

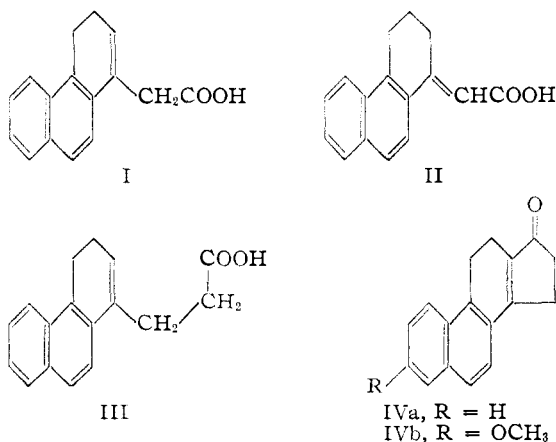
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

Synthesis of Compounds Related to Equilenin

BY W. E. BACHMANN AND R. E. HOLMEN¹

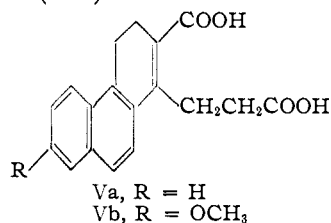
Cycloalkenepropionic acids were prepared by an Arndt-Eistert synthesis on the unsaturated acids obtained from 1-oxo-1,2,3,4-tetrahydrophenanthrene and its 2-methyl and 2-methyl-7-methoxy derivatives by the Reformatsky reaction. 14,15-Dehydroequilenin methyl ether was obtained by cyclization of one of the unsaturated acids and also by an extension of Bardhan's method.

From the Reformatsky ester prepared from 1-oxo-1,2,3,4-tetrahydrophenanthrene and methyl bromoacetate two unsaturated isomeric acids (m.p. 155–156° and 218–219°) were obtained by hydrolysis after dehydration of the ester thermally or by hydrogen chloride. Several reactions were carried out in order to determine whether the two unsaturated acids were structural isomers (I and II) or stereoisomers (geometrical isomers of II).² Both acids were decarboxylated to 1-methyl-3,4-dihydrophenanthrene when heated above their melting points and both were reduced by sodium amalgam and water at room temperature to 1,2,3,4-tetrahydrophenanthreneacetic acid. The latter reaction supported structure II for both acids. The formation of 1-oxo-1,2,3,4-tetrahydrophenanthrene in high yield on permanganate oxidation of the 218–219° acid definitely established structure II for the high-melting acid. However, none of the ketone was obtained on oxidation of the 155–156° acid; accordingly, structure I with an endocyclic double bond is assigned to the lower-melting acid. The differences in the ultraviolet absorption spectra of the isomeric acids were in agreement with these conclusions. The absorption curves were like those of similarly constructed compounds prepared through the Stobbe reaction and reported recently by Johnson and Stromberg.³



An Arndt-Eistert synthesis on acid I gave a fair yield of 3,4-dihydrophenanthrenepropionic acid (III), which was cyclized to 3'-oxo-3,4-dihydro-1,2-cyclopentenophenanthrene (IVa) by the procedure of Johnson and Petersen.⁴ The cyclic ketone IVa was also prepared by pyrolysis of a mixture of basic

lead carbonate and 2-carboxy-3,4-dihydrophenanthrenepropionic acid (Va). Bardhan⁵ had prepared the dicarboxylic acid Va in unspecified yield and had carried out the cyclization by means of acetic anhydride followed by distillation. We have repeated Bardhan's preparation of the acid with some modification for comparison with the method of Bachmann, Gregg and Pratt.⁶ Cyclization of the 7-methoxy unsaturated dicarboxylic acid Vb by pyrolysis with basic lead carbonate gave the known 3'-oxo-7-methoxy-3,4-dihydro-1,2-cyclopentenophenanthrene (IVb).



The Reformatsky ester obtained from 1-oxo-2-methyl-1,2,3,4-tetrahydrophenanthrene also yielded a separable mixture of the α,β - and β,γ -unsaturated acids (VII and VIa) on dehydration and hydrolysis, whose structures likewise were established by permanganate oxidation. The ultraviolet absorption spectrum of VIa was like that of I, and the spectrum of VII was similar to that of II. The β,γ -unsaturated acid VIa was converted into 2-methyl-3,4-dihydrophenanthrenepropionic acid (VIIIa) by an Arndt-Eistert synthesis.

Dehydration of the Reformatsky ester from 1-oxo-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene by hydrogen chloride gave a crystalline methyl ester in good yield, from which 2-methyl-7-methoxy-3,4-dihydrophenanthreneacetic acid (VIb) was obtained on hydrolysis. An Arndt-Eistert synthesis on the unsaturated acid gave 2-methyl-7-methoxy-3,4-dihydrophenanthrenepropionic acid (VIIIb), which on cyclization yielded some 14,15-dehydroequilenin methyl ether (IX). Johnson and Stromberg³ also have prepared IX by this cyclization and Johnson, Stromberg and Petersen⁷ made the desmethoxy derivative (IX, R = H) from VIIIa.

In an extension of Bardhan's method 6-methoxy-1-naphthylethyl iodide was condensed with the potassium derivative of diethyl α -methyl- β -oxoadipate to yield the diethyl ester of 4-oxo-5-carboxy-5-methyl-7-(6'-methoxy-1'-naphthyl)-heptanoic acid

(1) From the Ph.D. dissertation of R. E. Holmen, 1948.

(2) J. Hoch, *Bull. soc. chim.*, **5**, 264 (1938), had isolated a single acid (m.p. 147°) from the same reaction and assigned structure I to it.

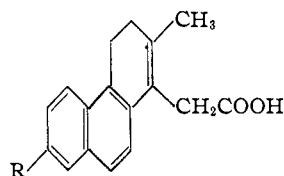
(3) W. S. Johnson and V. L. Stromberg, *THIS JOURNAL*, **72**, 505 (1950).

(4) W. S. Johnson and J. W. Petersen, *ibid.*, **67**, 1367 (1945).

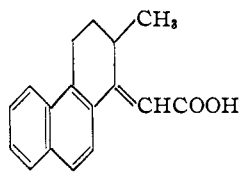
(5) J. C. Bardhan, *Nature*, **134**, 217 (1934); *J. Chem. Soc.*, 1848 (1936).

