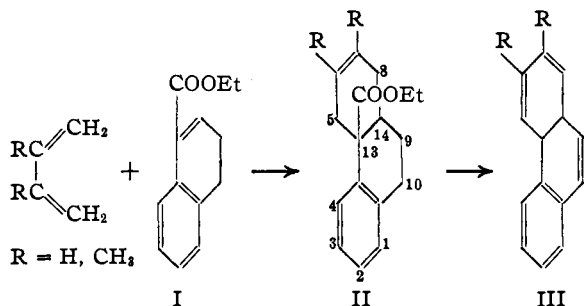


[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Synthesis of Phenanthrene and Hydrophenanthrene Derivatives. V. The Addition of Dienes to Cyclic α,β -Unsaturated Esters

BY L. F. FIESER AND H. L. HOLMES

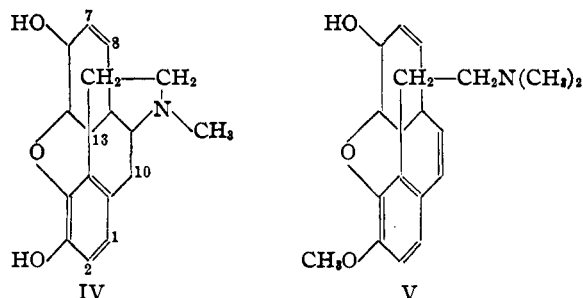
Having found that derivatives of maleic anhydride in which the active ethylenic linkage is incorporated in an alicyclic ring are capable of entering into the Diels-Alder reaction with dienes,¹ the possibility of effecting a similar addition in the case of cyclic α,β -unsaturated esters has been investigated in the hope that this might provide a route to hydrophenanthrene derivatives of a type hitherto inaccessible by synthesis. The reaction was tried first with ethyl Δ^1 -dihydro-1-naphthoate (I) prepared by reducing α -naphthoic acid with sodium amalgam and rearranging the labile Δ^2 -dihydro derivative with alkali according to v. Baeyer and Schoder,² followed by Fischer esterification.³ With both butadiene and 2,3-dimethylbutadiene addition to the double bond of the ester was found to occur slowly, giving hexahydrophenanthrene carboxylic esters of the type II. The reactions did not proceed as well as



in the case of Δ^1 -dihydronaphthalene-1,2-dicarboxylic anhydride¹ and the conversion invariably was far from complete, but the pure esters (II) were obtained in 21-27% yield by heating the components at 100° for eight days or at 150° for forty-one hours. The addition products, one of which was obtained as a liquid and the other as a low-melting solid, are easily separated from the starting material by taking advantage of the great resistance to hydrolysis of the tertiary ester group. By refluxing a mixture of I and II with 10% potassium hydroxide the unsaturated ester can be completely hydrolyzed without appreciably affecting the addi-

tion product. The corresponding acids were obtained as crystalline solids by saponification of the esters with sodium ethylate at 180°. The substances have not yet been investigated in sufficient quantity to determine whether more than one *dl*-mixture is present. That the addition products have the expected structures was established by their conversion on dehydrogenation with selenium, either as the esters or as the free acids, into phenanthrene and 2,3-dimethylphenanthrene.^{1,4}

These observations are of particular interest in connection with the morphine problem. In the Gulland-Robinson formula (IV) for this alkaloid the ethanamine chain is assumed to be attached to the phenanthrene skeleton at a posi-



tion (C₁₃) corresponding to that occupied by the carbonyl group of the synthetic compounds described above. The location of this end of the C-C-N chain, however, is the one point regarding the structure which still remains to be unambiguously established. The present synthesis makes available for the first time substances of known structure having a carbon substituent at the position which is indicated as being the most likely point of attachment of the ethanamine chain, and it offers promise of providing a route to compounds which may be obtainable from morphine, for example by the further degradation of α -methylmorphimethine, V.

