FURTHER STUDIES ON CERIN AND FRIEDELIN

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Thesis submitted to the Faculty of the Graduate School
of the University of Maryland in partial
fulfillment of the requirements for
the degree of Doctor of Philosophy
1941

ACKNOWLEDGMENT

The author is grateful for the many helpful suggestions offered by Dr. Nathan L. Drake who directed this research.

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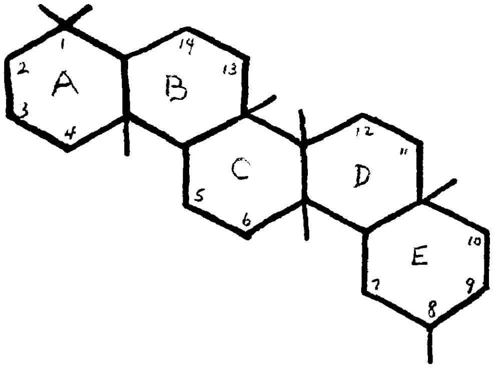
INTRODUCTION

The first serious investigation of the structure and properties of cerin and friedelin, two pentacyclic triterpenoids extracted from cork, was begun in the organic chemistry laboratories of the University of Maryland in 1932. Drake and Jacobsen (11) worked out a method of extracting, separating and purifying these two compounds in adequate quantities and determined their molecular weights and empirical formulae. That friedelin is a readily enolizable ketone, and cerin an hydroxy ketone was established by Drake and Shrader (12). By a series of oxidation studies Drake and Campbell (9) obtained evidence for the existence of the group $—CH_2COCH<$ in friedelin. The dehydrogenation studies of Drake and Haskins (10) and of Drake and Houston (16) coupled with the synthesis of 1,8 dimethyl picene by Drake and Howard (19) have established the basic structure of friedelin as being that of a pentacyclic triterpenoid. Drake and Wolfe (13), by their surface film studies of derivatives of cerin and of friedelin, have tentatively located the functional groups in ring B, D or E of the molecule. Most recently, Drake and Holmes (17) have advanced the study of the structure of cerin by demonstrating that the carbonyl group in cerin is located in the same position with respect to the rest of the molecule as is the carbonyl group in friedelin. Finally they have shown that cerin is an alpha hydroxy ketone and therefore cerin is alpha hydroxy friedelin. It was originally the purpose of this research to locate the carbonyl group in friedelin by dehydrogenation studies on friedelinyl methyl ether. The method attempted having been proven ineffective, further studies were made on the hydrogenation of friedelin and cerin, and the oxidation of cerin by lead tetraacetate.

DISCUSSION

Dehydrogenation

The parent hydrocarbon of both cerin and friedelin as indicated by analyses and molecular weight (11) and by dehydrogenation studies (10) (18) is an octamethyl perhydropicene with two of the eight methyl groups located in the one and eight positions. The remaining methyl groups have been tentatively located by application of the isoprene rule, and of the many possibilities thus postulated, two structures are preferred.



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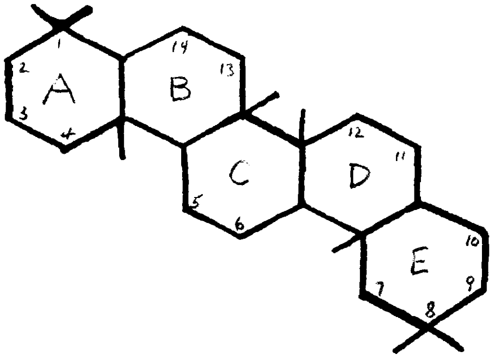

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Structure I explains satisfactorily the products obtained by dehydrogenation whereas structure II, proposed by Haworth (16), fits the surface film data more closely. Previous work done in this laboratory has been aimed at locating the carbonyl group, and has been successful to some extent. The work of Campbell showing the presence of the group ($-CH_2COCH<$) (9) and that of Wolfe on friedonic acid (14) and surface films (13) has limited the possible locations to positions 5, 9 and 14 in structure I; and 5, 10, 11 and 14 in structure II. The dehydrogenations of Haskins and of Houston were disappointing insofar as locating the functional group was concerned because the hydroxyl group split out as water.

Houston cites Ruzicka's work (20) as evidence that methoxyl groups survive dehydrogenation, and it was hoped that by converting friedelinol to the corresponding methyl ether, the functional group would be stabilized to such an extent that it would survive the drastic dehydrogenation treatment. In this particular reference, however, the dehydrogenation was used in the syntheses of five isomeric 1, 2, 7 trimethyl methoxy naphthalenes, but in every instance, the methoxyl group was appended to an aromatic ring and hence had no chance to split out as methyl alcohol.

That the mechanism of dehydrogenation of friedelinyl methyl ether involves the splitting out of methyl alcohol was effectually demonstrated, at least in the palladium dehydrogenation experiment, by the isolation, characterization and estimation of the methyl alcohol produced in the reaction. Though the quantitative estimation of the alcohol accounted for only fifty per cent of the theoretical amount, and thus leaves something to be desired from an analytical standpoint, there are several possible reasons for the deficiency. The methyl alcohol was estimated by a modification of the Viēbock and Schwappach method for the microanalysis for methoxyl, and since the boiling point of methyl alcohol is very low, it is uncertain that all of it was converted to methyl iodide. During the dehydrogenation experiment the trap twice became clogged, causing the nitrogen inlet tube to blow off with consequent loss of reaction gases, and necessitating the removal of the trap for draining. Further, since there was formed such a small amount of alcohol in comparison to the quantity of gases passing through the system, it is by no means certain that all of the methanol was collected in the trap even though it was cooled in carbon dioxide snow.