(6) W. E. Bachmann, R. A. Gregg and E. F. Pratt, *THIS JOURNAL*, **65**, 2314 (1943).

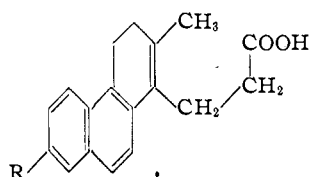
(7) W. S. Johnson, V. L. Stromberg and J. W. Petersen, *ibid.*, **71**, 1384 (1949). Our work was carried out before the appearance of this paper.



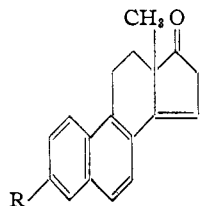
VIa, R = H
VIb, R = OCH₃



VII

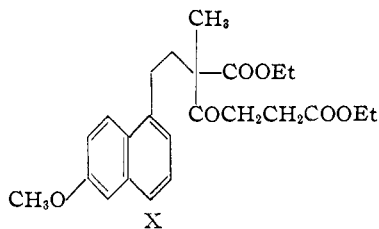


VIIIa, R = H
VIIIb, R = OCH₃

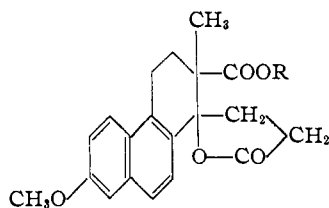
IX, R = OCH₃

(X). Cyclodehydration of the oxo-ester by 85% sulfuric acid in ether yielded two crystalline neutral compounds which appear to be the two possible stereoisomeric (*cis* and *trans*) lactones of 1-hydroxy-2-carboethoxy-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene propionic acid (XIb). A Dieckmann cyclization of the lactone esters (apparently the first recorded reaction of this type) yielded a solid which melted with evolution of gas and formation of 14,15-dehydroequilenin methyl ether (IX). Further work is required to show whether the product of the Dieckmann reaction has the structure XII.

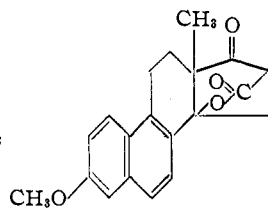
By hydrolysis of the cyclodehydration product with strong aqueous alcoholic potassium hydroxide two crystalline acids were isolated in low yield. The lactone structure was indicated by the lack of unsaturation toward permanganate and the neutral equivalent. Unexpectedly, the lactone acids underwent decarboxylation when an attempt was made to purify them through solution in aqueous sodium bicarbonate; on acidification 2-methyl-7-methoxy-3,4-dihydrophenanthrene propionic acid (VIIIb) was obtained. The same acid (VIIIb) was produced by hydrolysis of the product of the reaction of 1-oxo-2-carbomethoxy-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene with methyl



X



XIa, R = H
XIb, R = C₂H₅
XIc, R = CH₃



XII

β -bromopropionate and magnesium⁸; here also the tertiary carboxy group was eliminated at some stage of the process.

Experimental⁹

Reformatsky Reaction with 1-Oxo-1,2,3,4-tetrahydrophenanthrene.—To a solution of 5 g. of 1-oxo-1,2,3,4-tetrahydrophenanthrene in 16 ml. of dry benzene and 5 ml. of anhydrous ether was added 3.6 ml. of methyl bromoacetate and 12 g. of amalgamated 20-mesh zinc. When the mixture was warmed, an exothermic reaction set in. After about eight minutes the reaction subsided and heating was resumed for 1.5 hours with occasional swirling, when 3 ml. of methyl bromoacetate was added. A further addition of amalgamated zinc (15 g.) was made after another hour of refluxing. After a total time of 4 hours, the organic layer was decanted from the zinc, which was washed with benzene containing a little acetic acid and methanol. The combined organic fractions were washed twice with 5% hydrochloric acid, with 1% ammonium hydroxide until most of the color was removed, and finally with water. The dried solution was evaporated in a current of air.

A solution of the crude Reformatsky ester in 20 ml. of benzene containing 2 g. of anhydrous calcium chloride was saturated with dry hydrogen chloride. The cloudiness caused by the dehydration of the ester disappeared as the solution was swirled. After 1.3 hours at room temperature the filtered solution was evaporated and the residue was refluxed for 1.5 hours with 5 ml. of a 23% solution of potassium hydroxide in methanol, 5 ml. of water and 10 ml. of methanol. The solution was evaporated, water was added, and after extraction with ether (the ethereal solution contained some product; see below) the aqueous fraction (125 ml.) was acidified with dilute hydrochloric acid, allowed to digest for an hour on a steam-cone, cooled and filtered; weight of crude unsaturated acids, 4.26 g.; m.p. 137–160°, with evolution of gas. The yield, including unhydrolyzed methyl ester recovered from the ethereal extract, was 84%.

After digestion of the mixture of acids with 110 ml. of boiling 80% methanol and cooling there remained 0.78 g. of solid with m.p. 208.5–210.5°. After two recrystallizations from ethyl acetate–petroleum ether, 1,2,3,4-tetrahydrophenanthrylideneacetic acid (II) formed colorless needles; m.p. 218–219° with evolution of gas, when introduced into the bath at 200°. It readily reduced ethanolic permanganate.¹⁰

Anal. Calcd. for C₁₆H₁₄O₂: C, 80.65; H, 5.92. Found: C, 80.38; H, 6.36.

The ultraviolet spectrum of the acid in 95% ethanol showed the following maxima: 216 m μ (log *E* 4.24), 263 (4.51), 298 (4.29), 308 (4.25); the curve has the same shape as the curve of the similarly constructed 210° β -carboxy-2-methyl-1,2,3,4-tetrahydrophenanthrylidene propionic acid (Fig. 3 in reference 3) which has maxima at 260 (4.56), 298 (4.15), 307 (4.11).

The methyl ester (0.86 g., m.p. 95–97°) of the above acid was isolated from the ethereal extract of the hydrolysis mixture. It crystallized from methanol in colorless, glistening leaflets; m.p. 96.5–97°.

Anal. Calcd. for C₁₇H₁₆O₂: C, 80.92; H, 6.39. Found: C, 80.84; H, 6.58.

