iodide *in vacuo* the partly crystalline colored residue weighed 94.8 mg. This was purified by taking up in alcohol (acetone may be used) and precipitating with dry ether; 59.6 mg. of not quite colorless leaf-like crystals was obtained and a portion dried for analysis *in vacuo* at room temperature. *Anal.* Calcd. for $C_7H_{12}NSOI$: N, 4.91; S, 11.25. Found: N (Dumas), 4.70; S, 11.25. The methiodide is hygroscopic, quite insoluble in ether and chloroform, soluble in acetone and alcohol and readily soluble in water. It is extremely unstable toward alkali. A portion treated with 20% sodium hydroxide liberated no ether-soluble base but on standing at room temperature a dark tar was formed, insoluble in water and acid. The nitroprusside test was strongly positive. The methiodide as well as the other compounds described here has no vitamin B_1 activity.

Action of Nitric Acid on (II).—The hydrochloride of (II) was first converted into the nitrate or better into the free base and then oxidized with nitric acid (d. 1.42); 101 mg. of the hydrochloride gave with silver nitrate 115.7 mg. of the nitrate which was dissolved in 1 cc. of nitric acid. After short heating at 40° the reaction started, as evidenced by the darkening of the solution and the evolution of nitrogen oxides. The solution was kept at about 40° until no more gas bubbles formed and then most of the nitric acid was removed *in vacuo*. Quantitative removal of sulfate with baryta gave 50.2 mg. of barium sulfate. The remaining solution was evaporated to dryness, the residue suspended in water and extracted repeatedly with ether. Evaporation of the ether gave 42.0 mg. of white crystalline material which crystallized from methanol in cubes; yield 20.7 mg. After drying at 55° *in vacuo* it was analyzed. *Anal.* Calcd. for $C_5H_5NSO_2$: C, 41.93; H, 3.52; N, 9.79; S, 22.40. Found: C, 41.70; H, 3.51; N (Dumas), 9.20; S, 22.99. In later experiments it was found more convenient, instead of extracting the substance from its aqueous suspension with ether, to dissolve it in alkali and reprecipitate it by bringing to neutrality with acid. The properties of the substance are identical with those given by Windaus[7] for an acid of the same constitution obtained from the vitamin. It sublimes *in vacuo* at about 160°; on heating in a capillary tube it becomes colored above 200° and decomposes at about 250° with gas evolution. It is rather difficultly soluble in hot water and ether, soluble in alcohol and readily soluble in acids and in alkali. It gave a weak positive nitroprusside reaction. When heated with concentrated nitric acid no sulfate was formed. With ethereal diazomethane the methyl ester of m. p. 74° described by Windaus was obtained.

Action of Iodine and Alkali on (II).—The reaction was carried out on a 10-mg. portion of the hydrochloride according to the technique described by Mulliken.[14] No iodoform was formed.

We wish to acknowledge our indebtedness to Drs. H. T. Clarke and O. Wintersteiner for securing the microanalyses and to the Carnegie Corporation for a grant of funds through the Carnegie Institution of Washington.

Summary

1. The basic cleavage product (II) gives on oxidation an acid C_4H_4NS—COOH identical with the product obtained by Windaus directly from the vitamin.

2. Evidence is presented for regarding (II) as a tertiary heterocyclic base with a β-hydroxyethyl side chain C_4H_4NS—CH_2CH_2OH.

3. Evidence is presented consistent with the view that the vitamin is a quaternary salt of the base (II).

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The Synthesis of Phenanthrene and Hydrophenanthrene Derivatives. I. The Bougault Reaction

By Louis F. Fieser and Emanuel B. Hershberg

In recent years γ-arylbutyric acids have acquired a position of considerable importance in the synthesis of polynuclear hydrocarbons, and several excellent methods have been developed for the preparation of these acids. Butyric acids of the benzene, naphthalene, phenanthrene, anthracene, and pyrene series are readily available as starting materials, as are many of their derivatives substituted in either the nucleus or the side-chain.[1] It occurred to us to submit some of these acids in the form of the esters to a special cyclization procedure which hitherto has been applied only to the simplest member of the series.

