

phorquinone to 2,2,3-trimethylcyclohexan-4-one-1-carboxylic acid is another case where it has recently been established that the product resulting from migration to the pinane system is not obtained.<sup>6</sup>

### Experimental<sup>7</sup>

Camphenilone (V) was prepared by the method of Snitter<sup>8</sup> from camphene<sup>9</sup>; m. p. 36–37°, b. p. 191–193°.

Rearrangement of Camphenilone.—The fate of V under a variety of conditions is summarized in Table I.

TABLE I

Reagent	Temp., °C.	Time	Volatile, %	Recov. V, %	VI isolated, %
H <sub>2</sub> SO <sub>4</sub>	95–100	1 hr.	26	17	..
H <sub>2</sub> SO <sub>4</sub>	110	20 min.	15	7.5	7.5
H <sub>2</sub> SO <sub>4</sub>	120	1 hr.	18	2	14.5
Fum. sul.	R. T.	2 days	5	5	..
Ac <sub>2</sub> O					

The best conditions are as follows: Sulfuric acid (40 ml.) was heated to 65° in a 3-neck, 200-ml. r. b. flask with stirrer, thermometer and exit tube for sulfur dioxide. V (13.8 g., 0.1 mole) was added all at once. The temperature rose to 75°, and there was appreciable darkening. The mixture was then heated to maintain a temperature of 110–120° for one hour, during which time there was a vigorous evolution of sulfur dioxide and considerable charring. After cooling to room temperature, the con-

tents of the flask were poured into 250 ml. of water and steam distilled. The distillate was extracted three times with ether, the ethereal solution washed with 1 N sodium hydroxide, dried and concentrated. The yield of crude product was 2.50 g. (18.5%). Distillation afforded pure VI, b. p. 221°,  $n_D^{20}$  1.5330.

A solution of 0.5 g. of the crude product in dilute ethanol was treated with semicarbazide hydrochloride and sodium acetate on the steam-bath. On cooling, *p*-methylacetophenone semicarbazone crystallized in 80% of the theoretical yield, m. p. 204.5–205.5°. There was no depression of the m. p. of an authentic sample.

The mother liquors on standing overnight yielded a further crop of crystals (10%) which was largely camphenilone semicarbazone, m. p. 210–217°. Recrystallization gave camphenilone semicarbazone, m. p. and mixed m. p. 222–224°. <sup>11</sup>

Oxidation to *p*-Toluic Acid.—One gram of crude VI was treated with excess sodium hypobromite at room temperature. After destroying the excess hypobromite, the solution was steam distilled to remove a small amount of camphenilone and acidified with sulfuric acid. The precipitate which formed was filtered off and sublimed to yield 0.6 g. of *p*-toluic acid, m. p. and mixed m. p. 179–180°. <sup>12</sup> Various fractions of the sublimate showed no difference in m. p. behavior.

### Summary

Camphenilone rearranges to *p*-methylacetophenone when heated with concentrated sulfuric acid. A possible reaction mechanism is discussed.

(6) Chakravarti, *J. Chem. Soc.*, 1565 (1947).

(7) Analyses by the Micro Analytical Laboratories of The University of California. Melting points are corrected.

(8) Snitter, *Bull. Inst. Pin.*, 178 (1933) (*C. A.*, **28**, 139 (1934)).

(9) Generously supplied by The Glidden Company.

(10) Sorge, *Ber.*, **35**, 1070 (1902).

(11) Jagelki, *ibid.*, **32**, 1503 (1899).

(12) Fischli, *ibid.*, **12**, 615 (1879).