From the methanolic filtrate of the acid, after treatment with Norit and evaporation to 50 ml., 2.7 g. of the isomeric acid was isolated; m.p. 145–147°. From the mother liquor further crops of the same acid were recovered. After two recrystallizations from ethyl acetate–petroleum ether the 3,4-dihydrophenanthreneacetic acid (I) formed clusters of colorless prismatic needles; m.p. 155–156° with evolution of gas. An ethanolic solution readily reduced potassium permanganate.

Anal. Calcd. for C₁₆H₁₄O₂: C, 80.65; H, 5.92. Found: C, 80.70; H, 6.07.

The ultraviolet absorption spectrum of this acid in 95% ethanol has maxima at 215 m μ (log *E* 4.44), 235 (4.5), 254

(8) G. Haberland, *Ber.*, **72**, 1215 (1939); G. Haberland and E. Heinrich, *ibid.*, **72**, 1222 (1939); G. Haberland, *ibid.*, **76**, 621 (1943).

(9) Microanalyses by Micro-Tech Laboratories, Skokie, Illinois. Melting points below 250° are corrected.

(10) V. N. Ipatieff, N. W. Thompson and H. Pines, *THIS JOURNAL*, **70**, 1658 (1948).

(4.56), 263 (4.62) and 310 (3.82); the curve is like that of the curve of the similarly constructed β -carboxy-3,4-dihydrophenanthrenepropionic acid (Fig. 4 in reference 3) which has maxima at 253 (4.68), 262.5 (4.70) and 310 (3.85).

Reactions of the Unsaturated Acid (a) Decarboxylation.—A few milligrams of each of the acids (I and II) was heated separately above the melting point and the product was evaporatively distilled at 0.1 mm. Recrystallization of each lot from methanol-water gave colorless crystals of 1-methyl-3,4-dihydrophenanthrene; m.p. 83–85°, alone and when mixed with an authentic specimen.¹¹

(b) **Reduction by Sodium Amalgam and Water.**—Quantitative yields of 1,2,3,4-tetrahydrophenanthreneacetic acid with m.p. 130–132° were obtained by shaking vigorously a mixture of 0.24 g. of the acid (either one), 1 ml. of *N* potassium hydroxide (or sodium hydroxide, which gives a less soluble salt), 4 ml. of water and 10 g. of 2% sodium amalgam for 15 minutes. After recrystallization from dilute methanol, the acid melted at 134° in agreement with the reported value.²

(c) **Oxidation by Aqueous Permanganate.**—A solution of 0.31 g. of potassium permanganate in 50 ml. of water was added gradually with vigorous shaking to a chilled solution of 0.24 g. of the acid (m.p. 215–218°) in 30 cc. of water and 1.5 cc. of *N* sodium hydroxide covered with 20 ml. of benzene. After treatment with sodium bisulfite and dilute sulfuric acid, water and sodium bicarbonate, 0.175 g. (92%) of 1-oxo-1,2,3,4-tetrahydrophenanthrene with m.p. 90–92° was isolated from the ether-benzene. By recrystallization from methanol (Norit) a first crop of 0.09 g. with m.p. 95–96° was obtained. None of the ketone was obtained on oxidation of the 155–156° acid.

The Arndt-Eistert Reaction on 3,4-Dihydrophenanthreneacetic Acid.—Oxalyl chloride (0.17 ml.) in 3 ml. of benzene was added to a solution of 225 mg. of the acid (m.p. 155°) in 5 ml. of benzene. After the evolution of gas had ceased, the solution was warmed to 40° for a few minutes, the benzene was removed at room temperature under reduced pressure, 5 ml. of benzene was added and then removed as before. The residual acid chloride was then added dropwise to a rapidly swirled, ice-cold ethereal solution of diazomethane from 1.1 g. of *N*-nitroso- β -methylaminoisobutyl methyl ketone. The resulting solution was allowed to come to room temperature, and after four hours the ether was removed under reduced pressure. To the diazoketone was added 5 ml. of dry methanol and silver oxide (from 0.4 ml. of 10% silver nitrate) and the solution was kept at 60°. Another equal quantity of silver oxide was added in four portions at intervals over a 40-minute period. The mixture was finally refluxed for 40 minutes, treated with Norit, filtered, and evaporated. A solution of the product in a small volume of acetone-methanol deposited 60 mg. of colorless lustrous leaflets of the methyl ester of 3,4-dihydrophenanthrenepropionic acid; m.p. 85.5–87°, raised to 90–91.2° by two recrystallizations.

Anal. Calcd. for C₁₃H₁₈O₂: C, 81.18; H, 6.81. Found: C, 80.91; H, 7.17.

Alkaline hydrolysis of the product in the combined mother liquors yielded 80 mg. of the acid with m.p. 168–178° after clarification with Norit in benzene-alcohol and recrystallization from aqueous acetone and aqueous methanol. After two more recrystallizations from ethyl acetate-petroleum ether the 3,4-dihydrophenanthrenepropionic acid (III) formed colorless rectangular plates; m.p. 183.5–184.5° (reported⁴ 181.8–182.9°). In ethanolic solution it readily reduced potassium permanganate.

For confirmation of the structure 40 mg. of the crude acid (168–178°) was cyclized by acetic anhydride, zinc chloride and acetic acid according to the procedure of Johnson and Petersen⁴ except that the solution was kept at room temperature for about 24 hours and then heated for 30 minutes at 70–80° under nitrogen; yield 20 mg.; m.p. 201–212°. Sublimation at 130–145° and 0.1 mm. followed by recrystallization from methanol gave colorless plates of 3'-oxo-3,4-dihydro-1,2-cyclopentenophenanthrene (IVa); m.p. 216–217°, undepressed on admixture with the ketone prepared by cyclization of the unsaturated dicarboxylic acid Va described below.

2-Carboxy-3,4-dihydrophenanthrenepropionic Acid (Va) and Derivatives.—To 0.43 g. of potassium sand (or an equivalent amount of potassium *t*-butoxide) in 8 ml. of xy-

lene was added 2.6 g. of diethyl β -oxoadipate¹² in 5 ml. of xylene followed by refluxing under nitrogen until all the potassium had reacted. After cooling and the addition of 2.28 g. of 1-naphthylethyl bromide in 5 ml. of xylene, refluxing under nitrogen was continued for 63 hours. Dilute acetic acid and ether were added to the chilled mixture and the ether layer was washed with aqueous bicarbonate, dried and evaporated.