Bougault[2] discovered that the condensation product from β-phenylpropionic ester and oxalic ester is converted by concentrated sulfuric acid into the diester of indene-1,2-dicarboxylic acid,

(1) "Organic Syntheses," John Wiley and Sons, Inc., 440 Fourth Ave., New York City, 1935, Vol. XV, p. 64; Haworth and co-workers, *J. Chem. Soc.*, 1125, 1784, 2248, 2717, 2720 (1932); 1012 (1933); 454 (1934); Cook and Hewett, *ibid.*, 398 (1933); Cook and Haslewood, *ibid.*, 767 (1935); Fieser and Peters, This Journal, 54, 4347, 4373 (1932).

(2) Bougault, *Compt. rend.*, 159, 745 (1915).

and von Auwers and Möller[3] applied the Bougault cyclization reaction to the next higher homolog. α-Oxalyl-γ-phenylbutyric acid (I) was prepared by these investigators in excellent yield by the condensation of phenylbutyric ester and oxalic ester with potassium ethylate.
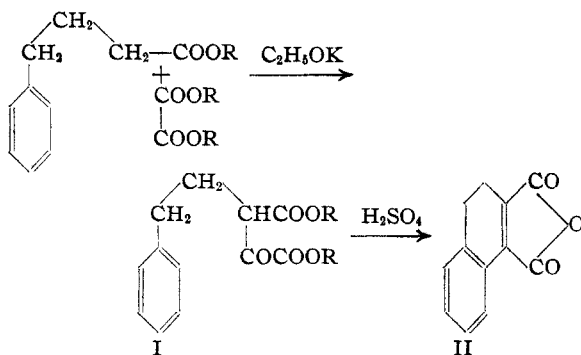
At −15° the ester (I) was converted by sulfuric acid into the diethyl ester of 3,4-dihydronaphthalene-1,2-dicarboxylic acid, while at room temperature the reaction product was obtained in the form of the corresponding anhydride, II, in nearly quantitative yield. In repeating the work of von Auwers and Möller it has been found that the ester condensation can be carried out with equally satisfactory results using sodium ethylate.

Starting with γ-(1-naphthyl)-butyric ester and γ-(2-naphthyl)-butyric ester we prepared the oxalic ester condensation products and submitted them to the Bougault reaction. With concentrated sulfuric acid there was extensive sulfonation, but the esters were converted smoothly by 80% acid into the cyclic anhydrides III and IV.[3a]
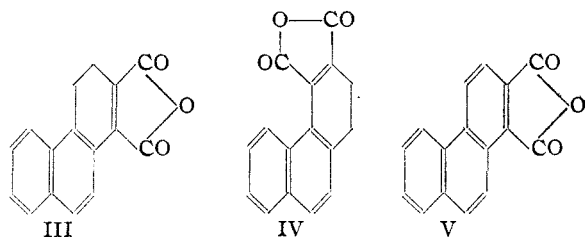
The structure of III is established by the method of synthesis and the fact that the new ring can be aromatized, 3,4-dihydrophenanthrene-1,2-dicarboxylic acid anhydride (III) being converted in good yield into phenanthrene - 1,2 - dicarboxylic acid anhydride (V) on treatment with sulfur. This method was applied with equally good results to the dihydronaphthalene derivative, II,

whereas von Auwers and Möller found that dehydrogenation with bromine proceeds very poorly. The anhydride of naphthalene-1,2-dicarboxylic acid may now be classed as a readily available compound.

The new phenanthrene and hydrophenanthrene derivatives substituted in the 1,2-positions (III and V) offer many interesting possibilities for further synthesis, and we are investigating particularly the synthesis of substances related to the oestrogenic hormones and their transformation products. Preliminary results indicate that both phenanthrene-1,2-dicarboxylic acid anhydride and the 3,4-dihydro derivative have oestrogenic activity.