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## The Stobbe Condensation with 6-Methoxy-2-propionyl-naphthalene. A Synthesis of Bisdehydrodoisynolic Acid<sup>1</sup>

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Bisdehydrodoisynolic acid, VI (R = H), which is one of the most potent estrogens known, was discovered by Miescher, Heer and Billeter<sup>3</sup> as a degradation product of the hormone equilenin. In the course of their brilliant study the Swiss workers also effected the total synthesis of this important acid, starting from 1-naphthylamine-6-sulfonic acid (Cleve's acid).<sup>3,4</sup> Since the conversion of the latter substance into the necessary intermediate, *viz.*,  $\beta$ -(6-methoxynaphthyl)-ethyl bromide, is quite laborious,<sup>5</sup> we were prompted to investigate a completely different approach, starting with 6-

methoxy-2-propionyl-naphthalene (I) which is readily available by Friedel-Crafts acylation of  $\beta$ -methoxynaphthalene.<sup>6</sup> The details of this new synthesis, which is depicted in the accompanying flow sheet, are reported herewith.<sup>7</sup>

The Stobbe condensation of the ketone I with diethyl succinate and potassium *t*-butoxide<sup>8</sup> or sodium hydride<sup>9</sup> gave in practically quantitative yield an oily mixture of half-esters which upon catalytic hydrogenation over platinum followed by saponification afforded a mixture which was easily separated into the desired dihydro acid III (R = H) melting at 165° (49% yield) and a crystalline dibasic acid (27% yield), m. p. 172°, which was shown (see below) to be a molecular compound between an unsaturated acid (VII) (R = H) melt-

(1) Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

(2) U. S. Rubber predoctoral fellow, 1948–1949. Present address: Merck and Co., Inc., Rahway, New Jersey.

(3) Miescher, *Helv. Chim. Acta*, **27**, 1727 (1944); Heer, Billeter and Miescher, *ibid.*, **28**, 991, 1342 (1945).

(4) Anner and Miescher, *ibid.*, **29**, 586 (1946).

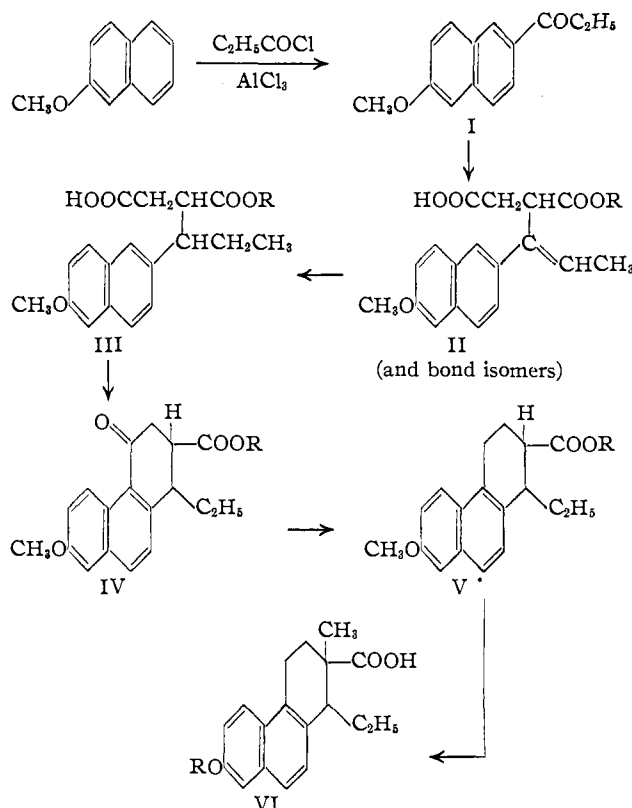
(5) See Wilds and Close, *THIS JOURNAL*, **69**, 3079 (1947), for best procedures.

(6) Haworth and Sheldrick, *J. Chem. Soc.*, 864 (1934).

(7) A preliminary account of this work appears in *THIS JOURNAL*, **70**, 2612 (1948).

(8) Cf. Johnson, Petersen and Schneider, *ibid.*, **69**, 74 (1947).

