

material from the neutral fraction of the reaction mixture was refluxed for one hour with alcoholic potassium hydroxide, and from the alkaline extract there was obtained on acidification and crystallization (28% yield) a substance identified as the lactone of 2-(α -hydroxy-*o*-methylbenzyl)-1-naphthoic acid. The substance forms colorless, pearly plates from benzene-hexane, m. p. 157-157.8°.

Anal. Calcd. for $C_{19}H_{14}O_2$: C, 83.18; H, 5.15. Found: C, 83.23, 83.16; H, 5.27, 5.32.

From the residue unsaponified in the above treatment there was isolated in small amount a substance having the properties of *n*-hexatriacontane, pearly white plates, m. p. 77-78°.

A reducing action also was observed in the reaction of 2-(*o*-toluyl)-1-naphthoic acid (free acid) with ethylmagnesium bromide (3 equivalents), but in this case some of the normal reaction product also was isolated. The neutral fraction from the reaction mixture was first crystallized from a rather dilute solution in benzene-hexane, when crystals of 2-(α -hydroxy-*o*-methylbenzyl)-1-naphthoic acid lactone were deposited in nearly pure condition and in 34% yield. The material in the mother liquor was recovered and crystallized from alcohol, affording fairly pure 2-(α -hydroxy-*o*-methyl- α -ethylbenzyl)-1-naphthoic acid lactone in 23% yield. On further crystallization from alcohol the substance formed thin hexagonal plates, m. p. 124-125°.

Anal. Calcd. for $C_{21}H_{18}O_2$: C, 83.41; H, 6.00. Found: C, 83.24; H, 6.13.

2-(*o*-Methylbenzyl)-1-naphthoic Acid.—This was obtained in 38% yield by the Clemmensen-Martin reduction of 2-(α -hydroxy-*o*-methylbenzyl)-1-naphthoic acid lactone and also, in very poor yield, by the zinc amalgam acid reduction of 2-*o*-toluyl-1-naphthoic acid in acetic acid solution. Attempted reduction with zinc dust and alkali was unsuccessful. The acid forms clusters of small, thick needles from benzene-hexane, m. p. 144-145°.

Anal. Calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.56; H, 6.05.

5-Methyl-1,2-benzanthracene was obtained by cyclization and reduction exactly as described above, the yield of purified product being 78%. Crystallized from benzene-hexane, the hydrocarbon formed fluorescent, colorless plates, m. p. 158.5-159.1°; picrate, m. p. 165.8-166.3°. Cook¹² reports the melting point 157.5-158.5°, uncorr., for the hydrocarbon and 163-163.5°, uncorr., for the picrate.

Anal. Calcd. for $C_{19}H_{14}$: C, 94.17; H, 5.83. Found: C, 93.80; H, 6.20.

Summary

A rather general method is described for the synthesis of substituted 1,2-benzanthracenes, with or without a methyl group at the 10-position, starting with 1,2-naphthalic anhydride (naphthalene-1,2-dicarboxylic anhydride) and an arylmagnesium halide. The methyl group is introduced if desired by the reaction of the free 2-*o*-royl-1-naphthoic acid with an excess of ethylmagnesium bromide. The 5-methyl, 10-methyl and 5,10-dimethyl derivatives of 1,2-benzanthracene have been prepared in this way for comparison with the carcinogenically active 5,10-dimethylene derivative (cholanthrene). Preliminary results of biological tests indicate that 5,10-dimethyl-1,2-benzanthracene has cancer-producing properties and is comparable in potency with methylcholanthrene, cholanthrene and 3,4-benzpyrene.

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The Synthesis of Phenanthrene and Hydrophenanthrene Derivatives. VII. 5,9-Dimethoxy-1',3'-diketo-1,2-cyclopentenophenanthrene