Since half of the methoxyl was accounted for, and since no methoxyl could be determined present in any of the products of the reaction, it seems quite certain that the mechanism of dehydrogenation of friedelinyl methyl ether, as in the case of friedelinol, consists of a splitting out of the functional group, in this instance as methyl alcohol.

If the mechanisms of dehydrogenation of friedelinol and of friedelinyl methyl ether are the same, it follows that the products formed should be the same except in so far as differences in the experimental conditions cause differences in the quantities of the various compounds produced. Confirmation of this statement is indicated by the isolation of 1, 8 dimethyl picene from both dehydrogenation experiments. With the elimination from the molecule of the group to be located and the probability that no new compounds were likely to be isolated, it appeared that to carry on the investigation would contribute nothing further to the elucidation of the structure of friedelin, and the project was accordingly discontinued.

Hydrogenation

The catalytic hydrogenation of friedelin results in the production of two isomeric friedelinols depending upon the conditions employed in the reduction. Unquestionably the only difference in these two molecules is the position of the hydroxyl group on one side or the other of the carbon atom. A study of the conditions necessary to produce either of the two isomers at will has shown that reduction in dioxane using Raney nickel catalyst invariably produces the lower melting isomer at any of the temperatures used. The reduction does not proceed with appreciable speed below 120° C, and since reduction using dioxane as solvent with Raney nickel at temperatures above 200° C is dangerous, the experiments were restricted to these limits.

Hydrogenation using the "copper chromite" catalyst of Adkins (1) presents a different picture. Depending upon the temperature at which the reaction is carried out, either of the two isomeric modifications is obtainable. If the reduction proceeds at a temperature between 140° C and 160° C, the product which results melts at 278 to 282° C and the melting range is not changed either by recrystallization or by further hydrogenation. If the reduction proceeds at 180° C or above, the product obtained is identical with that obtained by the reduction of friedelin with sodium and amyl alcohol. The melting range of the product, as first isolated, is broader than that of pure friedelinol, probably due to the presence of small quantities of the lower melting isomer formed while the reaction temperature is being obtained.

The catalytic hydrogenation of cerin is apparently a highly complex reaction. Shrader has reported a dihydrocerin of melting point 293°C to 295°C which he prepared by reduction of cerin with sodium and amyl alcohol; and Holmes has reported another of melting point 251-254°C which he prepared once by reduction of cerin in dioxane solution at 150°C using a copper chromite catalyst, and which he was unable to prepare again in several subsequent attempts. An investigation was therefore begun to determine a set of conditions which would result in formation of this isomer. Although four different catalysts, prepared under different conditions, were used at temperatures varying from 100°C to 250°C, this product was never isolated. While the product of hydrogenation in some cases melted in the range specified, in every instance recrystallization caused a rise in the melting point. The conclusion is therefore suggested that perhaps the product obtained by Holmes was in reality a eutectic consisting of a mixture of several or all of the possible isomers.

Dihydrocerin contains two hydroxyl groups on adjacent carbons; there are, therefore, four possible isomers, two cis forms and two trans forms, from the stereochemistry of these two carbons only. Obviously the separation of a mixture of four compounds so similar in structure into its components would be extraordinarily difficult; nor does this exhaust the possibilities. According to Adkins(2) hydrogenolysis of a carbon-hydroxyl bond as in the equation

$$ROH + H_2 \longrightarrow RH + H_2O$$

is a definite possibility. He states that this reaction does not normally occur below 250°C <u>unless</u>, (as in the compound under discussion), the radical R contains a phenyl, <u>carbonyl</u> or <u>hydroxyl</u>

group. Should hydrogenolysis occur, four possible isomers might result. If the carbonyl should cause hydrogenolysis of the hydroxyl group of cerin, the subsequent reduction of the carbonyl group would result in formation of one of the two friedelinols; if the carbonyl should be first reduced, and one of the hydroxyls should cause hydrogenolysis of the other, then two isomers of the friedelinols would be added possibilities. The writer is of the opinion that the former alternative actually takes place for the reasons which follow.

Experimentally, the products of hydrogenation were found to melt over a long range, and in some cases to be very difficult to crystallize, separating as gelatinous substances. Only two pure compounds were isolated; the lower melting isomer of friedelinol was obtained in very small yield from one reduction which was carried out at 125°C, while the higher melting isomer of friedelinol was obtained in somewhat higher yield from a reduction at 250°C. It is interesting that in each instance the isomer of friedelinol was obtained which would have been formed by reduction of friedelin under the same conditions. The significance of this fact may be that the carbonyl group in cerin causes hydrogenolysis of the hydroxyl group. The isolation of friedelinol from the catalytic hydrogenation of cerin substantiates the relationship between cerin and friedelin established by Holmes.

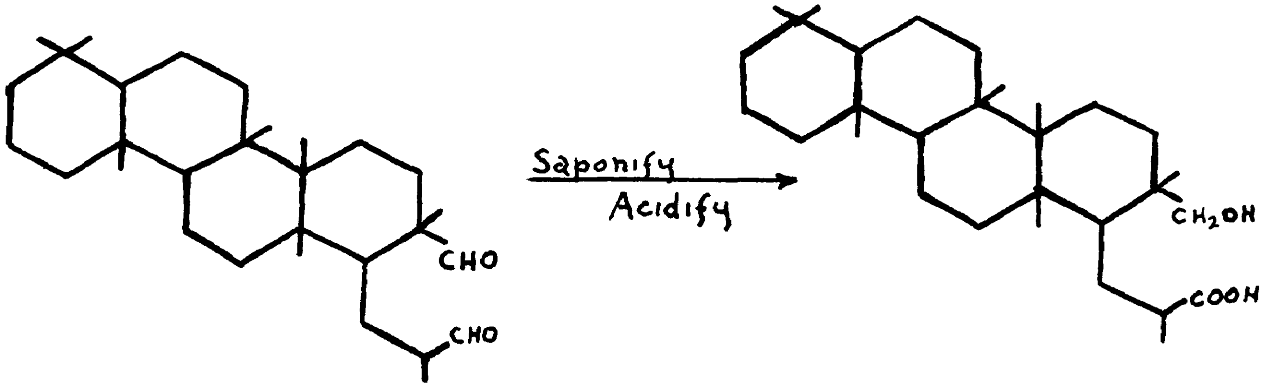
The cerin used in these reductions was prepared in the usual manner except that it was crystallized twice from chloroform, in which friedelin is very soluble, before it was purified by the five recrystallizations from pyridine. Analyses of the product were quite satisfactory. It hardly seems credible that the cerin so prepared could have contained enough friedelin to make possible the isolation of friedelinol from the reduction product.

