second paper of this series, and because the Bougault reaction provides a convenient route to 1,2-substituted phenanthrenes of a type which may prove useful in the synthesis of compounds related to the sex hormones. It has been found that the anhydrides of both 3,4-dihydrophenanthrene-1,2-dicarboxylic acid and phenanthrene-1,2-dicarboxylic acid have oestrogenic properties.

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[CONTRIBUTION FROM THE UNIVERSITY OF MARYLAND]

Cerin and Friedelin. II. Some Functional Derivatives[1]

BY NATHAN L. DRAKE AND STERL A. SHRADER

Earlier investigation has shown[2] that cerin and friedelin possess the same polycyclic nucleus of thirty carbon atoms. It is the purpose of this paper to describe certain functional derivatives of these substances, thereby confirming the carbonyl nature of friedelin and demonstrating that cerin is an hydroxy ketone.

In keeping with its carbonyl nature friedelin reacts with hydroxylamine, with *p*-nitrophenylhydrazine, and with 2,4-dinitrophenylhydrazine, yielding the corresponding derivatives of the carbonyl group. Friedelin oxime is converted by treatment with phosphorus pentachloride into an isomeric substance which is no longer an oxime. This rearrangement product is not at all altered by any hydrolytic agent which does not decompose it, does not form an acetate with acetic anhydride and cannot be reconverted to friedelin by any method that we have been able to discover. The oxime, on the other hand, can be hydrolyzed readily to friedelin, and gives an acetate with acetic anhydride.

Cerin, like friedelin, can be converted into an oxime and a 2,4-dinitrophenylhydrazone. When treated with Purdie's reagents, cerin yields a monomethyl ether. An oxime or a 2,4-dinitrophenylhydrazone can be prepared from this ether without removal of the methyl group. When reduced in *n*-amyl alcohol by means of sodium, cerin yields a dihydroxy derivative which is characterized by the formation of a diacetate. It is apparent, therefore, that cerin must contain a carbonyl and an hydroxyl group. Whether the hydroxyl or the carbonyl of cerin occupies the same position in the nucleus as the carbonyl group of friedelin we do not know, for all attempts to obtain friedelin from cerin have failed.

Experimental

Friedelin Oxime.—Ten grams of friedelin was dissolved in 200 ml. of benzene containing 50 ml. of alcohol, and 3.5 g. of hydroxylamine hydrochloride, dissolved in 25 ml. of alcohol, was added. Three grams of potassium hydroxide dissolved in 25 ml. of alcohol was added to the reaction mixture through the reflux condenser and the mixture was refluxed for one hour, cooled and poured into 400 ml. of water. The resulting solution was acidified with sulfuric acid, and the product filtered, washed and recrystallized from a 2 to 1 mixture of benzene–ethyl acetate; 7.9 g. of oxime was obtained. The substance melts at 290–294° and crystallizes in thin hexagonal plates.

Anal. Calcd. for $C_{30}H_{51}ON$: C, 81.56; H, 11.65; N, 3.17. Found: C, 81.29, 81.25; H, 11.57, 11.71; N, 3.32, 3.25.[3]

Hydrolysis of Friedelin Oxime.—One-half gram of friedelin oxime was dissolved in 90 ml. of *n*-amyl alcohol and 6 ml. of 50% phosphoric acid was added. The mixture was refluxed for seven hours, and 50 ml. of alcohol was removed by distillation. The crystals which separated overnight were recrystallized from an ethyl acetate–benzene mixture, and melted at 257–262°. No change in the melting range was observed when this material was melted mixed with friedelin.

Anal. Calcd. for $C_{30}H_{50}O$: C, 84.43; H, 11.82. Found: C, 84.26, 84.00; H, 11.88, 11.71.

Friedelin Oxime Acetate.—0.6 g. of friedelin oxime was dissolved in 20 ml. of acetic anhydride and refluxed for one-half hour. The acetate which separated from the cold solution was recrystallized from ethyl acetate from which it separates in the form of hexagonal plates. The product melted at 237–239°.

Anal. Calcd. for $C_{32}H_{53}NO_2$: C, 79.28; H, 11.23. Found: C, 79.52; H, 10.97.