A solution of 4.4 g. of the crude diethyl ester of 4-oxo-5-carboxy-7- α -naphthylheptanoic acid in 4 ml. of dry ether was added dropwise to 50 ml. of 85% sulfuric acid and 2 ml. of ether at about 0° and the resulting viscous mixture was kept near this temperature for 16 hours. The mixture was poured over ice, extracted with ether, and the ether layer washed four times with 15% sodium carbonate solution. The alkaline washings were poured into dilute hydrochloric acid and the precipitated acid ester extracted with ether. Evaporation to a small volume and collection of the precipitated acid ester yielded, after washing with a little ethanol, 0.8 g. of nearly colorless solid melting at 158.5–160.5°. Second and third crops of only slightly less pure, flaky crystals amounted to 0.3 g. A recrystallized sample of the 2-carboxy-3,4-dihydrophenanthrenepropionic acid, after sublimation under reduced pressure, melted at 161–162.5°.

Anal. Calcd. for C₂₀H₂₀O₄: C, 73.98; H, 6.21. Found: C, 73.56; H, 6.08.

Alkaline hydrolysis of 32 mg. of the acid ester yielded 27 mg. of 2-carboxy-3,4-dihydrophenanthrenepropionic acid which melted at 235–237° (reported, 237–238°⁶) after recrystallization from acetone-benzene. By hydrolysis of the neutral residue from the ethereal fraction after the extractions with sodium carbonate, a further amount of the acid was obtained. The melting point (73–74.5°) of the dimethyl ester, prepared with diazomethane and recrystallized from methanol, agreed with the reported value.

Treatment of the acid ester with diazomethane formed the methyl ester of 2-carboxy-3,4-dihydrophenanthrenepropionic acid, which formed lustrous leaflets after repeated recrystallizations from methanol and a little water; m.p. 55.5–57°.

Anal. Calcd. for C₂₁H₂₂O₄: C, 74.53; H, 6.55. Found: C, 74.10; H, 6.35.

When an intimate mixture of 50 mg. of the dicarboxylic acid (Va) and an equal volume of basic lead carbonate was heated to 260° in a sublimation tube at 0.1 mm., 20 mg. of crude ketonic sublimate was collected. The 3'-keto-3,4-dihydro-1,2-cyclopentenophenanthrene (IIIa) crystallized from methanol in colorless plates; m.p. 215–216° in agreement with reported values.

In an experiment in which 25 g. of the diethyl ester of 4-oxo-5-carboxy-7- α -naphthylheptanoic acid and 10 g. of 100% phosphoric acid was kept at 64° for 36 hours, and the product of the reaction was hydrolyzed with methanolic potassium hydroxide, some dehydrogenation and decarboxylation as well as cyclization took place, for 110 mg. of β -1-phenanthrenepropionic acid was isolated; m.p. 189–190° (reported,¹³ 189–189.5°). The methyl ester melted at 91–92° and did not depress the m.p. (90–91°) of an authentic specimen¹⁴; it depressed the m.p. (90–91°) of the methyl ester of 3,4-dihydrophenanthrenepropionic acid 8°.

Reduction of the Unsaturated Dicarboxylic Acid Va.—A solution of 300 mg. of the acid in 6 ml. of water containing sufficient potassium hydroxide to neutralize the acid was shaken vigorously with 12 g. of 2% sodium amalgam for 25 minutes. A solution of the mixture of reduced acids in the minimum amount of boiling ethyl acetate deposited 160 mg. of colorless solid when cooled; m.p. 175–178°. Recrystallization from ethyl acetate gave coarse colorless prisms of 2-carboxy-1,2,3,4-tetrahydrophenanthrenepropionic acid, m.p. 182–183°.

Anal. Calcd. for C₁₈H₁₈O₄: C, 72.47; H, 6.08. Found: C, 72.36; H, 6.11.

The Reformatsky Reaction with 1-Oxo-2-methyl-1,2,3,4-tetrahydrophenanthrene.—The reaction of 5 g. of the ketone with methyl bromoacetate and the isolation and dehydration of the product were carried out as described for the previous Reformatsky reaction. The crude dehydrated product was

(12) B. Riegel and W. M. Lilienfeld, *ibid.*, **67**, 1273 (1945).

(13) W. E. Bachmann, *ibid.*, **57**, 1381 (1935).

(14) W. E. Bachmann and M. C. Kloetzel, *ibid.*, **59**, 2207 (1937).

(11) W. E. Bachmann and A. L. Wilds, *ibid.*, **60**, 824 (1938).

refluxed for 1.5 hours with 10 ml. of alcohol and 4 ml. of a solution of 5 g. of potassium hydroxide in 5 ml. of water. After the removal of the solvent, the residue was diluted with water, extracted twice with ether (from which 0.7 g. of ketone was recovered) and the aqueous fraction was acidified. After digestion of the precipitated mixture of isomeric unsaturated acids (4.55 g., m.p. 222–230°) with acetone, there remained 3.7 g. of product (m.p. 230–233°), which after two recrystallizations from acetone-ethyl acetate (in which the acid is not very soluble) gave 2-methyl-3,4-dihydrophenanthreneacetic acid (VIa) as colorless prismatic needles; m.p. 238.5–239.5° with vigorous evolution of gas.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39; neut. equiv., 252. Found: C, 80.42; H, 6.32; neut. equiv., 252.

The ultraviolet spectrum of the acid in methanol had the following maxima: 215 $m\mu$ (log E 4.45), 255 (4.62), 264 (4.69), 311 (3.89).

The filtrate yielded 0.52 g. of acid (m.p. 189–193°) which after recrystallization from ethyl acetate-petroleum ether and from dilute methanol gave colorless needles of 2-methyl-1,2,3,4-tetrahydrophenanthrylideneacetic acid (VII); m.p. 193–194°, with a trace always persisting to 200°. The m.p. was not improved by further recrystallization.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.22; H, 6.36.

The ultraviolet spectrum in methanol had maxima at 213 $m\mu$ (log E 4.41), 255 (4.55), 264 (4.60), 299 (4.22), 307 (4.21).