(9) Carried out by Guido H. Daub according to the procedure of Daub and Johnson, *ibid.*, **70**, 418 (1948).



ing at  $154^\circ$  and a second lower-melting dihydro acid apparently the diastereoisomeric form of the  $165^\circ$  acid III ( $R = H$ ). Reduction of the molecular compound with nickel-aluminum alloy and alkali,<sup>10</sup> gave additional  $165^\circ$  dihydro acid III which evidently arose from the  $154^\circ$  unsaturated acid component of the molecular compound. The resistance of the  $154^\circ$  acid to catalytic hydrogenation, coupled with its susceptibility to chemical reduction represents behavior consistent with the alkylidenesuccinic acid structure VII ( $R = H$ ).<sup>11,12</sup> Further evidence for this structure is given below. The  $165^\circ$  dihydro acid III produced by catalytic hydrogenation evidently was formed largely from the unsaturated ester having the alkenylsuccinic acid structure II ( $R = C_2H_5$ ).<sup>11</sup> The latter was expected to be the preponderant product of the Stobbe condensation with an ethyl aryl ketone<sup>13</sup> and the corresponding dibasic acid II ( $R = H$ ), m. p.  $166^\circ$ , could indeed be isolated as the main product on saponification of the half-ester mixture. The pure acid, moreover, absorbed hydrogen com-

(10) Cf. Papa, Schwenk and Whitman, *J. Org. Chem.*, **7**, 587 (1942).

(11) In our experience the ethylenic bond of alkylidenesuccinic acids having no  $\gamma$ -hydrogen atoms, is relatively resistant to catalytic hydrogenation.

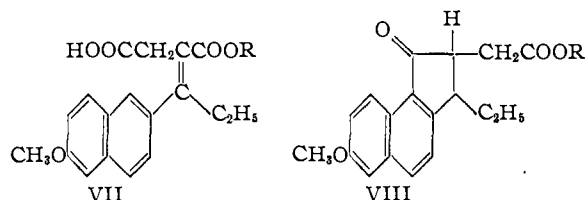
(12) Stobbe has found that alkylidenesuccinic acids but not alkenylsuccinic acids (like II) are reduced by sodium amalgam; see for example Stobbe, *Ann.*, **308**, 114 (1899).

(13) The ratio of alkenyl to alkylidenesuccinic acids produced from propiophenone for example is about 9 to 1; Stobbe, *Ann.*, **321**, 83, 105 (1902).

paratively readily giving the  $165^\circ$  dihydro acid III in good yield.

The  $165^\circ$  acid III could be cyclized with sulfuric acid,<sup>14</sup> or better *via* the anhydride with aluminum chloride in nitrobenzene.<sup>15</sup> The best results were realized with the latter method when nitromethane was used in place of nitrobenzene. In addition to the expected keto acid, IV ( $R = H$ ), m. p.  $216^\circ$ , (isolated in about 20% yield), an isomeric substance, m. p.  $151^\circ$ , was obtained in 55% yield (crude) which proved to be the product, VIII, of five-membered ring closure. This was indeed unexpected and constitutes an exception to the observation of v. Braun that in similar instances the six- is formed to the exclusion of the five-membered ring.<sup>16</sup> The course of the present cyclization may possibly be explained by a greater steric hindrance (by the 8-position of the naphthalene nucleus) toward the expected ring closure.

The  $216^\circ$  keto acid (IV,  $R = H$ ) was hydrogenated over palladium-charcoal catalyst in the presence of a trace of perchloric acid,<sup>17</sup> and the resulting crystalline acid V ( $R = H$ ) esterified with diazomethane and methylated with sodium triphenylmethyl and methyl iodide.<sup>18</sup> Saponification of the product followed by crystallization gave racemic  $\alpha$ -bisdehydrodoisynolic acid methyl ether, VI ( $R = CH_3$ ) in 55% over-all yield from IV ( $R = H$ ). The mother liquor yielded a small amount of the diastereoisomeric racemic  $\beta$ -bisdehydrodoisynolic acid methyl ether, m. p.  $204^\circ$ . The identity of the  $\alpha$ -isomer was ascertained by comparison of the free acid and the crystalline methyl ester with authentic specimens derived from material synthesized by the Swiss method and kindly supplied by Dr. C. R. Scholz of Ciba Pharmaceutical Products. Bioassays kindly performed by Drs. R. K. Meyer and E. G. Shipley of the University of Wisconsin Zoology Department showed our specimen to have the same order of estrogenic activity as the Ciba material.