The Beckmann Rearrangement of Friedelin Oxime.—7.5 g. of friedelin oxime was dissolved in 2500 ml. of dry chloroform, the solution was cooled to −5°, and 4.5 g. of phosphorus pentachloride added in small portions during the course of fifteen minutes. The mixture was allowed to stand in an ice- and salt-bath for twelve hours, and then allowed to warm up to room temperature; 80% of the

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[1] From the Ph.D. dissertation of Sterl A. Shrader.

[2] Drake and Jacobsen, THIS JOURNAL, **57**, 1570 (1935).

[3] We are indebted to Dr. T. B. Smith for the nitrogen determinations.

chloroform was distilled off and the remainder poured into ice water. After neutralization of the acid with 10% potassium hydroxide solution, the chloroform was removed by distillation, and the solid filtered and recrystallized from benzene containing one-fourth its volume of alcohol; 6.5 g. of product was obtained. Recrystallization from ethyl acetate–chloroform–ethyl alcohol, and finally from dioxane yielded a product which melted at 316–318°. The substance crystallizes in the form of hexagonal plates.

Anal. Calcd. for $C_{30}H_{51}ON$: C, 81.56; H, 11.65; N, 3.17. Found: C, 81.32, 81.38; H, 11.87, 11.67; N, 3.34, 3.32.[4]

Attempts to Hydrolyze the Rearrangement Product.—Many attempts were made to hydrolyze the product obtained by the action of phosphorus pentachloride on friedelin oxime, but none were successful. Alkali or acid in aqueous *n*-amyl alcohol under reflux or in a sealed tube at 200–250° did not effect a cleavage of the substance. Aqueous ethylene glycol and phosphoric acid at the reflux temperature were without effect. Phenol containing some water and hydriodic acid had no effect under reflux. Likewise, acetic acid and phosphoric acid containing water did not effect hydrolysis. Sulfuric acid and sodium nitrite in *n*-amyl alcohol were similarly without effect. In all but one of these experiments the original substance was recovered; phenol, hydriodic acid and the material heated in a sealed tube produced a tar.

Friedelin-2,4-dinitrophenylhydrazone.—One-half gram of friedelin was dissolved in 60 ml. of hot methyl cellosolve, and 0.3 g. of 2,4-dinitrophenylhydrazine added. The mixture was warmed until homogeneous. Two drops of concentrated hydrochloric acid were added and the mixture boiled for five to ten minutes. On cooling, the solution deposited narrow orange-colored lath-like crystals which were recrystallized from benzene. The product melted with decomposition at 297–299°.

Anal. Calcd. for $C_{36}H_{54}N_4O_4$: C, 71.24; H, 8.98; N, 9.23. Found: C, 71.50, 71.24; H, 9.05, 8.92; N, 9.26, 9.27.

Friedelin *p*-nitrophenylhydrazone was prepared by a method similar to that described above for the 2,4-dinitrophenylhydrazone; the *p*-nitrophenylhydrazone melted with decomposition at 277–279°.

Anal. Calcd. for $C_{36}H_{55}N_3O_2$: C, 76.95; H, 9.85; N, 7.47. Found: C, 77.41, 77.58, 77.42; H, 9.95, 9.78, 9.89; N, 7.58, 7.52.

We are unable to account for the poor carbon determinations. Further crystallization from dioxane, benzene and ethyl acetate–benzene results in a product whose percentage composition is essentially that recorded above. This substance crystallizes in the form of narrow hexagonal laths.

Cerin Methyl Ether.—Ten grams of cerin was dissolved in 500 ml. of dry dioxane, and treated with 50 g. of methyl iodide and 4 g. of silver oxide. The mixture was refluxed for nine hours with the addition of a gram of fresh silver oxide every two hours. The solution was then freed of silver oxide and iodide by filtration, and concentrated to about 50 ml.; 4.5 g. of methylated product separated from the cold solution. This substance melted at 235–245°. An additional gram of product which melted at 204–230° was obtained by concentrating the solution to about 30 ml. The remainder of the material would not crystallize, and was obtained as an amorphous white precipitate by adding water. We were unable to obtain this material in crystalline form by use of any of the usual solvents or solvent combinations. The two crystalline fractions were combined and again treated with methyl iodide and silver oxide using dioxane as a solvent; 3.5 g. of a product melting at 259–262° and 2 g. melting at 200–215° were obtained from this methylation. Recrystallization of the high melting product from benzene–acetone yielded a substance that crystallized in narrow laths and melted at 265–270°. Extensive recrystallizations did not serve to raise the melting point of the low-melting fraction very much and analysis indicated it to be considerably deficient in methoxyl content.