We are indebted to Dr. G. Pincus of the Harvard Biological Laboratory for studying the physiological activity of the compounds. He reports that the anhydrides produced prolonged oestrus in mice, the effect lasting over a period of as much as two weeks. Cornification resulted in every case after the administration of as little as 0.05 mg. of either compound. The completely aromatic anhydride V acts slightly more rapidly than the dihydro compound III. Because of the protracted action it is difficult to make a direct comparison with the follicular hormone, but on the basis of the ordinary method of assay the minimum activity of both phenanthrene-1,2-dicarboxylic acid anhydride and the 3,4-dihydro compound is approximately 20,000 mouse units per gram.

The investigation of various substitution products and derivatives of the above compounds and related substances is in progress.

Experimental Part[4]

3,4-Dihydronaphthalene-1,2-dicarboxylic Acid Anhydride.—After several experiments on the ester condensation, the procedure of von Auwers and Möller[3] was modified in certain respects. The proportions of reagents found most satisfactory were as follows: 50 g. of ethyl phenylbutyrate, 57 g. of diethyl oxalate (1.5 equiv.), 10.4 g. of potassium (1.02 equiv.) and 12.6 g. of absolute ethyl alcohol (1.05 equiv.). The amount of alcohol is about one-third that specified,[3] and to promote a rapid reaction it was necessary to use powdered potassium. The metal was cleaned by melting it under toluene and powdered in the same solvent in an all-glass apparatus. After cooling, the metal powder was washed by decantation with ether in an atmosphere of nitrogen. After the completion of the condensation reaction the mixture containing

(3) Von Auwers and Möller, J. prakt. Chem., 217, 124 (1925).

(3a) Bardhan, Nature, 134, 217 (1934), has reported the synthesis of a dihydrophenanthrene derivative by a similar cyclization.

(4) All melting points are corrected. Analyses by Mrs. G. M. Wellwood, Dr. R. G. Larsen and Mr. E. L. Martin. For a part of the synthetical work we are indebted to Mary Fieser.

the potassium salt was decomposed with dilute acid and the ethereal solution of the oxalyl ester and excess oxalic ester was washed, dried with sodium sulfate and the solvent was evaporated in vacuum. In our experience the separation of the potassium salt from the mixture is incomplete.

In other experiments an equivalent amount of sodium ethylate, prepared as above, was found equally satisfactory, the only difference being that it was necessary to reflux the mixture for twenty-four hours in order to bring the reaction to completion.

For the cyclization the residual light yellow oil (containing oxalic ester) was dissolved in 500 cc. of concentrated sulfuric acid, keeping the temperature below 25°. After one and one-half hours the deep red solution was poured onto ice and the crude anhydride (m. p. 117–122°) was collected and washed. One distillation in vacuum gave 42–44 g. (81–85%) of light yellow material, m. p. 122–124°, b. p. 227–230° at 23 mm. The distillate exhibits triboluminescence. Once crystallized from benzene–ligroin the product melted at 126–127°.

Naphthalene-1,2-dicarboxylic Acid Anhydride.—A mixture of 17.8 g. of the dihydro compound and 2.85 g. of sulfur was heated with shaking in a nitrate bath at 230° until the sulfur had dissolved, and the bath temperature was then raised to 240–250° until the evolution of hydrogen sulfide was at an end (about thirty minutes). The residue was then distilled (b. p. 211–214° at 11 mm.) and crystallized from benzene–ligroin, giving 13.3 g. (76%) of pale yellow needles, m. p. 164–165°.

Condensation with β-Methoxynaphthalene.—The reaction of naphthalene-1,2-dicarboxylic acid anhydride with this ether was investigated in preliminary work which was later abandoned. The Friedel and Crafts reaction in warm tetrachloroethane solution gave, as in the case of phthalic anhydride,[5] a lactone: pale yellow prisms, m. p. 238–239°.

Anal. Calcd. for $C_{22}H_{12}O_3$: C, 81.49; H, 3.71. Found: C, 81.85; H, 3.98.

Heated in tetrachloroethane solution with aluminum chloride for three hours on the steam-bath, the lactone was isomerized to a naphthaloylnaphthol; thick yellow prisms from toluene, m. p. 264–265°.

Anal. Calcd. for $C_{22}H_{12}O_3$: C, 81.49; H, 3.71. Found: C, 81.91; H, 3.52.