In order to approach sufficiently closely to the morphine type of structure it seemed essential to develop a flexible method of procuring substituted dihydro- α -naphthoic esters suitable for the preparation of hydrophenanthrene carboxylic

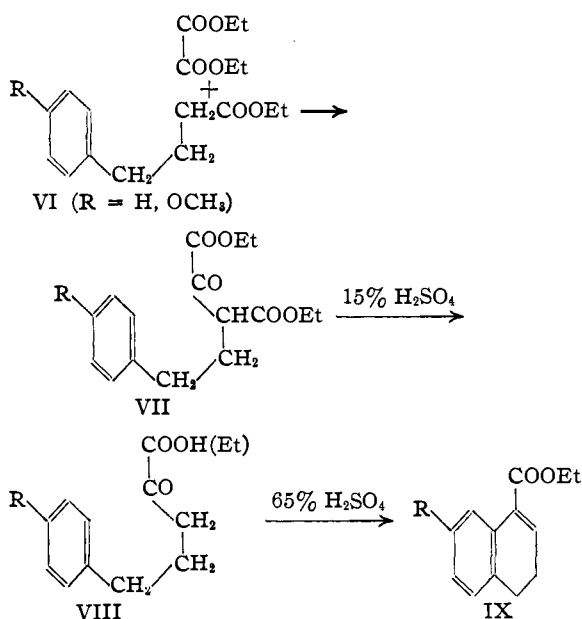
(1) Part II. Fieser and Hershberg, *THIS JOURNAL*, **57**, 2192 (1935).

(2) v. Baeyer and Schoder, *Ann.*, **266**, 176 (1891).

(3) Rahe, *Ber.*, **31**, 1896 (1898).

(4) Haworth, Mavin and Sheldrick, *J. Chem. Soc.*, **454** (1934).

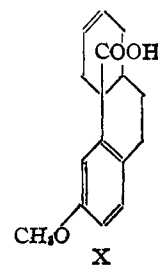
acids carrying a hydroxyl or methoxyl group in the 3-position (morphine numbering, see formula II), and possibly also in the 4-position. The method used by v. Baeyer and Schoder² in the case of the parent compound would require difficultly accessible or unknown aromatic acids as starting materials, if indeed it is applicable to such substances, and we turned to synthesis. α -Oxalyl- γ -phenylbutyric esters of the type VII are readily obtainable by the ester condensation from the γ -phenylbutyric esters easily prepared



from benzene or anisole and succinic anhydride, and after some trial it was found that hydrolysis and decarboxylation can be accomplished by boiling the esters for fifteen to eighteen hours with 15% sulfuric acid. α -Keto- δ -phenylvaleric acid (VIII) and its *p*-methoxy derivative were obtained in this way in over-all yield from VI of about 70%. Cyclization to the dihydro- α -naphthoic ester (IX) was brought about by warming the keto esters (VIII) with 65% sulfuric acid for one to two hours on the steam-bath, and the yields again were good. The Δ^1 -dihydro-1-naphthoic acid obtained by this synthesis was fully identified by comparison with the product prepared by the previous method.² The 7-methoxy- Δ^1 -dihydro-1-naphthoic acid yielded on dehydrogenation with sulfur an acid having the properties recorded for 7-methoxy-1-naphthoic acid.⁵ Contrary to the experience of Darzens⁶

in an analogous case, no decarboxylation occurred in the course of the dehydrogenation of the above acid or of 7-methoxy-1,2,3,4-tetrahydro-1-naphthoic acid. The synthesis provides a convenient route to aromatic acids of the type indicated as well as to their dihydro derivatives, and further applications are being investigated.

Butadiene was successfully added, if in low yield, to ethyl 7-methoxy- Δ^1 -dihydro-1-naphthoate, affording after hydrolysis 3-methoxy-5,8,9,10,13,14-hexahydrophenanthrene-13-carboxylic acid (X). With the introduction of a methoxyl group in the position occupied by a similar group in the case of codeine, a part of the proposed program has been realized. A start has been made in the direction of introducing a second methoxyl group at C₄ by the synthesis of 5-bromo-7,8-dimethoxy-3,4-dihydro-1-naphthoic acid, but a report of this work will be deferred to a later publication. In addition to the proposed inquiry regarding the structure of morphine it is planned to investigate the use of acids such as X as starting materials for the synthesis of basic substances of possible morphine-like actions.