Anal. Calcd. for $C_{31}H_{52}O_2$: C, 81.58; H, 11.48; OCH_3, 6.80. Found: C, 81.55, 81.47; H, 11.44, 11.28; OCH_3, 6.81, 6.84, 6.82, 6.73.

The specific rotation of cerin methyl ether in chloroform solution is $[\alpha]_{5461}^{26}$ −58.9° (C = 2.76).

The Oxime of Cerin Methyl Ether.—Cerin methyl ether (0.5 g.), dissolved in a 2 to 1 mixture of benzene and alcohol, was converted by refluxing for an hour with hydroxylamine hydrochloride (0.2 g.) and potassium hydroxide (0.5 g.) into an oxime. The product crystallized in narrow laths and melted at 258–262°.

Anal. Calcd. for $C_{31}H_{54}NO_2$: C, 78.71; H, 11.52; N, 3.06; OCH_3, 6.57. Found: C, 78.72, 78.93; H, 11.29, 11.24; N, 3.37, 3.17; OCH_3, 6.66, 6.83, 6.79.

2,4-Dinitrophenylhydrazone of Cerin Methyl Ether.—The method employed was identical with the one described above for preparing the 2,4-dinitrophenylhydrazone of friedelin. The product crystallizes in narrow laths, almost needle-like, and melts with decomposition at 284–285°.

Anal. Calcd. for $C_{37}H_{56}N_4O_5$: C, 69.82; H, 8.86; N, 8.80. Found: C, 69.81, 69.83; H, 8.78, 8.89; N, 8.87, 8.90.

2,4-Dinitrophenylhydrazone of Cerin.—Prepared as above, this product crystallized from a benzene–alcohol mixture in the form of orange laths with a pronounced tendency to form spherulites and melted with decomposition at 253–255°.

Anal. Calcd. for $C_{36}H_{54}N_4O_5$: C, 69.42; H, 8.74; N, 9.00. Found: C, 69.50, 69.53; H, 8.78, 8.86; N, 9.04, 9.36.

Cerin Oxime.—One and nine-tenths grams of cerin dissolved in a mixture of 150 ml. of benzene and 100 ml. of ethyl alcohol was heated under reflux for three hours with hydroxylamine hydrochloride (0.8 g.) and potassium hydroxide (1 g.). Water was then added and the mixture made acid to Congo red. The benzene was removed by steam distillation and the crude product recrystallized from benzene–ethyl acetate. A final recrystallization from ethyl alcohol yielded a product which crystallized in lath-like plates and melted at 266–272°.

Anal. Calcd. for $C_{30}H_{51}NO_2$: C, 78.71; H, 11.24. Found: C, 78.56, 78.57; H, 11.62, 11.35.

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(4) We wish to thank Dr. J. R. Spies for these analyses.

Dihydrocerin (Cerinol).—One and one-half grams of cerin in 100 ml. of *n*-amyl alcohol was reduced by adding 3 g. of sodium to the hot solution over a period of fifteen minutes. After the sodium had dissolved completely, the alcohol was removed by steam distillation and the product recrystallized from dioxane. The dicarbinol, for which we propose the name *cerinol*, crystallized from dioxane in narrow white laths, which melted at 293–295°; $[\alpha]^{25}_{5461}$ +9.4 (C = 0.48).

Anal. Calcd. for $C_{30}H_{52}O_2$: C, 81.01; H, 11.75. Found: C, 81.05, 80.86; H, 11.63, 11.77.

Cerinol Diacetate.—Cerinol is smoothly converted by acetic anhydride alone into a diacetate. This product crystallizes from ethyl acetate–ethyl alcohol in narrow almost needle-like laths which melt at 267–269°.

Anal. Calcd. for $C_{34}H_{56}O_4$: C, 77.22; H, 10.67. Found: C, 77.04, 77.05; H, 10.35, 10.40.