The structure of the abnormal cyclization product (VIII,  $R = H$ ) evolved from the following considerations. When the synthetic sequence (IV $\rightarrow$ VI) described above for the  $216^\circ$  keto acid was applied to the  $151^\circ$  isomer, an intractable

(14) Cf. Robinson and Thompson, *J. Chem. Soc.*, 2009 (1938).

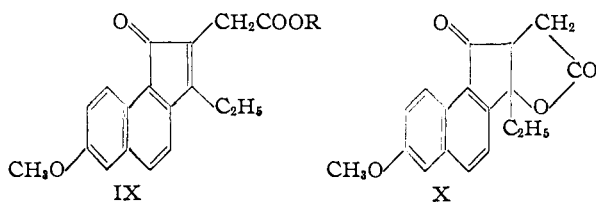
(15) Cf. Cook and Robinson, *ibid.*, 505 (1938).

(16) See Johnson in Adams, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, pp. 116-118.

(17) Cf. Rosenmund and Karg, *Ber.*, **75**, 1850 (1942).

(18) Cf. Hogg, *THIS JOURNAL*, **70**, 161 (1948).

product was obtained from which neither  $\alpha$ - nor  $\beta$ -bisdehydrodoisynolic acid could be isolated, thus suggesting that the keto acid in question was not the diastereoisomeric form of the 216° keto acid (IV, R = H). That the ring had actually closed into the 1-position, however, was suggested by the similarity of the ultraviolet absorption spectra of the two keto acids (see Fig. 1), and was proved conclusively by nitric acid oxidation of the 151° isomer to give benzene-1,2,3,4-tetracarboxylic acid. That the difference between the two keto acids was structural and not stereochemical was suggested, moreover, by the fact that the 151° keto acid did not form a semicarbazone at all under conditions which produced the derivative in 73% yield from IV (R = H), a behavior which is consistent with the more hindered ketone structure VIII for the former substance. Further structural proof was afforded by formation of the 151° keto acid by catalytic hydrogenation of the red benzindoneacetic ester IX which was prepared in low yield by cyclization of the crude mixture of half-esters from the Stobbe condensation with zinc chloride, acetic acid and acetic anhydride as in a related series.<sup>19</sup> The benzindoneacetic ester IX probably arises from the alkylidenesuccinic half-ester with Ar/COOC<sub>2</sub>H<sub>5</sub> *cis*, namely, XI (R = C<sub>2</sub>H<sub>5</sub>), the cyclization involving an ester exchange as proved in a related series.<sup>20</sup> The corresponding dibasic acid XI (R = H), m. p. 172°, has indeed been isolated in low yield from the mixture of acids produced by saponification of the crude mixture of half-esters, and on treatment with hydrogen fluoride it was converted in excellent yield into the lactone X, a behavior which is consistent with the configuration XI (R = H) by analogy to a related series.<sup>19</sup> The relationship between the benzindoneacetic ester IX and the 172° acid was established by conversion of the former into the lactone X with alcoholic hydrogen chloride.



A third keto acid, m. p. 200°, was isolated in very low yield from the residues of the cyclization of the 165° dihydro acid III described above. This substance was isomeric with the main products IV (R = H) and VIII (R = H) of the cyclization. It formed a semicarbazone readily, but was not diastereoisomeric with the keto

(19) Johnson and Goldman, *THIS JOURNAL*, **66**, 1030 (1944).

(20) Johnson and Goldman, *ibid.*, **67**, 430 (1945).