Oxidation

The oxidation by lead tetraacetate of the products of catalytic reduction of cerin proceeds at a more rapid rate than does the oxidation of dihydrocerin prepared by reduction with sodium and amyl alcohol. Holmes found that at a temperature of 50°C, 0.57 mols of lead tetraacetate was consumed per mol of dihydro cerin after fourteen days; the writer found that at the same temperature after 35 hours 0.91 mols of lead tetraacetate was consumed per mol of catalytically hydrogenated cerin. The inference is that the hydrogenated product used consisted predominately of the two cis forms. The hydrogenated material used was reduced under the same conditions as that reported by Holmes to melt at 251-254°C but it actually melted from 252-268°C. It was observed that the reaction velocity of the oxidation varied with different samples of hydrogenated product, but no attempt was made to correlate conditions of reduction with speed of reaction. The difference may have been due to a difference in the ratio of cis to trans forms.

The reaction between lead tetraacetate and hydrogenated cerin was found to be more complex than was expected. Normally the reagent is used at room temperature, and it is known to react with 1, 2 glycols under these conditions to form dialdehydes. Use of an excess has been known to oxidize glycols to dibasic acids but not normally in acetic acid solution; in this medium the reaction stops almost invariably after the dialdehyde has been formed. In order to increase the concentration of the hydrogenated cerin and to increase the rate of reaction, the temperatures used in this research were varied from 40° C to 80° C, and the abnormalities observed may have been caused by this change of conditions.

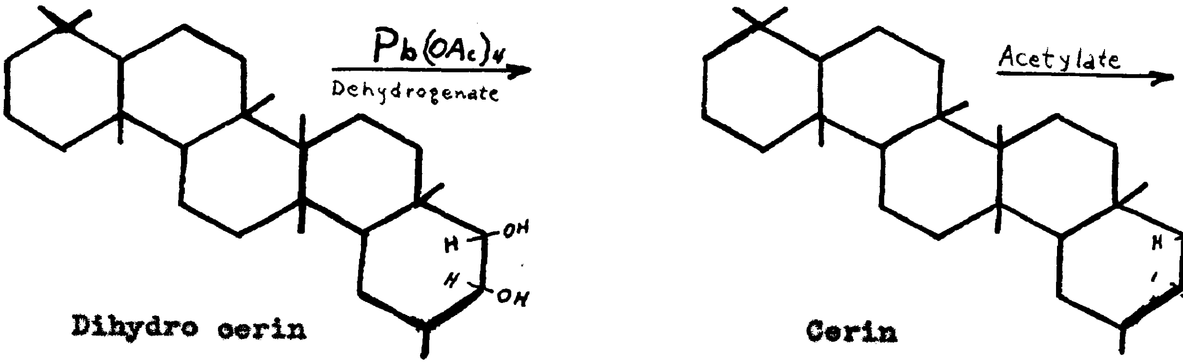
Three products were isolated from the various oxidations. The expected product, the dialdehyde obtained by Holmes, was obtained and further attempts made to demonstrate its structure. The amount obtained was small, and the experiments therefore were limited. An attempted reduction to the corresponding dihydric alcohol was unsuccessful. Conversion of the dibasic acid obtained from the oxidation of cerin into the dialdehyde by use of the Rosenmund reduction also failed because the dibasic acid, on being refluxed with thionyl chloride, forms the anhydride instead of the expected diacyl chloride. However, the dialdehyde, when refluxed in alcoholic potassium hydroxide and then poured into dilute acid , forms a new compound which is acidic and which contains three instead of two oxygen atoms. This compound has a saponification equivalent of 460, and the product recovered from the saponification is identical with the starting material. The new compound can be explained on the basis of the following reaction, an intramolecular Cannizzaro reaction:



The second product of lead tetraacetate oxidation of hydrogenated cerin proved to be identical with the dibasic acid obtained from the oxidation of cerin with chromic anhydride. It is the product which would be expected to result from the further oxidation of the dialdehyde, and its isolation probably indicates that the dialdehyde actually has the structure suggested because the dialdehyde results from the oxidation of dihydrocerin by one mol of lead tetraacetate, and the dibasic acid results from oxidation by three mols of lead tetraacetate per mol of dihydrocerin. Although the dibasic acid on pyrolysis forms a pyroketone instead of an anhydride, on being refluxed with thionyl chloride it forms an anhydride instead of a diacyl chloride. The anhydride, on being refluxed with potassium methylate and poured into dilute hydrochloric acid forms again a dibasic acid, or a mixture of dibasic acids, for the melting range of the product varies with the length of time it is refluxed in alkaline solution. Unquestionably there are several possible isomers; that obtained by oxidation being probably a trans form, and that formed by regeneration from the anhydride being probably a cis form.