Experimental Part⁷

Synthesis of Δ^1 -Dihydro- α -naphthoic Acids

α -Keto- δ -phenylvaleric Acid.—One hundred grams of ethyl γ -phenylbutyrate was condensed with ethyl oxalate in the presence of sodium ethylate according to the procedure previously outlined¹ and the crude α -oxalyl- γ -phenylbutyric ester, after removal of the solvent ether and the excess diethyl oxalate by vacuum distillation, was refluxed vigorously with 700 cc. of 15% sulfuric acid for fifteen hours, when the at first steady evolution of carbon dioxide had practically ceased. The keto acid appeared as a viscous brown oil. This was taken up in ether, washed with water, and the acid was extracted with 200 cc. of 10% sodium hydroxide solution. The alkaline extract was clarified with Norite and acidified, and the light yellow oil was taken up in ether and dried. Evaporation of the solvent left an oil which failed to solidify, and this was consequently esterified with ethyl alcohol and hydrogen chloride. The ethyl ester distilled at 165–170° (12 mm.); yield 72 g. (62.5%). On redistillation the chief fraction boiled at 164° (13 mm.), and 5 g. of the purified ester was saponified by refluxing for one hour with 25 cc. of 20% alkali. The solution was clarified and acidified, and after thorough cooling the keto acid solidified; yield 4.3 g. (98%). The substance crystallized from hexane in the form of colorless blades, m. p. 68–69.5°. It is very soluble in alcohol or benzene in the cold and moder-

(5) Davies, Heilbron and Irving, *J. Chem. Soc.*, 2715 (1932).

(6) Darzens, *Compt. rend.*, 199, 1132 (1934).

(7) All melting points are corrected.

ately soluble in boiling hexane. A sodium salt crystallizing in plates separates from an aqueous solution containing a moderate excess of sodium carbonate.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 68.75; H, 6.25. Found: C, 68.56; H, 6.25.

Δ^1 -Dihydro- α -naphthoic Acid.—For cyclization 72 g. of ethyl α -keto- δ -phenylvalerate was stirred mechanically with 450 cc. of 65% sulfuric acid and heated for two hours on the steam-bath. The material did not dissolve and changed little in appearance in the course of the reaction. The mixture was cooled and poured onto 1 kg. of ice, and the light green oil was extracted with ether and the solution washed with water. The ethereal extract was mixed with 500 cc. of 5% sodium hydroxide and after boiling off the ether the mixture was refluxed for two hours to hydrolyze some ester present and the solution was clarified with Norite, cooled and acidified. The product separated as a solid (56.5 g.) which was obtained in a nearly pure condition by crystallization from hexane; yield 48.5 g. (85%). After several recrystallizations the acid melted constantly at 120–121°.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.86; H, 6.72. Found: C, 69.71; H, 7.07.

A sample of the unsaturated acid prepared according to v. Baeyer and Schoder² and crystallized from ethyl acetate and from hexane melted at the same temperature as the synthetic substance and did not depress its melting point. The observations are in agreement with the statement of v. Auwers and Möller³ that the acid melts at 121° rather than 125°.²

The ethyl ester was prepared according to Rabe³ in 91% yield, b. p. 170–172° (19 mm.), n_D^{20} 1.5561. Dehydrogenation of the unsaturated acid (1 g.) with sulfur (0.19 g.) at 230–240° gave after vacuum distillation 0.93 g. of light yellow α -naphthoic acid which on crystallization was obtained colorless, m. p. 161.4–161.6°.

α -Keto- δ -(4-methoxyphenyl)-valeric Acid.—Ethyl γ -(4-methoxyphenyl)-butyrate (90 g.) was condensed with ethyl oxalate (90 g.) using the ethylate from 9.88 g. of sodium (twenty hours of refluxing) and following the procedure¹ for the parent compound. After removing the ether from the reaction product the crude oxalyl derivative was refluxed vigorously with 800 cc. of 15% sulfuric acid for eighteen to twenty-four hours. The oily layer was taken into ether and dried, and on removing the solvent the keto acid was obtained as a solid; yield, after one crystallization, 72.2 g. (80%). The acid is sparingly soluble in hexane and crystallizes as thin colorless plates. The melting point is like that of camphor;⁹ the substance begins to liquefy at about 65° and the last crystal skeleton disappears at 74°. Addition of sodium chloride to the sodium carbonate solution causes the separation of characteristic hair-fine needles of the sodium salt.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 64.87; H, 6.35; neut. eq., 222. Found: C, 64.70; H, 6.46; neut. eq., 219.