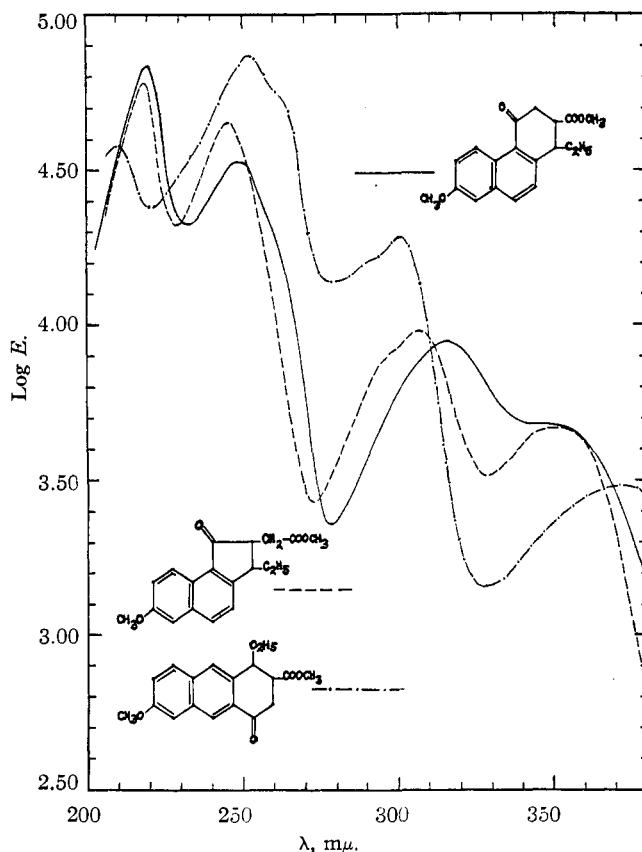
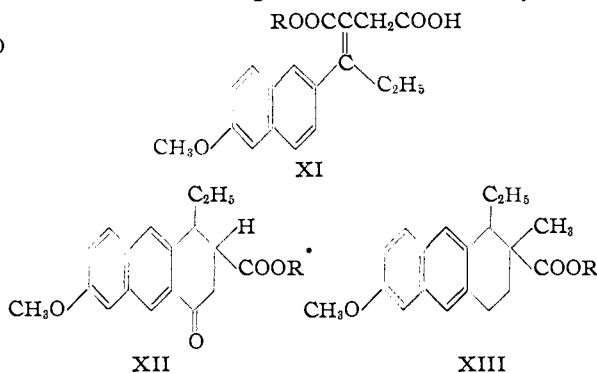


Fig. 1. —, IV (R = CH<sub>3</sub>); ----, VIII (R = CH<sub>3</sub>); - · - ·, XII (R = CH<sub>3</sub>).

acid IV as suggested by its dissimilar ultraviolet absorption spectrum (Fig. 1). Application of the synthetic sequence described above for the conversion of IV into VI (R = CH<sub>3</sub>) gave neither the  $\alpha$ - nor  $\beta$ -forms of VI (R = CH<sub>3</sub>), but instead, a new structural isomer of bisdehydrodoisynolic acid methyl ether which undoubtedly corresponds to XIII (R = H).<sup>21</sup> The 200° keto acid, therefore, is probably the product XII (R = H) of linear, six-membered ring closure. The alternate structure arising from five-membered cycliza-



(21) Preliminary tests by Drs. R. K. Meyer and E. G. Shipley indicate that this material has considerable estrogenic activity.