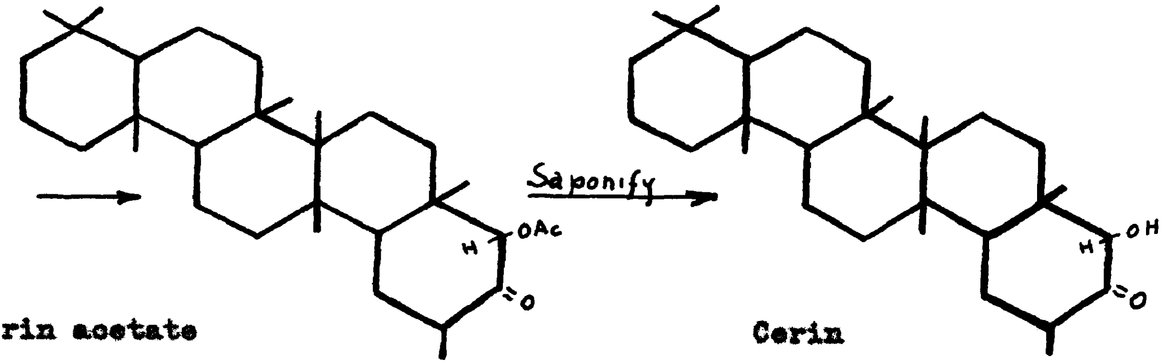
In an attempt to obtain more dialdehyde for further study, dihydrocerin identical with that used by Holmes in his experiment was prepared by the reduction of cerin with sodium and alcohol. This compound, dissolved in acetic acid, was oxidized at 70° C using an excess of lead tetraacetate. The chief product obtained was apparently an ester for it had a saponification equivalent of 475, whereas the product recovered from the saponification had no saponifiable group and contained one less oxygen atom. The best conclusion to be drawn from the analytical data is that the ester is the monoacetate of cerin or an isomer of cerin and that the product obtained by saponification is cerin or an isomer of cerin. Cerin, as it is usually purified, melts at 247-51° C; but by extensive recrystallizations from chloroform and from pyridine, a product can be obtained which melts at 251-57° C. This observation was first made by Shrader (12) and has been confirmed by the writer. The product obtained by saponification of the material resulting from reaction of dihydrocerin with lead tetraacetate at 70° C melts at 258-64° C, and two mixed melting points with cerin of melting point 251-57° C melted at 254-61° C. That cerin and friedelin are mixtures of isomers has long been suspected because of the rather long ranges of temperature over which they melt; this evidence seems to confirm that suspicion.

It should be noted that this monoacetate represents only twenty per cent of the total material used and does not account for the three mols of lead tetraacetate consumed in the reaction; in the formation of this product only one mol would be used. One mechanism by which the monoacetate might be formed is a dehydrogenation at one of the hydroxyl groups to form a ketone followed by direct acetylation of the remaining hydroxyl.



Dihydro cerin

Cerin



Cerin acetate

Cerin

The reaction involved in the mechanism postulated above is a well-known reaction of lead tetraacetate. (3)

EXPERIMENTAL

Preparation of Friedelin

The friedelin used in this research was obtained by a modification of the method used by Drake and Jacobsen. The "friedelin rich" material, obtained by addition of acetone to the concentrated chloroform filtrate from the precipitation of cerin, was filtered off, then crystallized five times from pyridine and dried over phosphorous pentoxide or sulfuric acid. The elimination of the purification as the enol-benzoate, and substitution of crystallization from pyridine was suggested by Holmes, and contributes a great saving in time, yield and effort. The product melts at 257 to 263° C.

Friedelinol

1) 0.05 mols (21.3 g.) of friedelin (M.P. 257-63° C), dissolved in 700 c.c. of dioxane, was reduced in the high pressure hydrogenator at 150° C with three grams of copper chromite catalyst. After two hours the temperature was raised to 180° C, and after one hour more to 200° C. The maximum pressure recorded was 2200 pounds per square inch. After allowing the bomb to cool, the mixture of contents was removed and heated on the steam bath to dissolve the product, the catalyst was filtered off, the filtrate was concentrated, and the friedelinol

allowed to crystallize. The product melted at 278-82° C. Several crystallizations from amyl alcohol failed to change the melting point. Further hydrogenation caused no change in the product.

Analysis:[1]

Calculated for $C_{30}H_{52}O$ $\quad$ C = 84.04
H = 12.23

Found $\quad$ C = 83.97 , 83.71
H = 12.22 , 12.25

2) Five grams of friedelin was dissolved in 200 c.c. of dioxane and reduced for six hours over three grams of copper chromite catalyst at a temperature of 200° C and a pressure of 2400 lbs. per sq. in. The product of hydrogenation was obtained as above and found to melt at 291-300° C. A mixed melting point with friedelinol prepared by reduction of friedelin with sodium and amyl alcohol showed no depression. Several crystallizations from amyl alcohol raised the melting point to 295-301° C.

3) Twenty grams of friedelin dissolved in 700 c.c. of dioxane was reduced for four hours over Raney nickel catalyst at 150° C using a pressure of 2000 lbs. per sq. in. The product melted at 278-82° C.

4) Five grams of friedelin dissolved in 200 c.c. of dioxane was reduced at 200° C over Raney nickel catalysts for four hours at a

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[1] The author thanks Mr. W. A. Stanton for these analyses.

pressure of 3000 lbs. per sq. in. The product melted at 278-82° C.

5) An attempted reduction over Raney nickel catalyst at room temperature failed completely. Reduction at 100° C was incomplete after six hours.

A total of 155 grams of the lower melting isomer of friedelinol and 25 grams of the higher melting form were prepared by catalytic hydrogenation. The yields were quantitative.

Friedelinyl Acetate

One gram of friedelinol (M.P. = 278-82° C) in 100 c.c. of acetic anhydride was boiled under reflux for three hours. After four recrystallizations from benzene the product was found to melt with decomposition from 273° to 285° C. Placed in the melting point bath at 285° C, the substance melts from 285° to 287° C with decomposition. A mixed melting point with friedelinol melted at 240° C.