Permanganate oxidation of the 193–194° acid gave a 60% yield of 2-methyl-1,2,3,4-tetrahydrophenanthrene; none of the ketone was obtained from the higher-melting acid. A few milligrams of the higher-melting acid was heated at 240° and then sublimed at 170° and 0.1 mm. Recrystallization of the sublimate after removal of unchanged acid with alkali gave colorless, glistening leaflets of 1,2-dimethyl-3,4-dihydrophenanthrene; m.p. 95–100° (reported, 99–100°)¹⁶; m.p. of picrate, 119° (reported,¹⁶ 120–121°).

Arndt-Eistert Reaction on the Unsaturated Acid.—A suspension of 2 g. of the 238.5–239.5° acid in 12 ml. of dry benzene, 1.87 ml. of oxalyl chloride, and a drop of pyridine was warmed for 1.5 hours at 45–50°; the reaction was then carried out as described for the previous case, except that the product was hydrolyzed directly with 45% potassium hydroxide solution. By recrystallization of the resulting acid (1.4 g.) from benzene-petroleum ether a first crop of 0.56 g. of needles with m.p. 127–129° was obtained. A second recrystallization gave flakes which melted at 131°, resolidified and then melted at 141–144°. A third recrystallization from ethyl acetate-petroleum ether gave colorless blades of 2-methyl-3,4-dihydrophenanthrenepropionic acid (VIIIa); m.p. 131–132° (reported after our work had been completed,⁷ 131–132°). It readily decolorized ethanolic potassium permanganate, and was immediately soluble in dilute aqueous ammonia.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.18; H, 6.81. Found: C, 80.82; H, 7.02.

2-Methylphenanthrenepropionic Acid.—A mixture of 128 mg. of the 2-methyl-3,4-dihydrophenanthrenepropionic acid and 30 mg. of sulfur was heated to 220–230° until the evolution of hydrogen sulfide had nearly ceased and then at 260° for a few minutes. The product was sublimed at 0.1–0.2 mm. and the sublimate was dissolved in hot alcohol-acetone. A small amount of a compound of undetermined structure with m.p. 119–121° crystallized in needles from the cooled solution. The product isolated from the solution was recrystallized from ethyl acetate-petroleum ether; yield 86 mg., m.p. 180–182°. After two further recrystallizations the acid formed colorless plates; m.p. 183–183.5°.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.79; H, 6.10. Found: C, 82.00; H, 6.20.

The methyl ester prepared with diazomethane crystallized from methanol in colorless needles; m.p. 114–115°, raised to 115–116° by further recrystallization.

Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 81.82; H, 6.45.

The same acid was obtained by way of Haberland's β -bromopropionate synthesis. A mixture of 1.5 g. of 1-oxo-2-methyl-1,2,3,4-tetrahydrophenanthrene, 1 ml. of methyl

β -bromopropionate, 0.16 g. of magnesium, a trace of mercuric chloride and 7 ml. of dry benzene was refluxed for 1.5 hours. Alkaline hydrolysis yielded 0.68 g. of crude acid and 1.08 g. of unchanged ketone. By heating the acid with sulfur some of the 119° compound and chiefly 2-methylphenanthrenepropionic acid were produced; m.p. after purification, 184–185.5°, not depressed when mixed with the acid above.

Reformatsky Reaction with 1-Oxo-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene.—The reaction of 1.5 g. of the ketone with 1.1 ml. of methyl bromoacetate and 10 g. of zinc was carried out in 20 ml. of benzene and 22 ml. of ether at 60–70° for 13 hours; an additional 2 g. of zinc was introduced and heating was continued for 2 hours. The product from the cooled reaction mixture was isolated and dehydrated with dry hydrogen chloride as in the previous examples. Recrystallization of the crude ester (1.7 g.) from methanol yielded 1.18 g. (64%) of the product with m.p. 95–96.5°. After two more recrystallizations the colorless rhombs of the methyl ester of 2-methyl-7-methoxy-3,4-dihydrophenanthreneacetic acid melted at 97–98.5°.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.00; H, 7.04.

Alkaline hydrolysis of the ester gave the acid with m.p. 203–205° in practically quantitative yield. The 2-methyl-7-methoxy-3,4-dihydrophenanthreneacetic acid (VIb) crystallized from ethyl acetate-petroleum ether in colorless needles; m.p. 205–206° with evolution of gas.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.42. Found: C, 76.26; H, 6.40.

The ultraviolet absorption curve of the acid in methanol had the following maxima: 219 $m\mu$ (log E 4.49), 256 (4.70), 265 (4.69), 303.5 (4.08), 316 (4.05) and was similar in shape to the curve (Fig. 1 in reference 3) of 2-methyl-7-methoxy-3,4-dihydrophenanthrenepropionic acid which has the following maxima: 219.5 $m\mu$ (4.35), 256 (4.68), 265 (4.68), 303 (4.02), 315.5 (3.99).

After a mixture of 0.87 g. of the unsaturated acid and an equal volume of powdered glass had been heated above the melting point, the product was evaporatively distilled at 230° and 0.4 mm.; weight 59 mg.; m.p. 97–100°. Two recrystallizations from methanol gave colorless 1,2-dimethyl-7-methoxy-3,4-dihydrophenanthrene; m.p. 110–111° (reported³).

Anal. Calcd. for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.43; H, 7.45.

2-Methyl-7-methoxy-3,4-dihydrophenanthrenepropionic Acid and Its Cyclization.—A suspension of 600 mg. of the unsaturated acid VIb in 5 ml. of dry benzene, 0.75 ml. of oxalyl chloride and a drop of pyridine was allowed to stand at room temperature for 11 hours. The acid chloride and diazomethane were kept in contact for 2.5 hours. The crude crystalline diazoketone was rearranged in 25 ml. of absolute methanol with the aid of 0.15 g. of silver oxide (U.S.P.) followed by three 0.1-g. additions at 40-minute intervals. After 11 hours of refluxing the mixture was treated with Norit, cooled, filtered and evaporated. The partly crystalline residue was stirred with methanol containing a few drops of acetone and the solid was collected. Recrystallization from methanol containing a little acetone gave 47 mg. of the methyl ester of 2-methyl-7-methoxy-3,4-dihydrophenanthrenepropionic acid as colorless needles melting at 100.5–102.5°. When recrystallized from petroleum ether-ethyl acetate the needles melted at about 78° with resolidification and final melting at 101–103° (reported,⁸ 114°, supposedly the same compound). Sublimation did not alter the melting point, but the prior melting and solidification were not noted.