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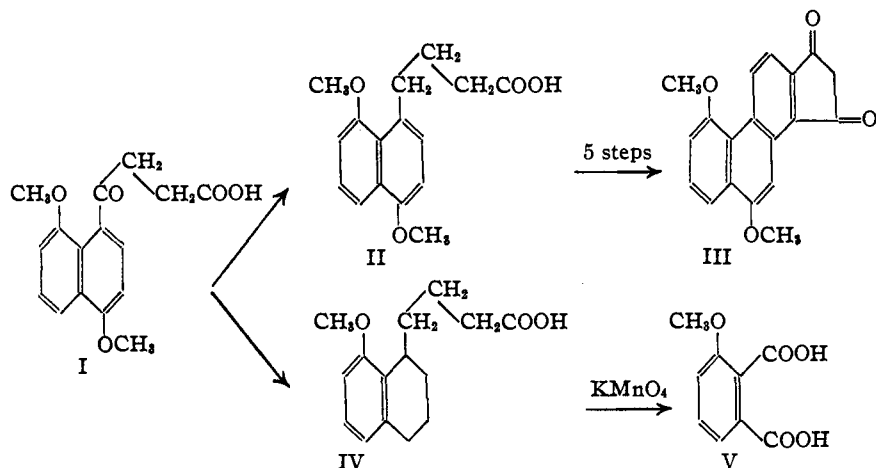
In continuation of other work^{1,2} it seemed desirable to prepare for bio-assay a methoxylated derivative of the previously described 1',3'-diketo-1,2-cyclopentenophenanthrene.² It was thought that the keto acid I would afford a convenient starting point for the synthesis of such a compound, but, although this acid was obtained in nearly quantitative yield by the condensation of 1,5-dimethoxynaphthalene with succinic anhydride, an unexpected difficulty was encountered

(1) Part IV. Fieser and Hershberg, *THIS JOURNAL*, **58**, 2314 (1936).

(2) Part VI. Fieser, M. Fieser and Hershberg, *ibid.*, **58**, 2322 (1936).

in the reduction of the substance with amalgamated zinc and hydrochloric acid, using toluene with or without the addition of acetic acid.³ Considerable resinification occurred and the desired product of normal reduction (II) was isolated in only 20-25% yield from the distillable material present, although it crystallized well and could be separated readily from more soluble substances. The acid was converted successfully by the sequence of reactions previously described² into 5,9-dimethoxy-1',3'-diketo-1,2-cyclopentenophenanthrene (III), although an unexpected

(3) Martin, *ibid.*, **58**, 1438 (1936).



ether-interchange necessitated the repetition of some of the steps of the process. On boiling 1,5-dimethoxyphenanthrene - 1,2 - dicarboxylic anhydride with ethyl alcoholic hydrogen chloride for conversion to the corresponding diethyl ester, a methyl \rightarrow ethyl interchange occurred at one of the two methoxyl groups, probably that located at the more reactive 9-position. This was established by the analyses and by the observation that the diketone obtained differed from the true dimethoxy compound (III) subsequently prepared through the corresponding dimethyl ester.

The Clemmensen reduction of methoxylated keto acids has been observed to proceed rather poorly in certain other cases,³ but the present reduction appeared exceptional not only because of the very low yield but because the normal reaction product evidently was accompanied by a considerable amount of monomeric material. In the hope of discovering the nature of the side reaction this material was examined carefully and, after some trials, the principal constituent was isolated in a pure, crystalline condition. The substance is acidic, and from the analyses and properties, and from the conversion of the compound by alkaline oxidation into 3-methoxyphthalic acid (V), it can be assigned the structure of γ -(8-methoxytetralyl-1)-butyric acid (IV). While Haberland⁴ has reported that the 6-substituted isomer, which he prepared synthetically, is smoothly dehydrogenated by sulfur to the corresponding γ -naphthylbutyric acid, the acid IV on similar treatment gave no crystalline products and the formation of butyric acid was indicated by the odor. Selenium, acting on a crude acid fraction

containing IV, gave α -methoxynaphthalene as the only identified product.

The abnormal product of the Clemmensen reduction probably is formed as a result of the primary addition of hydrogen to the conjugated system formed by the carbonyl group and the nuclear double linkages, the elimination of methyl alcohol and the

complete saturation of the hydro-aromatic ring occurring at some stage of the process. The mechanism is still obscure. Boiling hydrochloric acid alone slowly attacks the keto acid I with cleavage to 1,5-dimethoxynaphthalene, and consequently it is not likely that the abnormal reduction proceeds through a partially demethylated intermediate. There are no indications that a similar side reaction takes place to an appreciable extent even with similarly constituted compounds. β -*p*-Methoxybenzoylpropionic acid and β -(4-methoxy-1-naphthoyl)-propionic acid give the normal reduction products in 85% and 53% yields,³ and the by-products are resinous. The reduction of β -(2,6-dimethoxy-1-naphthoyl)-propionic acid was investigated but no by-product comparable with IV was discovered. In view of these observations it is hardly possible to define any general features of structure responsible for the abnormal hydrogenating action noted in this one example of the Clemmensen reduction.