Analysis:[2]

Calculated for $C_{32}H_{54}O_2$		C = 81.64 H = 11.56
Found	C = 81.50 H = 11.65	81.80 11.70

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[2] The author thanks Mr. P. J. Wingate for these analyses.

Friedelinyl Methyl Ether

1) Ten grams of friedelinol (M.P. 278-82° C) was dissolved in 250 c.c. of specially purified dioxane in a two-necked, one liter flask with standard tapered glass connections and fitted with a Hershberg stirrer. Four grams of potassium metal was added, and the mixture was heated under reflux for five hours with vigorous stirring. At the end of this period, three portions of methyl iodide, each consisting of 20 c.c., were added at one hour intervals, and the mixture was then allowed to reflux for four hours longer. The excess potassium was then destroyed by the addition of alcohol followed by a little water, and the methyl iodide was recovered by fractional distillation through an efficient fractionating column. The dioxane solution of the product was evaporated to dryness under reduced pressure on the steam bath to yield a white powder which was stirred vigorously with water at a temperature of about 80° C, filtered, washed thoroughly with water and dried. The extent to which friedelinol was converted to methyl ether was estimated by quantitative determination of the methoxyl content of this white powder and was found to average 90 to 95 per cent of the theoretical amount. The white powder was recrystallized several times from pyridine to yield a white, nicely crystalline material which melted from 253-64° C. The product is undoubtedly a mixture of two isomeric methyl ethers since refluxing either friedelinol with an alkali metal would probably cause racemization.

Analysis:[3]

Calculated for $C_{31}H_{54}O$		C = 84.10 H = 12.29
Found	C = 84.45 , 84.47 H = 12.27 , 12.21	

Methoxyl Determination:[4]

Calculated for $C_{31}H_{54}O$	Methoxyl = 7.01
Found	7.00 , 6.95

2) Ten grams of friedelinol (M.P. 291-300° C) was methylated using exactly the same procedure described above. The product melted at 291-99° C.

Analysis:

Calculated for $C_{31}H_{54}O$		C = 84.10 H = 12.29
Found	C = 84.08, 83.92 H = 12.22, 12.27	

Methoxyl Determination:[5]

Calculated for $C_{31}H_{54}O$	Methoxyl = 7.01
Found	6.99 , 6.99

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[3] The author thanks Mr. L. Goldman for these analyses.

[4] The author thanks Mr. A. F. Chapman for these methoxyl determinations.

[5] The author thanks Mr. R. F. Tollefson for these methoxyl determinations.

3) The following methods of synthesis of methyl ethers were attempted but were found to yield little or no methoxyl containing compound.

1) Addition of dimethyl sulfate to a quinoline solution of friedelinol.

2) Preparation of friedelinyl p-toluene sulfonate and heating it with methyl alcohol in a sealed tube at 200° C for four hours.

3) Warming a mixture of friedelinol, dimethyl sulfate and powdered calcium carbonate.

4) Preparation of friedelinyl chloride and reacting it with sodium methylate.

5) Refluxing friedelinol with methyl iodide over silver oxide.

6) Reacting friedelinol with methyl magnesium iodide and the product of this reaction with methyl iodide.

7) Reacting friedelinol with sodium followed by addition of methyl iodide.

8) Reacting friedelinol in benzene solution with potassium followed by addition of methyl iodide.

Selenium Dehydrogenation

The apparatus used in the dehydrogenation experiments was similar to those used by Haskins and by Houston. It consisted of a 125 c.c. round bottom flask sealed to an air condenser which was 15 mm. in diameter and one meter long. A capillary side arm was sealed into the top of the bulb and a six mm. side arm was sealed into the air condenser about 10 cm. from the top, which was closed by a rubber stopper. The upper, or exit side arm, led to a trap of the cold finger type, which was immersed in ice water. The gases were led from the trap through a bubble counter to a 15 mm. tube, 50 cm. long, filled with bleaching powder, the purpose of which was to decompose the hydrogen selenide formed in the experiment. A stream of nitrogen was passed through the apparatus to remove the gaseous products and thus to increase the speed of reaction.

Ten grams of friedelinyl methyl ether was mixed thoroughly with one gram of powdered selenium and placed in the reaction bulb. The apparatus was swept out with nitrogen, and the salt bath in which the reaction flask was placed was heated to a temperature of 300° C in about one hour. When, after a short period, no evidence of reaction was observed, the temperature was gradually increased to 350° C at which temperature reaction apparently began. It was deemed advisable to keep the reaction at as low a temperature as possible in order to prevent, if possible, cleavage of the functional group. The temperature was maintained for fifty hours during which 20 grams of selenium in four gram portions was added at intervals.

When no further evolution of hydrogen selenide was observed, the flask was cut off and broken; the product was a dark brown, almost black tar. The tar was ground up, placed in a Soxhlet apparatus and extracted with ether. This solution was evaporated to a red oil, which was treated with strong sodium cyanide solution to remove any colloidal selenium which might be present. The red oil was dissolved in benzene, washed free of cyanide, dried over calcium chloride and evaporated, then separated by distillation at a pressure of three mm. of mercury into four fractions. Methoxyl determinations were made on each of these fractions, but no methoxyl was found.

The residue from ether extraction was exhaustively extracted with benzene, and the solution was evaporated to dryness to yield a red powder. This was sublimed at 350° C, but the red selenium present was not removed. It was then heated for three hours on the steam bath with strong sodium cyanide solution. The yellowish powder which resulted was washed thoroughly with water, dried and crystallized from benzene. A methoxyl determination showed that no methoxyl was present. This product, which melted at 292-93° C, was crystallized once from acetic anhydride, three times from benzene, and three times from pyridine. The melting point gradually rose to 303-05° C when scarcity of material prevented further purification. A mixed melting point with synthetic 1, 8 dimethyl picene prepared by Howard showed no depression.