The ethyl ester was prepared by esterification with absolute alcohol and hydrogen chloride, washed and dried in ether with magnesium sulfate, and distilled; b. p. 190–

192° (10 mm.), n_D^{20} 1.5080, yield 92%. In another experiment 150 g. of ethyl γ -(4-methoxyphenyl)-butyrate, run in two portions, gave 169 g. (72%) of the keto ester.

7-Methoxy- Δ^1 -dihydro-1-naphthoic Acid.—A mixture of 25 g. of ethyl α -keto- δ -(4-methoxyphenyl)-valerate and 200 cc. of 65% sulfuric acid was stirred vigorously on the steam-bath (75–80°) for one hour and then poured onto ice. The oily product, which appeared to be partially hydrolyzed ester, was taken into ether and, after removal of solvent, refluxed for two hours with 100 cc. of 9% sodium hydroxide, and the alkaline solution was clarified with Norite and acidified. The acid separated as an oil which soon solidified (19.8 g.). On crystallization from water, in which the substance is moderately soluble, 14 g. (68.5%) of pure material was obtained as colorless plates, m. p. 116–117°. It also crystallizes well from hexane (sparingly soluble) in plates; it is very soluble in benzene in the cold.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.54; H, 5.94. Found: C, 70.09; H, 5.96.

The ethyl ester was obtained by Fischer esterification in 85% yield, b. p. 186–187° (9 mm.).

7-Methoxy-1-naphthoic Acid.—7-Methoxy- Δ^1 -dihydro-1-naphthoic acid (0.6 g.) was heated with 0.1 g. of sulfur at 230–240° for one-half hour and the product distilled at 9 mm. and crystallized from hexane, yielding 0.5 g. of yellow needles. After further recrystallization the substance was obtained as long, slender, colorless needles, m. p. 169–170° (lit. 167–168°, uncorr.).⁵ Demethylation with hydrobromic and acetic acids and crystallization from water gave 7-hydroxy-1-naphthoic acid, m. p. 255–256° (lit. 253–254°, uncorr.).¹⁰

7-Methoxy-1,2,3,4-tetrahydro-1-naphthoic acid, prepared by hydrogenation with Adams catalyst, crystallized from dilute alcohol as colorless prisms, m. p. 137.5–138.5°.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.86; H, 6.72. Found: C, 69.75; H, 6.96.

Like the dihydro derivative, the tetrahydro compound gave 7-methoxy-1-naphthoic acid on dehydrogenation with sulfur. In neither case was any β -naphthol methyl ether detected in the mother liquors.

Diels-Alder Reaction

5, 8, 9, 10, 13, 14 - Hexahydrophenanthrene - 13 - carboxylic Acid.—A mixture of 11 g. of ethyl Δ^1 -dihydro-1-naphthoate and 10 g. of butadiene was heated in a sealed tube at 150° for forty-one hours. After evaporating the butadiene still present the liquid material was distilled from the polymer, the boiling range being 155–214° at 8 mm. (7 g.). This was refluxed for four hours with 30 cc. of 10% potassium hydroxide and the unsaponified oil remaining was washed and dried in ether and distilled. The ethyl ester was obtained after redistillation as a viscous oil, b. p. 164–166° (5 mm.), yield 3 g. (21%).

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.99; H, 7.99. Found: C, 79.40; H, 7.89.

For saponification 0.48 g. of the ester was heated with a solution prepared from 2 g. of sodium and 30 cc. of absolute alcohol at 170° for eighteen hours. On diluting the alkaline solution and acidifying, the acid separated as a solid (0.4 g.). Crystallized from dilute methyl alcohol it

(8) v. Auwers and Möller, *J. prakt. Chem.*, **217**, 144 (1925).

(9) This was not recognized at the time of the preliminary report, *Science*, **83**, 558 (1936).

(10) Royle and Schedler, *J. Chem. Soc.*, **123**, 1641 (1923).

formed rectangular microprisms, m. p. 137–138°. Further crystallization from hexane, in which the acid is readily soluble, gave compact clusters of microprisms, m. p. 141.5–142.5° with some previous softening. An extensive fractionation was not undertaken.

Anal. Calcd. for $C_{15}H_{10}O_2$: C, 78.97; H, 7.02. Found: C, 79.37; H, 7.40.

On dehydrogenation with selenium at 300° for twenty-one hours the once crystallized acid (0.55 g.) yielded a hydrocarbon (0.21 g.) which after crystallization melted at 96–97° and was identified as phenanthrene by mixed melting point.