Experimental Part⁵

β -(1,5-Dimethoxy-4-naphthoyl)-propionic Acid.—1,5-Dimethoxynaphthalene was prepared conveniently by methylating the technical dihydroxy compound, distilling the product at 25 mm., and crystallizing the ether from glacial acetic acid. Colorless material melting at 178–180° was obtained in 65–70% yield by weight. A solution of 0.4 mole of the ether and 0.41 mole of succinic anhydride in 400 cc. of tetrachloroethane and 80 cc. of nitrobenzene was cooled and kept at 0 to 5° while adding 0.85 mole of aluminum chloride. After standing at 0° for forty hours, the red-brown solution was poured onto ice and 100 cc. of concentrated hydrochloric acid, the solvent was removed with steam, and the product was precipitated from a sodium carbonate solution after clarification. A pale brown

(5) All melting points are corrected. Analyses by Mrs. G. M. Wellwood.

(4) Haberland, *Ber.*, 69, 1380 (1936).

product, m. p. 168–170°, was obtained in 93% yield. Using three equivalents of aluminum chloride instead of two, the yield of material, m. p. 172–175°, was 98%. Crystallized twice from benzene, the acid formed clusters of small, colorless leaflets, m. p. 175–176°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 66.64; H, 5.59. Found: C, 66.33; H, 5.30.

The ethyl ester, obtained in 87% yield by the Fischer method, distilled at 200–210° at about 7 microns without decomposition and separated from ether–petroleum ether as lustrous leaflets, m. p. 53–53.5°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 68.31; H, 6.39. Found: C, 68.06; H, 5.82.

Clemmensen Reduction.—In a typical experiment 20 g. of β -(1,5-dimethoxy-4-naphthyl)-propionic acid was suspended in a mixture of 125 g. of amalgamated zinc, 100 cc. of concentrated hydrochloric acid, 50 cc. of water, 75 cc. of toluene and 5 cc. of glacial acetic acid. The keto acid dissolved after refluxing the mixture for about two hours; the boiling was continued for a total of twenty-five hours, during which time 100 cc. more acid was added in portions. The toluene layer was separated after some cooling and the aqueous layer was diluted and extracted with benzene. After washing the hydrocarbon solution with water, 25 cc. of 6 *N* sodium hydroxide and 50 cc. of water were added, together with 0.5 g. of sodium hydrosulfite, and the solvent was removed with steam. For remethylation the alkaline solution was treated with 13 cc. of dimethyl sulfate, and the solution was then acidified. The crude acid which precipitated was dried in vacuum in a distilling flask and distilled at 3 mm. There was obtained at 200–240° 13.5–14.5 g. of a colorless distillate which partially solidified in the receiver, and a considerable amount of resinous material was left as a residue. The distillate was triturated with about 50 cc. of ligroin, which dissolved some of the oil and left a somewhat oily solid. On dissolving this material in 35 cc. of benzene and adding an equal volume of ligroin there was deposited on cooling 3.9–4.8 g. (20–25%) of γ -(1,5-dimethoxy-4-naphthyl)-butyric acid in a nearly pure condition, m. p. 152–154°. Very little of this acid appeared to be left in the ligroin or benzene–ligroin mother liquors while the by-product was isolated from both sources, as described below.

In other experiments the conditions were varied by doubling the time of refluxing, by using as much as 20 cc. of acetic acid, by substituting 50 cc. of methyl alcohol for this solvent, or by omitting a water-miscible solvent, but there was no material change in the total amount of distillable product or in the yield of the easily isolated normal reduction product. The results also were essentially the same when the ethyl ester of the keto acid was employed.

γ -(1,5-Dimethoxy-4-naphthyl)-butyric Acid (II).—Purified by crystallization from benzene, the acid formed small, glistening, colorless blades, m. p. 154–154.5°.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.07; H, 6.57. Found: C, 69.93; H, 6.95.

The methyl ester, obtained in 94% yield, formed large thin plates from methyl alcohol, m. p. 65–65.5°.

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.78; H, 7.01. Found: C, 70.72; H, 7.06.

The ethyl ester (90% yield), b. p. 201–203° (1 mm.), crystallized as thin plates, m. p. 47–47.5°.