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.28; H, 7.01.

Extraction of the Norit with boiling acetone yielded 100 mg. of liquid product which with the residue from the mother liquors gave 200 mg. of acid on alkaline hydrolysis. Recrystallization from dilute acetone (Norit) gave 88 mg. of 2-methyl-7-methoxy-3,4-dihydrophenanthrenepropionic acid (VIIIb) as glistening colorless flakes melting at 186–189°. After recrystallization from aqueous methanol and sublimation the acid melted at 186–187.5° (reported 194° and 230°,⁸ 184–185°³). The acid was readily soluble in dilute aqueous ammonia and rapidly decolorized ethanolic permanganate.

(15) R. D. Haworth, C. R. Mavin and G. Sheldrick, *J. Chem. Soc.*, 454 (1934).

In our hands the reaction of 1-oxo-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene, methyl β -bromopropionate and magnesium in benzene gave the acid (VIIIb) with m.p. 187–188° (reported,⁸ 194° for acid by this method) identical with the acid from the Arndt-Eistert synthesis. We also obtained the same acid in low yield by alkaline hydrolysis of the product of the reaction of 1-oxo-2-carbomethoxy-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene, magnesium and methyl β -bromopropionate.

Cyclization of 2-methyl-7-methoxy-3,4-dihydrophenanthrenepropionic acid by zinc chloride, acetic anhydride and acetic acid gave 14,15-dehydroequilenin methyl ether³ in low yield; m.p. 159.5–161.5° alone and when mixed with an authentic sample.

2-Carboxy-7-methoxy-3,4-dihydrophenanthrenepropionic Acid (Vb).—To a solution of potassium *t*-butoxide from 1.01 g. of potassium and 20 ml. of dry *t*-butyl alcohol under nitrogen was added 5.64 g. of dimethyl β -oxoadipate⁶ in 7 ml. of *t*-butyl alcohol, followed by 5.3 g. of 6-methoxy-1-naphthylethyl bromide in 10 ml. of dry benzene. After 11 hours at room temperature the mixture was refluxed for 36 hours. A total of 6.3 g. of neutral product was isolated, from which 3.6 g. of low boiling material was removed by distillation at 0.05 mm.

The residual liquid (2.4 g.), comprising crude dimethyl ester of 4-oxo-5-carboxy-7-(6'-methoxy-1'-naphthyl)-heptanoic acid, was diluted with 11 ml. of dry ether and added dropwise over a period of 20 minutes to 60 ml. of 80% sulfuric acid at –10 to –12°, then allowed to stand 7.5 hours at this temperature before it was poured over ice and treated as described in the previous cyclization of this type. The alkaline washings yielded 157 mg. of acid ester melting at 168–179°; an additional 39 mg. of the same compound was obtained by treating the low-boiling distillate with sulfuric acid. After recrystallization once from methanol and twice from ethyl acetate-petroleum ether the 2-carbomethoxy-7-methoxy-3,4-dihydrophenanthrenepropionic acid formed colorless needles; m.p. 183.5–184.5°.

Anal. Calcd. for C₂₀H₂₀O₆: C, 70.57; H, 5.92. Found: C, 70.30; H, 6.15.

The neutral ethereal fraction yielded 500 mg. of the dimethyl ester of 2-carboxy-7-methoxy-3,4-dihydrophenanthrenepropionic acid melting at 100–104°. After two recrystallizations from methanol and one from ethyl acetate-petroleum ether the ester formed lustrous, colorless flakes; m.p. 106–107.5°. The same ester was obtained from the acid ester and diazomethane.

Anal. Calcd. for C₂₁H₂₂O₆: C, 71.15; H, 6.26. Found: C, 70.98; H, 5.98.

The filtrates from the recrystallizations of the acid ester and diester were evaporated and hydrolyzed with methanolic potassium hydroxide. A solution of the crude acid in acetone and 10 ml. of xylene was heated with Norit, filtered, and boiled until most of the acetone had been removed. On cooling, 156 mg. of the dibasic acid precipitated; m.p. 226–230°. The 2-carboxy-7-methoxy-3,4-dihydrophenanthrenepropionic acid (Vb) crystallized from acetic acid-water in fine colorless needles; m.p. 238.5–239.5° dec. The same acid was obtained by saponification of the crystalline acid ester.

Anal. Calcd. for C₁₉H₁₈O₆: C, 69.93; H, 5.56. Found: C, 69.52; H, 5.70.

More of the same acid was obtained from the reaction of diethyl β -oxoadipate (17.3 g.), potassium *t*-butoxide (from 2.62 g. of potassium and 24 ml. of *t*-butyl alcohol), 6-methoxy-1-naphthylethyl bromide (14 g.) and 85 ml. of toluene. The mixture was refluxed under nitrogen for 3 days, cooled and neutralized with acetic acid. After the removal of the solvent in a current of air, a solution of the residue in ether-benzene was washed with aqueous sodium bicarbonate and with water, and dried over sodium sulfate. One-half of the solution was clarified by passing it through a column of alumina, followed by elution with ether-alcohol. The product obtained by removal of the solvent was freed of unchanged reagents by evaporative distillation at temperatures up to 140° at 0.1 mm. The residual 6.4 g. of viscous liquid containing the desired diethyl ester of 4-oxo-5-carboxy-7-(6'-methoxy-1'-naphthyl)-heptanoic acid was dissolved in 25 ml. of dry ether (25 ml.) and the resulting solution was added dropwise in 40 minutes to 160 ml. of 85% sulfuric acid diluted with 25 ml. of dry ether and maintained at –5°. After 3.5 hours at this temperature, the mixture

was poured over ice and extracted twice with ether, and the solution was washed twice with sodium bicarbonate solution.

Alkaline hydrolysis of the material in the ether solution yielded neutral material, chiefly 6-methoxynaphthylethyl alcohol (2.3 g.), and the acid Vb, which was washed with a little methanol, ether, and acetone in turn; m.p. 234–237° dec., yield 2.03 g.