6, 7 - Dimethyl - 5, 8, 9, 10, 13, 14 - hexahydrophenanthrene-13-carboxylic Acid.—The ethyl ester was prepared as above from 15 g. of the unsaturated ester and 18 cc. of 2,3-dimethylbutadiene, heating being continued for eight days at 100°. After treatment with 10% potassium hydroxide the ethyl ester was distilled as a liquid which solidified; b. p. 166° (4 mm.), m. p. 49.5–50°, yield 5.7 g. (27%).

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.23; H, 8.51. Found: C, 79.61; H, 8.84.

The free acid, prepared as above (85% yield), crystallized from very dilute alcohol as small, colorless prisms, m. p. 162–163°. Recrystallization from hexane (readily soluble) gave small, hard, crystalline clusters, m. p. 168–169° with some previous softening.

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.70; H, 7.81. Found: C, 80.17; H, 7.87.

On dehydrogenation with selenium for thirty-six hours,

1.7 g. of the crude acid yielded 0.7 g. of purified crystals melting at 78–78.5° and identified by mixed melting point determination as 2,3-dimethylphenanthrene.¹

3 - Methoxy - 5, 8, 9, 10, 13, 14 - hexahydrophenanthrene-13-carboxylic Acid (X).—A mixture of 20 g. of ethyl 7-methoxy- Δ^1 -dihydro-1-naphthoate and 15 g. of butadiene was heated for twenty-one hours at 220–245°. The crude ester mixture (18.6 g.) was refluxed with 70 cc. of 20% alkali for four hours and the residual oil was dried and distilled, b. p. 202–204° (14 mm.); yield 3.3 g. (13%). On saponification of the ethyl ester with sodium ethylate as above the free acid was obtained from dilute alcohol as colorless microprisms, m. p. 139.5–141° with previous softening.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.41; H, 7.03. Found: C, 74.03; H, 7.01.

Summary

Hydrophenanthrene derivatives having a carboxyl group at the 13-(or 12-) position can be obtained by the addition of dienes to Δ^1 -dihydro-1-naphthoic esters. A convenient synthesis of the unsaturated esters consists in the acid hydrolysis of α -oxalyl- γ -arylbutyric esters to α -keto- δ -arylbutyric acids and cyclization of the keto esters with sulfuric acid. These methods afford a new approach to substances having some features of the morphine structure.

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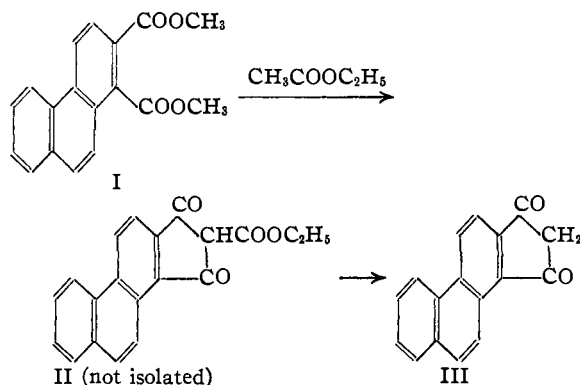
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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Synthesis of Phenanthrene and Hydrophenanthrene Derivatives. VI. 1',3'-Diketocyclopentenophenanthrenes

BY L. F. FIESER, M. FIESER AND E. B. HERSHBERG

Having found a convenient method of preparing phenanthrene-1,2-dicarboxylic anhydride by synthesis,¹ it was of interest to undertake the conversion of the substance into a compound having the 1,2-cyclopenteno ring system. The anhydride was converted into the dimethyl ester I either by the Fischer esterification of the corresponding acid, obtained through the dipotassium salt, or by the direct action of methyl alcoholic hydrogen chloride. On condensation with ethyl acetate in the presence of sodium I yielded a diketo ester II which was hydrolyzed to 1',3'-diketo-1,2-cyclopentenophenanthrene, III (or the enolic form). The pure diketone was obtained in 76% yield. Employing anhydrides prepared from interme-



diates already described,^{1,2} the isomeric diketone IV and the dimethylene (ace-) derivative V were synthesized in good yield.

(1) Fieser and Hershberg, *THIS JOURNAL*, **57**, 1851 (1935).

(2) Fieser, Fieser and Hershberg, *ibid.*, **58**, 1463 (1936).