The residual tar from benzene extraction was refluxed with pyridine and the mixture filtered, but no crystalline material was obtainable from the filtrate.

Palladium Dehydrogenation

1) Preparation of catalyst

The catalyst used in the palladium dehydrogenation was prepared according to the directions of Gilchrist and Wichers (15) from palladous chloride residues available. The palladium was precipitated as diammine palladous chloride, ignited in a stream of hydrogen to palladium sponge, dissolved in aqua regia, reprecipitated, ignited, and dissolved, then precipitated as ammonium palladic chloride. This was ignited in a stream of hydrogen, dissolved in aqua regia, and the solution was evaporated to dryness. The salt was then evaporated to dryness again with hydrochloric acid. Five grams of the resulting palladous chloride was then taken up in boiling water and added to a suspension of 27 grams of charcoal in 50 c.c. of water. The mixture was heated on the steam bath for two hours during which a constant stream of hydrogen was bubbled through the solution. The palladium on charcoal catalyst was filtered off, washed thoroughly with water, dried over calcium chloride mixed with soda lime, and finally dried over phosphorous pentoxide.

2) Apparatus

The apparatus used in this experiment was identical with that used in the selenium dehydrogenation, except that the reaction bulb had a capacity of 100 c.c., and the trap was immersed in a mixture of acetone and carbon dioxide snow.

3) Dehydrogenation

Fifteen grams of friedelinyl methyl ether was mixed thoroughly with five grams of palladium-charcoal catalyst and placed in the reaction flask, and the apparatus was swept out with nitrogen. The heating bath, a sodium nitrite-potassium nitrate equi-molar mixture, was then heated to 300° C, the flask was immersed and the bath temperature was regulated to 320° C. Three three gram portions of catalyst were added at intervals, the total length of the experiment being 52 hours. During the course of the run the trap clogged twice, causing the nitrogen inlet tube to blow off, and necessitating removal of the trap for clearing. This mishap undoubtedly caused a loss of some of the most volatile products.

At the end of the experiment the trap was found to contain about 0.5 c.c. of an oil and several cubic centimeters of an aqueous solution. The solution was washed from the oil in a separatory funnel using several small portions of water, and the washings were made up to a total volume of 10 c.c. Five c.c. of this solution was tested qualitatively for methyl alcohol by Denige's method. The alcohol was oxidized by potassium permanganate in phosphoric acid; the excess permanganate was reduced by oxalic acid in 50 per cent aqueous sulfuric acid, and Schiffs reagent was added. The intense red color which resulted even in the presence of sulfuric acid could only be due to the presence of formaldehyde, demonstrating that the tested solution contained methyl alcohol.

The remaining five c.c. of solution was diluted to 10 c.c. and one c.c. of this was again diluted to 50 c.c. so that the final solution represented a total dilution of one part of the original in 1000 c.c. of solution. A micro methoxyl determination was made on one c.c. of this final solution by adding it to previously chilled hydrogen iodide solution in the reaction flask of the Vieböck and Schwappach methoxyl apparatus, allowing the mixture to warm to room temperature, and finally heating as in the normal determination. The estimation accounted for about 50 per cent of the theoretically possible amount of methyl alcohol; the other 50 per cent may have been lost in the mishap previously described. It seems certain that there is little hope of isolating a methoxyl derivative by dehydrogenation.

As a check, the residue in the dehydrogenation flask was exhaustively extracted with benzene, the solution was evaporated to dryness and methoxyl content was determined on a 300 mg. sample. Similarly, a determination was made on the oil found in the trap. No methoxyl was found to be present in either case. Hence the dehydrogenation study was abandoned.

HYDROGENATION OF CERIN

Apparatus

The hydrogenator used consisted of a heating jacket mounted on a shaker in such a manner that the reaction bomb could be tilted back and forth to the extent of about 15 degrees on either side of the horizontal. Two interchangeable bombs having capacities of 100 c.c. and of 1200 c.c. were available. The apparatus was suitable for use at any pressure up to 6000 lbs. per sq. in. and any temperature between room temperature and 400° C. The temperature was controlled by a themocouple inserted in a hole drilled well into the bottom of the bomb and connected to a regulating potentiometer. A compressor was available for obtaining pressures higher than could be obtained from a hydrogen cylinder.

Preparation of Catalyst

The copper chromite catalyst was prepared according to the directions of Adkins (1). Before decomposition, the orange precipitate formed in the process was divided into two portions one of which was decomposed at as low a temperature as possible, and the other was decomposed at high temperature. The object was to prepare catalysts differing in activity in an attempt to prepare the dihydro cerin reported by Holmes which melted at 251-54° C. In addition to these two catalysts, two other copper chromite catalysts prepared by Wolfe and by Mozingo were used.

Purification of Dioxane

The dioxane used in these experiments was carefully purified by allowing it to stand for 30 days with 10 per cent of its volume of 10 per cent hydrochloric acid. The water and hydrochloric acid were removed by addition of solid potassium hydroxide, and the dioxane was then refluxed over sodium for two hours before distillation.

Friedelinol from Reduction of Cerin

1) One gram of cerin (M.P. 247-51° C) was dissolved in 60 c.c. of dioxane and reduced over one gram of copper chromite catalyst for six hours at 250° C using a pressure of 3000 lbs. per sq. in. Six crystallizations of the product yielded approximately 50 milligrams of friedelinol melting at 299-302° C. A mixed melting point with friedelinol prepared by catalytic hydrogenation of friedelin showed no depression.