From the bicarbonate washings 0.15 g. of the monoethyl ester with m.p. 145–149° was obtained. After several recrystallizations from aqueous alcohol and from ethyl acetate-petroleum ether the 2-carbomethoxy-7-methoxy-3,4-dihydrophenanthrenepropionic acid melted at 150–151°.

Anal. Calcd. for C₂₁H₂₂O₆: C, 71.17; H, 6.26. Found: C, 70.87; H, 6.19.

The over-all yield of acid plus acid ester from the bromide was 25%. If the recovered alcohol and bromide are considered, this figure is about doubled.

When 47 mg. of the unsaturated dicarboxylic acid was heated with basic lead carbonate in a sublimation tube at 250–265° and 0.1 mm., 12 mg. of crude ketonic sublimate was collected; m.p. 208–211°. Recrystallization from methanol (Norit) gave nearly colorless plates of 3'-oxo-7-methoxy-3,4-dihydro-1,2-cyclopentenophenanthrene (IVb); m.p. 211–212° (reported,¹⁶ 210–211°).

Reduction of the Dicarboxylic Acid Vb.—The product obtained by sodium amalgam-water reduction of Vb, was dissolved in hot ethyl acetate and some petroleum ether was added; from the cooled solution a quantity of fluffy solid acid precipitated; m.p. 177–186°. After three recrystallizations from ethyl acetate-petroleum ether the 2-carboxy-7-methoxy-1,2,3,4-tetrahydrophenanthrenepropionic acid formed colorless prisms; m.p. 190.5–191.5°.

Anal. Calcd. for C₁₉H₂₀O₆: C, 69.50; H, 6.13. Found: C, 69.24; H, 6.05.

Diethyl α -Methyl- β -oxoadipate and Related Compounds.

—A solution of 50 g. of diethyl β -oxoadipate in 175 ml. of benzene was added to a cold suspension of 5.7 g. of powdered sodium in 50 ml. of benzene under nitrogen. After 30 minutes of cooling the mixture was heated on a steam-bath for 3.5 hours. A solution of 40 ml. of methyl iodide in 40 ml. of benzene was added to the chilled mixture, after 20 minutes the cooling bath was removed, and after an hour more the mixture was refluxed for 0.5 hour. The isolated diethyl α -methyl- β -oxoadipate was distilled; b.p. 113–115° at 0.1 mm.; yield 35 g. (66%). Practically the same yield was obtained by employing a suspension of potassium *t*-amylate in xylene in place of metallic sodium. With alcoholic ferric chloride the ester gives practically no immediate color (the diethyl β -oxo-adipate gives an immediate magenta color); on addition of a drop of water a deep purple color results.

Anal. Calcd. for C₁₁H₁₈O₅: C, 57.36; H, 7.81. Found: C, 57.30; H, 7.84.

Following Ruggli and Maeder¹⁷ for the unmethylated ester, an ice cold solution of 0.5 g. of diethyl α -methyl- β -oxoadipate and 0.3 g. of benzylamine in absolute alcohol was kept at 7–10° for 12 hours, evaporated, and treated with concentrated aqueous ammonia. After 5 hours the solution was evaporated; from the residue after three recrystallizations from dilute alcohol the ethyl ester of 1-benzyl-5-oxo-2-pyrrolinemethylacetic acid was obtained as colorless pearly flakes; m.p. 134–136°.

Anal. Calcd. for C₁₆H₁₉NO₃: N, 5.13. Found: N, 5.17.

From the first mother liquor after several days there appears nearly colorless prismatic crystals of 5-oxo-2-pyrrolinemethylacetamide, m.p. 274–275° dec. when introduced at 220°. The same compound was obtained directly from diethyl α -methyl- β -oxoadipate and concentrated aqueous ammonia.

Anal. Calcd. for C₇H₁₀N₂O₂: C, 54.52; H, 6.53. Found: C, 54.74; H, 6.32.

Hydrolysis of the diethyl ester by nine volumes of hydrochloric acid at room temperature and evaporation gave crystals of α -methyl- β -oxoadipic acid, m.p. 110–113° dec. When the acid was warmed with aqueous semicarbazide hydrochloride and sodium acetate, gas was evolved and the semicarbazone of 4-oxocaproic acid was formed, which after

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(17) P. Ruggli and A. Maeder, *Helv. Chim. Acta*, **25**, 943 (1942).

recrystallization from aqueous alcohol had m.p. 174–176° dec. (reported,¹⁸ 176°).

Anal. Calcd. for $C_7H_{12}N_2O_3$: C, 44.91; H, 7.00. Found: C, 44.97; H, 6.88.

In experiments on the preparation of dimethyl β -oxoadipate, a suspension of the sodio derivative of 41.3 g. of methyl acetoacetate in 500 ml. of benzene was treated with 58 g. of β -carbomethoxypropionyl chloride and the mixture was refluxed for 4 hours. The isolated product (68 g.) was shaken with a cold mixture of 57 g. of cupric sulfate in 227 ml. of water and 62 ml. of concentrated aqueous ammonia. The blue precipitate of the copper derivative was collected, stirred with 50 ml. of methanol, collected, and the treatment with methanol was twice repeated; yield 30 g. After three recrystallizations from ethanol-cyclohexane a sample of the copper derivative of the dimethyl ester of α -acetyl- β -oxoadipic acid formed elongated, blue prisms; m.p. 145–146.5°.

Anal. Calcd. for $C_{20}H_{28}O_{12}Cu$: C, 46.00; H, 5.02. Found: C, 46.07; H, 5.18.

By stirring the blue chelate with 100 ml. of ether and a solution of 9 ml. of concentrated sulfuric acid and 50 ml. of water at 5–10° for 2.5 hours, the dimethyl ester of α -acetyl- β -oxoadipic acid (20 g.) was liberated and collected in the ethereal solution.

6-Methoxy-1-naphthylethyl iodide was prepared by refluxing 10 g. of the corresponding bromide with a solution of 6.5 g. of sodium iodide in 50 ml. of acetone for 2 hours. The isolated product crystallized from petroleum ether in lustrous plates; weight 10 g.; m.p. 64°, raised to 65–66° by two recrystallizations from methanol.

Anal. Calcd. for $C_{13}H_{13}IO$: C, 50.02; H, 4.19; I, 40.66. Found: C, 49.96; H, 4.43; I, 40.80.