3,4-Dihydrophenanthrene-1,2-dicarboxylic Acid Anhydride.—Ethyl γ-(1-naphthyl)-butyrate was prepared in 91% yield by esterification with alcohol and hydrogen chloride; b. p. 210–211° at 14 mm. The condensation with oxalic ester was carried out by the original procedure of von Auwers and Möller,[3] using excess alcohol and lumps of potassium. The potassium salt of the oxalyl ester in this case separated very completely from the ethereal solution, and it was collected, washed with ether and decomposed with ice-cold, dilute sulfuric acid. The oil which separated was collected and dried in ether, and after distillation of the solvent at diminished pressure, the product was obtained as a viscous yellow oil in 80% yield.

The oxalyl ester was warmed with 7–10 parts by volume of 80% sulfuric acid on the steam-bath with vigorous shaking, when it was soon converted into a bright yellow, granu-

(5) Fieser, THIS JOURNAL, **53**, 3546 (1931).

lar solid. The product was collected after diluting the mixture with water. This material was practically pure and the yield of the anhydride was quantitative.

The anhydride is sparingly soluble in glacial acetic acid or benzene and moderately soluble in dioxane. The solutions exhibit a brilliant greenish-yellow fluorescence. Crystallized from dioxane or acetic anhydride it formed golden yellow needles, m. p. 263.5–264.5°.

Anal. Calcd. for $C_{16}H_{10}O_3$: C, 76.77; H, 4.04. Found: C, 76.83; H, 4.37.

A solution of the anhydride in acetone, diluted with water, neutralized only one equivalent of methyl alcoholic potassium hydroxide, probably because of the formation of a mono-ester; neutralization equivalent found, 239; molecular weight 250.

Phenanthrene-1,2-dicarboxylic Acid Anhydride.—For the dehydrogenation, 5.7 g. of the above anhydride was heated with 0.73 g. of sulfur at 320–325° for ten minutes, and the residue was distilled at 15 mm. pressure directly from the bath. The yellow solid was crystallized from acetic anhydride, when it formed long yellow needles of m. p. 311–312°; yield, 5.1 g. (91%). The substance is only sparingly soluble in dioxane or acetic anhydride; it gives a phthalein test with resorcinol and sulfuric acid.

Anal. Calcd. for $C_{16}H_8O_3$: mol. wt., 248; C, 77.39; H, 3.25. Found: C, 77.55; H, 3.62; neutralization equivalent, 245.

1,2-Dihydrophenanthrene-3,4-dicarboxylic Acid Anhydride.—Ethyl γ-(2-naphthyl)-butyric ester (b. p. 227–228° at 25 mm.) was condensed with oxalic ester in the presence of potassium ethylate, exactly as described above for ethyl γ-phenylbutyrate. The potassium salt of the product remained dissolved in the ethereal reaction mixture, and the oil obtained on shaking the solution with dilute acid, drying and removing the solvent, contained ethyl oxalate. The crude oil from 19.6 g. of the arylbutyric ester was mechanically stirred with 125 cc. of 80% sulfuric acid at 80–90° for one hour. The oil partially dissolved at the start and after about ten minutes a yellow solid separated from the dark acid liquor. After cooling, the solid was collected on a glass funnel, washed with 80% sulfuric acid and, after thorough draining, with a liberal quantity of alcohol. The product was bright yellow and nearly pure; yield, 16.5 g. (81%). The anhydride is readily soluble in benzene; it dissolves only slowly in boiling alcohol or glacial acetic acid and tends to remain in solution. It crystallizes well from benzene–ligroin as bright greenish-yellow needles, m. p. 151–152°. The solution in concentrated sulfuric acid is bright red.

Anal. Calcd. for $C_{16}H_{10}O_3$: C, 76.77; H, 4.04. Found: C, 76.68, 76.65; H, 4.22, 4.28.

Summary

The anhydrides of dihydrophenanthrene-*o*-dicarboxylic acids can be prepared in good yield by extending an adaptation of the cyclization reaction of Bougault to α-oxalyl-γ-arylbutyric esters of the naphthalene series. These and other similar substances are being investigated both for use in the synthesis described in the

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.

CONVERSE MEMORIAL LABORATORY
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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

(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.