γ -(8-Methoxytetralyl-1)-butyric Acid (IV).—This by-product of the Clemmensen reduction was first isolated from the benzene mother liquors remaining after the crystallization of the normal product II resulting from 50 g. of the keto acid. The solution was concentrated to a small volume and diluted with ligroin, and on standing 12 g. of crystalline material separated. After two crystallizations from ligroin, in which it is moderately soluble even when pure, the acid was obtained as thick, colorless plates, m. p. 74.5–75.5°.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 72.52; H, 8.14. Found: C, 72.56; H, 8.24.

In earlier experiments the mother liquor remaining after triturating the crude distillate with ligroin was evaporated and the residual oil was fractionally distilled. A fraction taken at 183–184° (1 mm.) apparently contained a considerable amount of the above acid along with other substances (found: C, 73.63; H, 8.47), for on standing for several weeks it partially crystallized, and the solid material after purification was identical with the substance described above.

Attempts to dehydrogenate the tetralin derivative with sulfur at temperatures up to 230° were unsuccessful. No crystalline products were isolated and the formation of butyric acid was evident from the odor. Dehydrogenation with selenium was tried only with a liquid fraction of the crude acid, b. p. 203–204° (3 mm.). Considerable butyric acid was formed, and there was isolated after demethylation a small amount of a substance identified as α -naphthol. At a time when the identity was still in doubt, 1-methyl-4-methoxynaphthalene, b. p. 164.5–165° (21 mm.) (found: C, 83.55; H, 6.88) was prepared for comparison; its picrate forms red needles from alcohol, m. p. 148–149° (found: N, 10.61).

Evidence of the structure of the acid IV was obtained by exhaustive oxidation of the substance in dilute alkaline solution with potassium permanganate (steam-bath). The manganese dioxide was removed by centrifugation and on acidifying the filtrate a clear solution resulted. (When the oxidation is incomplete a gummy precipitate appears.) The solution was extracted with ether in a continuous extractor, and the residue remaining on evaporation of the ether was sublimed in vacuum and then extracted with water in order to remove oxalic acid. On twice crystallizing the residue from ether, elongated prismatic needles softening at 155° and melting at 160–161° were obtained. The substance did not depress the melting point of 3-methoxyphthalic anhydride prepared from 3-nitrophthalic acid.

5,9-Dimethoxy-3,4-dihydrophenanthrene-1,2-dicarboxylic Anhydride.—Ethyl γ -(1,5-dimethoxy-4-naphthyl)-butyrate (14.2 g.) was condensed with ethyl oxalate in the presence of potassium ethylate, following the standard procedure,¹ and the crude oxalyl derivative obtained by acidification and extraction was warmed on the steam-bath with 30 cc. of 70% sulfuric acid and then with 300 cc. of 78% acid. After one to two hours the at first oily product of cyclization became completely solid. After cooling it was collected and washed with acid, water and alcohol. The crude product (6.5 g.) gave satisfactory material on

one crystallization from 100 cc. of glacial acetic acid; yield 5.3 g. (36%), m. p. 227-230°. Recrystallized from the same solvent, the anhydride formed carmine-colored needles, m. p. 231-232°.

Anal. Calcd. for $C_{18}H_{14}O_8$: C, 69.66; H, 4.55. Found: C, 69.69; H, 4.62.

Incidentally it was noted that the ester condensation proceeded less satisfactorily using the methyl ester of the starting material (II) and ethyl oxalate. Using methyl oxalate the solubility of the potassium methylate addition compound was so slight that no appreciable reaction occurred on adding the ester of II.

5,9 - Dimethoxyphenanthrene - 1,2 - dicarboxylic Anhydride.—A mixture of 500 mg. of the unsaturated red anhydride and 55 mg. of sulfur was heated at 250-300° for three minutes and the product was distilled at 1 mm. and crystallized from glacial acetic acid. It formed cottony clusters of fine yellow needles, m. p. 288-289°, yield 430 mg. (85%). Recrystallized from dioxane the compound melted at 289-290°.

Anal. Calcd. for $C_{18}H_{12}O_8$: C, 70.11; H, 3.93. Found: C, 69.98; H, 4.24.

Dimethyl 5,9 - Dimethoxy - 3,4 - dihydrophenanthrene - 1,2 - dicarboxylate.—The ester was obtained in 72% yield by refluxing the corresponding anhydride with methyl alcohol saturated with hydrogen chloride for two days. It separated from benzene-ligroin as long, greenish-yellow prisms melting at 151-153° and turning red during the process.

