogenate the keto-ester using hydrogen and Adams' catalyst[34] or Raney nickel[35] at room temperature and atmospheric pressure, or at 45 lbs./sq. in. all gave a product melting at 58°-60°.

The keto-ester was hydrogenated by heating its methanol solution in a bomb at 2300 lbs./sq. in. hydrogen pressure at 150° for 4 hours in the presence of copper-chromium oxide catalyst.[36] The catalyst was filtered off, the solvent evaporated to dryness and the residue recrystallized from methanol to give a product melting at 67°-75°. Fractional crystallization from petroleum ether (60-75) gave two products one of which melted at 93.5°-99°. The other, after repeated crystallization from petroleum ether (60-75) melted at 73.8°-74.3°. A mixed melting point of this product with methyl phellonate gave no depression.

Anal. Calc'd for $C_{25}H_{50}O_3$: C, 75.32; H, 12.64. Found: C, 75.23, 75.19; H, 12.70, 12.73.

Saponification of this product yielded an acid which was purified by repeated recrystallization from petroleum ether (60-75), chloroform, and acetone. It melted at 92.8°-94.3° and a mixed melting point with phellonic acid gave no depression.

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

SUMMARY

1. A review of the literature on work on phellonic acid has been presented.

2. A method for extracting phellonic acid from cork and its subsequent purification has been described.

3. The old structure for phellonic acid, α-hydroxy behenic acid has been shown to be wrong, and the correct structure, 22-hydroxy n-tetracosanoic acid, has been proven by means of oxidation studies and by synthesis.

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