Analysis:

Calculated for $C_{30}H_{52}O$ C = 84.04
H = 12.23

Found C = 83.80 , 83.79
H = 12.22 , 12.27

2) One gram of cerin (M.P. 247-51° C) dissolved in 60 c.c. of dioxane was made acid to litmus by addition of one drop of acetic

acid. One gram of copper chromite catalyst was added and the mixture shaken for seven hours at 120° C at a pressure of 1900 lbs. per sq. in. Four crystallizations from dioxane yielded 20 milligrams of crystals which melted from 277-82° C. A mixed melting point with the lower melting isomer of friedelinol prepared by catalytic hydrogenation of friedelin showed no depression.

Analysis:

Calculated for $C_{30}H_{52}O$ $C = 84.04$
$H = 12.23$

Found $C = 83.64$, 83.14
$H = 12.35$, 12.14

The catalytic hydrogenation of cerin is highly complex. The only pure compounds which have been isolated are those described above. The table on page 28 is presented as a summary to show the scope of the conditions studied. Even when conditions are as carefully controlled as possible, the product formed cannot be duplicated in melting range.

HYDROGENATION TABLE

Temp. °C	Pressure in lbs./sq. in.	Time in hours	Catalyst	Melting Range of first product °C
30	106	5	Raney Nickel	231-48 (mostly cerin)
50	97	1	" "	257-81
100	100	16	" "	261-80
100	2400	4	" "	257-71
160	2400	7	" "	264-74
100	3000	5	" "	270-84
110	2950	8	Copper Chromite (Mozingo)	243-54
120	2000	4	" " "	257-70
120	2400	7	" " "	244-57
125	2000	6	" " "	253-60
125	2100	7	" " "	246-52
150	2400	6	" " "	270-77
150	2000	6	" " "	266-82
250	2400	6	" " "	235-72
240	4000	24	" " "	251-67
150	2000	4	Copper Chromite (Wolfe)	251-60
150	2000	4	" " "	255-72
250	2000	4	" " "	251-70
160	2000	4	Copper Chromite (High temp.)	275-79
160	2000	4	" " (Low temp.)	266-82

OXIDATION STUDIES

Preparation of Reagent

The lead tetraacetate was prepared according to the directions given by Dimroth (8). Two hundred grams of red lead was added in small portions to a liter of glacial acetic acid at a temperature of 80° C. On cooling, about 30 grams of lead tetraacetate, discolored with an appreciable amount of lead peroxide, was obtained. This product was recrystallized once from glacial acetic acid which had been distilled from chromic anhydride and stored in a glass stoppered flask under acetic acid.

Oxidation of Hydrogenated Cerin to Dibasic Acid

1.30 grams of hydrogenated cerin was dissolved in about 300 c.c. of glacial acetic acid which had been distilled from chromic anhydride. To this was added 50 c.c. of a solution of lead tetraacetate (saturated solution at 60° C) and the total volume was made up to 500 c.c. at 60° C. At the same time, 50 c.c. of the same lead tetraacetate solution was placed in a 250 c.c. volumetric flask and this solution was made up to volume at 60° C. When the reaction had proceeded for 40 hours, aliquots, five c.c. of blank and 10 c.c. of sample, were pipetted into 25 c.c. of a solution containing 400 grams of potassium acetate and 50 grams of potassium iodide per liter.

The iodine liberated from the potassium iodide by the lead tetraacetate of the aliquot was then titrated with standard sodium thiosulfate solution. For the blank 21.6 c.c. of 0.0183 normal thiosulfate was used by each five c.c. aliquot and, for the sample 3.1 c.c. of thiosulfate was used for each 10 c.c. aliquot. Calculation showed that 2.98 mols of lead tetraacetate was used up per mol of hydrogenated cerin present. This corresponds to the theoretical quantity of oxidant required to convert dihydrocerin into dibasic acid.

The acetic acid solution was poured into 1.5 liters of hot water, cooled and filtered. The precipitate, which was liberally contaminated with lead dioxide, was extracted six times with boiling benzene. The benzene solution was concentrated to about 100 c.c. and filtered several times through hardened filter paper to remove a small quantity of lead dioxide. The filtrate was concentrated and allowed to crystallize to yield about 500 mg. of a product which sintered at 265° and melted with decomposition at 273-77° C. Several crystallizations from benzene raised the melting point to 279-82° C. A mixed melting point with the dibasic acid obtained by Holmes from the chromic acid oxidation of cerin showed no depression.

Analysis:

Calculated for $C_{30}H_{50}O_4$ C = 75.89
H = 10.71

Found C = 75.65 , 75.59
H = 10.56 , 10.65

Oxidation of Hydrogenated Cerin to Dialdehyde

1.56 grams of hydrogenated cerin, dissolved in 500 c.c. of acetic acid, was oxidized at 60° C by a measured quantity of lead tetraacetate equal to a ten per cent excess of the theoretical quantity necessary to oxidize dihydro cerin to the corresponding dialdehyde. At the end of 60 hours no unused lead tetraacetate could be detected, and the solution was poured into 1500 c.c. of hot water (90°), cooled, and filtered. Purification, which was effected as described above, was simplified by the absence of any lead dioxide. After several crystallizations from benzene, the reaction product was found to melt from 310-14° C. A mixed melting point with the dialdehyde obtained by Holmes showed no depression.

Monobasic Acid from Dialdehyde

0.1 gram of dialdehyde (M.P. 310-14° C) was refluxed in alcoholic potassium hydroxide until solution was achieved and then the refluxing was continued for 30 minutes. The solution was poured into dilute hydrochloric acid, and the white precipitate was filtered off and crystallized from acetone to yield a white solid melting at 312-17° C. A mixed melting point with the dialdehyde showed the product to be a different compound. A saponification equivalent determination was made and the product was recovered and crystallized twice from acetone. The melting point of this product was 322-25° C. Three mixed melting points with the material used in the saponification were all intermediate between those of the two substances themselves.