The Purification of Cerin.—Several recrystallizations of crude material from chloroform are necessary to obtain pure cerin. A properly purified sample should melt at 250–256°; at least six recrystallizations are necessary starting with crude extract. A sample so prepared yielded the following analytical results. Calcd. for $C_{30}H_{50}O_2$: C, 81.38; H, 11.39. Found: C, 81.37; H, 11.35. Less extended recrystallizations result in products with a broader melting range and a considerably lower carbon content. Cerin is not at all affected by refluxing with alcoholic potassium hydroxide, but is very sensitive to mineral acids.

Cerin Acetate.—The treatment of cerin with boiling acetic anhydride alone or with boiling acetic anhydride containing a trace of sulfuric acid results in the formation of a mixture of products from which it is not possible to obtain a pure substance. The reaction products, even after many recrystallizations, possess carbon and hydrogen contents which do not correspond to any of those demanded by cerin monoacetate, cerin diacetate or the acetate of a dehydration product, $C_{30}H_{48}(OCOCH_3)$. Under much milder conditions, however, by the use of pyridine and acetic anhydride at room temperature, it is possible to obtain a monoacetate of cerin; 1 g. of cerin was dissolved in 80 ml. of dry pyridine and 10 ml. of acetic anhydride was added over a period of about five minutes. The mixture was allowed to stand at room temperature overnight (*ca.* 25°). The product was isolated by dilution of the pyridine with water, and recrystallized in succession from benzene–ethyl acetate, ethyl acetate, benzene, ethyl acetate, glacial acetic acid and ethyl acetate. The substance melted at 256–259° with decomposition.

Anal. Calcd. for $C_{30}H_{52}O_3$: C, 79.28; H, 10.82. Found: C, 79.05, 79.19; H, 10.82, 10.88.

This product was further crystallized from glacial acetic acid, and finally from ethyl acetate, from which it separated in narrow almost needle-like laths which melted at 259–261°.

Summary

1. Friedelin oxime, 2,4-dinitrophenylhydrazone and *p*-nitrophenylhydrazone have been prepared.

2. Friedelin oxime undergoes the Beckmann rearrangement and yields a product which so far has defied all attempts to cleave it by hydrolysis.

3. Cerin methyl ether, its oxime and 2,4-dinitrophenylhydrazone have been prepared.

4. Cerin has been reduced to a dihydroxy compound which was characterized by the formation of a diacetate.

5. Cerin has been characterized by the formation of an oxime and a 2,4-dinitrophenylhydrazone.

6. The monoacetate of cerin has been prepared by acetylation in pyridine at room temperature.

COLLEGE PARK, MD. RECEIVED JULY 24, 1935

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, TEACHERS COLLEGE, COLUMBIA UNIVERSITY]

Studies of Crystalline Vitamin B_1. XI. Presence of Quaternary Nitrogen[1]

BY ROBERT R. WILLIAMS AND A. E. RUEHLE

The necessity for reconciling the chemical characteristics of the basic cleavage product[2] of vitamin B_1 with the undoubted binuclear character of the vitamin led our associate, Dr. E. R. Buchman, to suggest the presence of quaternary nitrogen in the latter. If present, the tetrasubstituted nitrogen should be recognizable by its strong basicity. On titrating the vitamin hydrochloride with sodium hydroxide the presence of a moderately strong basic nitrogen was revealed, too strong for a tertiary base though not strong enough for a true quaternary base. The basic cleavage product behaved as a typical tertiary base but its methiodide[2b] closely resembled the vitamin not only in basic strength but also in exhibiting an unusual pseudo basic behavior. Both the vitamin and the methiodide of its basic cleavage product required an additional molecular equivalent of alkali for com-

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[1] Presented before the Division of Organic Chemistry at the New York Meeting of the American Chemical Society, April 22, 1935.

[2] (a) R. R. Williams, R. E. Waterman, J. C. Keresztesy and E. R. Buchman, THIS JOURNAL, **57**, 536 (1935); (b) Paper X of this series, E. R. Buchman, R. R. Williams and J. C. Keresztesy, *ibid.*, **57**, 1849 (1935).