Anal. Calcd. for $C_{20}H_{20}O_8$: C, 67.38; H, 5.68. Found: C, 67.41; H, 5.98.

Dimethyl 5,9 - Dimethoxyphenanthrene - 1,2 - dicarboxylate.—The unsaturated ester described immediately above (500 mg.) was dehydrogenated with sulfur (45 mg.) as described for the anhydride; yield 82%. Recrystallized from methyl alcohol, it formed light greenish-yellow prisms, m. p. 133-134°.

Anal. Calcd. for $C_{20}H_{18}O_8$: C, 67.78; H, 5.12. Found: C, 67.52; H, 5.23.

5,9 - Dimethoxy - 1',3' - diketo - 1,2 - cyclopentenophenanthrene (III).—The above ester (1.15 g.) was refluxed with 8 cc. of ethyl acetate and 0.5 g. of sodium for two hours, and then 5 cc. of ethyl acetate and 0.3 g. of sodium were added and the refluxing was continued for four hours longer. A yellow sodium derivative separated during the process, and after adding 50 cc. of dry ether to the cooled mixture this was collected; additional material was recovered from the ethereal filtrate. Decarboxylation to the diketone was effected by boiling the sodium derivative with dilute hydrochloric acid for a few minutes and the product was crystallized from dioxane; yield 0.56 g. (58%). The fully purified material formed deep yellow needles which softened at about 265° and melted at 281-283° with decomposition.

Anal. Calcd. for $C_{18}H_{14}O_4$: C, 74.49; H, 4.61. Found: C, 74.47; H, 4.91.

A Case of Ether-Interchange.—In an early experiment 5,9-dimethoxyphenanthrene-1,2-dicarboxylic anhydride

(3.75 g.) was refluxed for twenty-four hours with 150 cc. of ethyl alcohol saturated with hydrogen chloride, in the expectation of obtaining the corresponding diethyl ester. The crude product (4.29 g.) contained a persistent yellow impurity which was removed after six crystallizations from methyl alcohol, and the product was obtained as thick, colorless needles, m. p. 109.5-110°. Analysis indicated that one of the two phenolic ether groups had been transformed from methoxyl to ethoxyl in the course of the esterification and that the substance obtained is 5(9)-methoxy-9(5)-ethoxy-1,2-dicarbethoxyphenanthrene.

Anal. Calcd. for $C_{28}H_{24}O_6$: C, 69.67; H, 6.11. Found: C, 69.59, 69.71; H, 6.28, 6.02.

This conclusion was confirmed by conversion of the ester into a phenanthrindanedione as above, for the product (yield 81%) differed from the dimethoxy compound (III) already described and had the composition of 5(9)-methoxy - 9(5) - ethoxy - 1',3' - diketo - 1,2 - cyclopentenophenanthrene. The substance crystallized from dioxane-alcohol as fine, fluffy, yellow needles, m. p. 207-208°.

Anal. Calcd. for $C_{20}H_{16}O_4$: C, 74.98; H, 5.03. Found: C, 74.61; H, 4.83.

β -(2,6-Dimethoxy-1-naphthoyl)-propionic Acid.—Prepared as above by the Friedel and Crafts reaction in 82% yield, this acid crystallized from benzene as colorless needles which became opaque on drying, m. p. 156-156.5°.

Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.64; H, 5.59. Found: C, 66.40; H, 5.83.

γ - (2,6 - Dimethoxy - 1 - naphthyl) - propionic Acid.—Clemmensen reduction of 34 g. of the above keto acid by Martin's procedure³ gave, after remethylation and vacuum distillation, 17.5 g. of crude, solid reduction product, the residue being resinous. Crystallization from benzene gave, in the first crop, 11 g. of the normal reduction product in a nearly pure condition, and evaporation of the mother liquor yielded further crops of the same substance. No trace of a by-product comparable with that obtained in the other series was observed. The acid formed needles from benzene, m. p. 122-124°.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.04; H, 6.61. Found: C, 70.25; H, 6.92.

Summary

The diketone mentioned in the title was synthesized by standard methods and in the course of the work an interesting side reaction was observed to occur in the reduction of β -(1,5-dimethoxy-4-naphthoyl)-propionic acid by the Clemmensen method. In the formation of the abnormal product the ketonic group is reduced as usual, but the aromatic ring to which it is attached is hydrogenated in the course of the reaction and a methoxyl group in the para position is eliminated as well.

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