Analysis:

Calculated for $C_{30}H_{52}O_3$ $C = 78.20$
$H = 11.37$

Found $C = 78.24$, 78.50
$H = 11.18$, 11.11

Saponification Equivalent

Calculated for $C_{30}H_{52}O_3$ 460

Found 449, 453

Dibasic Acid from Oxidation of Hydrogenated Cerin

Four grams of hydrogenated cerin, dissolved in 1500 c.c. of glacial acetic acid, was allowed to stand at room temperature with a large excess of lead tetraacetate for 27 days. The product was obtained in exactly the same way as previously described and was found to be identical with the dibasic acid formed in the oxidation of cerin by chromic acid.

Anhydride of Dibasic Acid

To show, if possible, the relationship between the dibasic acid and the dialdehyde, an attempt was made to reduce the acid (as the diacyl chloride) to the dialdehyde by the Rosenmund method. 1.6 grams of dibasic acid was dissolved in 25 c.c. of thionyl chloride and refluxed for one hour on the steam bath. The thionyl chloride was distilled off under reduced pressure and the solid residue was dissolved in 20 c.c. of dry, thiophene-free benzene which was then distilled off. This evaporation of the benzene solution was repeated three times to insure removal of all thionyl chloride. Finally, the solid was dried over sodium hydroxide in a vacuum desiccator. When three separate experiments, using varying conditions and different preparations, failed to evolve hydrogen chloride the product of the reaction between dibasic acid and thionyl chloride was isolated and crystallized from benzene. After four recrystallizations the product melted at 274-78° C; a mixed melting point with the dibasic acid melted at 265°.

Analysis:[6]

Calculated for $C_{30}H_{48}O_3$ C = 78.89
H = 10.59

Found C = 79.05 , 79.10
H = 10.49 , 10.68

Dibasic Acid from Anhydride

0.1 grams of anhydride was refluxed for 30 minutes with methyl-alcoholic potassium hydroxide, then poured into dilute hydrochloric acid to yield a white precipitate which was filtered off and crystallized from acetone. The product crystallized in beautiful needles melting at 249-57° C. A portion of this product was refluxed again in alcoholic potassium hydroxide to yield a product melting at 269-84° C. Both products were apparently mixtures of dibasic acids.

Analysis:

Calculated for $C_{30}H_{50}O_4$ C = 75.89
H = 10.71

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[6] The author thanks Mr. E. G. Young for these analyses.

Found C = 75.42 , 75.65
H = 10.61 , 10.32

Dihydrocerin

Twenty-four grams of cerin (in two batches) was dissolved in 2400 c.c. of hot amyl alcohol. To this was added 25 grams of fine sodium shot in small portions. The amyl alcohol was distilled off, and the gel-like solid obtained was crystallized many times from an ethyl alcohol-benzene mixture to yield 1.8 grams of dihydrocerin melting at 293-96° C. A mixed melting point with dihydrocerin prepared by Holmes, and used by him in his experiment, showed no depression.

Lead Tetraacetate Oxidation of Dihydrocerin

1.86 grams of dihydrocerin was dissolved in hot acetic acid in a one liter volumetric flask. Into this was pipetted 100 c.c. of a lead tetraacetate solution which had been saturated at 70° C. Fifty c.c. of the same solution was pipetted into a 250 c.c. volumetric flask, and both flasks were made up to volume at 70° C. After 48 hours, aliquots were withdrawn and titrated with 0.0295 normal sodium thiosulfate solution. Five c.c. of blank used 15.30 c.c., while 10 c.c. of dihydrocerin solution used 6.60 c.c. Calculation shows that 3.07 mols of lead tetraacetate were used per mol of dihydrocerin.

The product was worked up in the usual manner and recrystallized several times by dissolving it in benzene and evaporating with simultaneous addition of ethyl alcohol. The white needles thus obtained melted at 254-57° C. A mixed melting point with cerin showed a marked depression. The yield of product obtained, 350 milligrams, represents only 20 per cent of the total material present and does not account for the total amount of lead tetraacetate used up in the reaction.

Analysis:

Calculated for $C_{32}H_{52}O_3$ — C = 79.29
H = 10.81

Found — C = 79.18, 79.33
H = 10.71 , 10.85

Saponification Equivalent:

Calculated for $C_{32}H_{52}O_3$ — 484

Found — 470, 478

The product of saponification was recovered and recrystallized from benzene and ethyl alcohol. It was found to melt at 258-64° C and a mixed melting point with the original showed a marked depression. A saponification experiment on the recovered product showed that this product was not acidic and did not possess a saponifiable group. Carbon and hydrogen analyses, combined with the data on the product saponified, indicate that the recovered material is cerin or an isomer of cerin. The indication is confirmed by mixed melting points. Two mixtures of the product recovered from saponification with cerin of melting point 251-57° C melted from 254-61° C.

Analysis:

Calculated for $C_{30}H_{50}O_2$ — C = 81.37
H = 11.39

Found — C = 80.97 , 81.02 , 81.19
H = 10.96 , 10.92 , 10.95

SUMMARY

1) An isomeric friedelinol has been isolated, and the conditions necessary to produce either isomer at will have been ascertained.

2) The isolation of friedelinol from the hydrogenation of cerin has demonstrated again the close relationship between the two compounds.

3) Location of the carbonyl group in friedelin by dehydrogenation of friedelinyl methyl ether has been proven impossible.

4) Supporting evidence for the structure of the dialdehyde obtained by lead tetraacetate oxidation of dihydrocerin has been obtained.

5) The existence of several stereoisomeric dibasic acids has been demonstrated.

6) Two new products of lead tetraacetate oxidation have been isolated. These are the dibasic acid which has been obtained previously by the oxidation of cerin with chromic anhydride, and the monoacetate of cerin or a compound which is isomeric with cerin.

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