Preparation of the Lactones XI.—To an ice-cold solution of 16 g. of diethyl α -methyl- β -keto adipate in 55 ml. of dry ether under nitrogen was added 60 ml. of a solution of potassium *t*-butoxide prepared from 3 g. of potassium and 56 ml. of dry benzene. After 15 minutes a solution of 11.2 g. of 6-methoxy-1-naphthylethyl iodide in 40 ml. of dry benzene was added and the reaction mixture was swirled in an ice-bath for 5 minutes before it was allowed to come to room temperature. After 1.5 hours the mixture was refluxed for 3 days, cooled and acidified.

Unchanged reagents were removed by evaporative distillation at temperatures up to 158° at 0.2 mm.; the residual 7.8 g., which presumably contained the diethyl ester of 4-oxo-5-carboxy-5-methyl-7-(6'-methoxy-1'-naphthyl)-heptanoic acid (X), was used in subsequent operations without further purification.

A solution of 2.9 g. of the product in 10 ml. of dry ether was added dropwise with constant stirring in 10 minutes to a mixture of 66 ml. of 85% sulfuric acid and 10 ml. of dry ether at a temperature of 0 to –3°; after 50 minutes the mixture was poured over ice. A solution of the isolated product in 30 ml. of petroleum ether and 20 ml. of benzene was passed through a column of activated alumina and was followed by 50 ml. of petroleum ether-benzene which served to remove impurities. Further elution with the same solvent mixture and with 70 ml. of benzene yielded 0.75 g. of a gum, which in ether-petroleum ether deposited platelets with m.p. 143–155°. The solution which was decanted from the crystals quickly deposited a second crop comprised of nearly colorless clusters of needles melting at 141–144°.

A single recrystallization raised the m.p. of the platelets to 159.5–161°, and after two more crystallizations from ethyl acetate-petroleum ether the compound, presumably one form of the lactone of 1-hydroxy-2-carboxy-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene propionic acid (XIb), melted at 160.5–162°.

Anal. Calcd. for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: 71.42; H, 6.51.

Recrystallization of the 141–144° fraction from ethyl acetate-petroleum ether gave lustrous colorless needles presumably of the stereoisomeric form of the lactone ester XIb;

m.p. 143.5–145°. The two forms were insoluble in cold dilute alkali and were unaffected by cold aqueous potassium permanganate.

Anal. Calcd. for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 70.91; H, 6.70.

A solution of the 145° lactone ester in methanolic potassium hydroxide was warmed for a few minutes and then allowed to stand at room temperature for two weeks. On acidification, extraction with ether, and evaporation of the solvent there remained glistening flakes of 2-methyl-7-methoxy-3,4-dihydro-1-phenanthrene propionic acid (VIIIb); m.p. 181–183°, undepressed in a mixed m.p.

In another run the crude cyclodehydration product representing the yield from an initial 5.6 g. of β -(6-methoxy-1-naphthyl)-ethyl iodide was refluxed with 10 g. of potassium hydroxide, 25 ml. of alcohol and 15 ml. of water for 2 hours. After evaporation the residue was dissolved in water and extracted with ether. Acidification of the aqueous fraction with dilute hydrochloric acid gave 1.9 g. of a crude mixture of acids which in benzene-acetone deposited a solid (m.p. 148–153°) with a neutral equivalent of 223, corresponding to a mixture of mono- and dicarboxylic acids. From the mother liquors 0.1 g. of cream-colored powdery acid eventually precipitated; m.p. 199–202°, raised to 210–212° dec. by recrystallization from ethyl acetate. It did not reduce ethanolic permanganate. In the cold, it gave a neutral equivalent of 338 in agreement with the value (340) calculated for the lactone of 1-hydroxy-2-carboxy-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene propionic acid (XIa). When warmed, it gave an equivalent of about 193 (end-point not sharp) which was near the value (170) for the dicarboxylic acid. Addition of mineral acid precipitated 2-methyl-7-methoxy-3,4-dihydrophenanthrene propionic acid (VIIIb); m.p. 184–186° after purification.

The methyl ester (presumably XIc) prepared from the lactone acid and diazomethane crystallized from ethyl acetate-petroleum ether in colorless blades; m.p. 166.5–168°. The ester did not reduce ethanolic potassium permanganate.

Anal. Calcd. for $C_{21}H_{22}O_5$: C, 71.17; H, 6.25. Found: C, 70.51; H, 6.14.

From another run there was recovered another colorless acid, presumably another stereoisomeric form of the lactone of 1-hydroxy-2-carboxy-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene propionic acid (XIa), which after recrystallization from acetone-water melted at 208–209° with evolution of gas. The acid did not reduce ethanolic permanganate solution and was decarboxylated in weakly alkaline solution to VIIIb.

Anal. Calcd. for $C_{20}H_{20}O_5$: C, 70.58; H, 5.92. Found: C, 70.82; H, 6.04.

Dieckmann Cyclization of the Lactone Esters.—A mixture of 0.28 g. of the lactone ethyl esters (XIb), 3 ml. of dry benzene, and the powdered sodium methoxide prepared from 60 mg. of sodium was refluxed under dry nitrogen for 7.5 hours, cooled under nitrogen and acidified with acetic acid. Ether was added and the resulting solution was washed with sodium bicarbonate solution and water. A methanolic solution of the residue remaining after evaporation of the dried solution deposited 80 mg. of solid, which may be the lactone of 2'-carboxy-3'-oxo-1-hydroxy-7-methoxy-1,2,3,4-tetrahydro-1,2-cyclopentenophenanthrene (XII).

When 32 mg. of the product was heated slowly to 165° in a sublimation tube at 0.1 mm., vigorous evolution of gas occurred at 130°. The sublimate of 14,15-dehydroequilenin methyl ether (IX) crystallized from methanol in diamond-shaped plates; yield 14 mg.; m.p. 162–163° (reported,¹⁹ 161.5–162.5°), undepressed on admixture with an authentic sample kindly supplied by Dr. W. S. Johnson.

The material isolated from the methanolic filtrate of the Dieckmann product yielded on similar treatment 29 mg. of recrystallized 14,15-dehydroequilenin methyl ether; m.p. 161–163°.

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