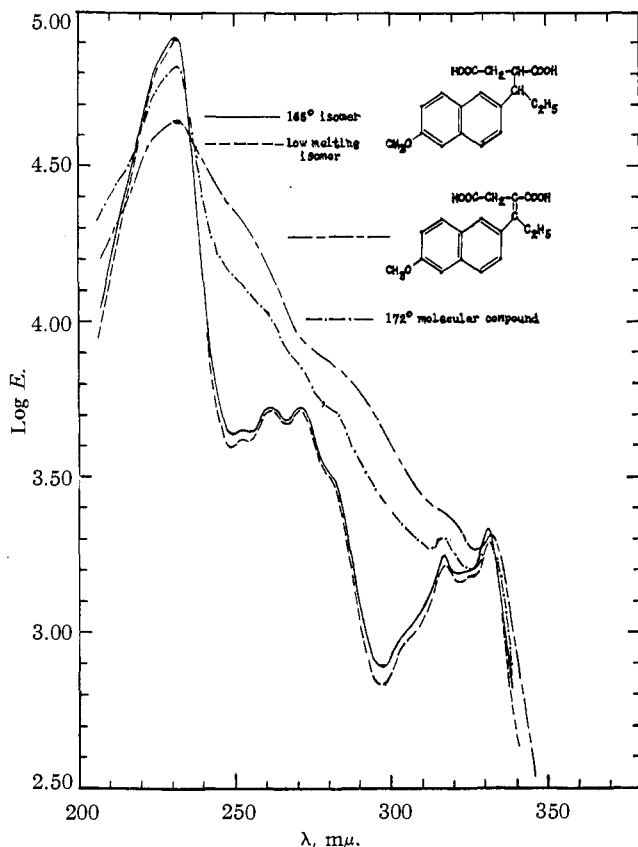


Fig. 2.———, high-melting isomer of III ( $R = H$ ); - - - - -, low-melting isomer of III ( $R = H$ ); - · - · - ·, VII ( $R = H$ ); - - - - -, molecular compound.

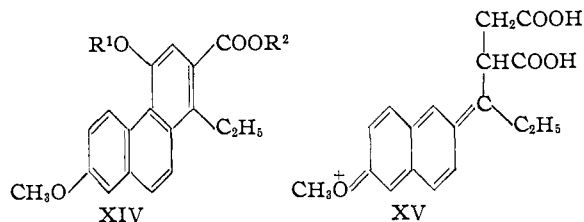
tion is reasonably precluded on the basis of the success of the methylation sequence XII  $\rightarrow$  XIII (*cf.* the failure of the keto acid VIII in this sequence considered above).

Cyclization of the crude mixture of half-esters from the Stobbe condensation with sodium acetate in acetic anhydride and acetic acid gave in 34% yield what is undoubtedly by analogy to a related study,<sup>19</sup> the acetoxyphenanthrenecarboxylate XIV ( $R^1 = \text{COCH}_3$ ,  $R^2 = \text{C}_2\text{H}_5$ ) which must have been formed from the alkylidenesuccinic half-ester VII ( $R = \text{C}_2\text{H}_5$ ) in which Ar/ $\text{COOC}_2\text{H}_5$  is *trans*. The corresponding dibasic acid VII ( $R = H$ ), m. p.  $154^\circ$ , was isolated from the mixture of acids obtained upon saponification of the crude mixture of half-esters, and the configuration was established by conversion to the dimethyl ester with diazomethane, followed by selective saponification to the half-ester VII ( $R = \text{CH}_3$ ) which upon cyclization by the sodium acetate method (see above) gave the acetoxyphenanthrenecarboxylate XIV ( $R^1 = \text{COCH}_3$ ,  $R^2 = \text{CH}_3$ ) in practically quantitative yield. The stereoisomeric  $172^\circ$  dibasic acid (XI,  $R = H$ ), upon treatment by the same sequence, yielded none of this cyclization product, and the molec-

ular compound (containing the  $154^\circ$  dibasic acid) which was obtained from the hydrogenation gave the crude phenanthrol derivative in about 50% yield. The acidic material which resisted cyclization in this last experiment yielded, after saponification, an acid, m. p.  $127\text{--}134^\circ$ , which was not obtained pure, but by analysis and similarity of ultraviolet absorption spectrum with that of the  $165^\circ$  dihydro acid III ( $R = H$ ) (see Fig. 2) appeared to consist largely of the diastereoisomeric form. This same low-melting form of III ( $R = H$ ) was produced in 74% yield by catalytic hydrogenation of the  $172^\circ$  acid XI ( $R = H$ ). When a mixture of approximately equal amounts of the  $127\text{--}134^\circ$  acid (obtained by either of the above methods) and the  $154^\circ$  acid was crystallized, the  $170^\circ$  molecular compound was reproduced in good yield, thus confirming the constitution of this complex.

The ultraviolet absorption spectra of the dibasic acids described above afforded additional evidence for the structures (see Fig. 3). The spectra of the two stereoisomeric alkylidenesuccinic acids VII ( $R = H$ ) and XI ( $R = H$ ) melting at  $154^\circ$  and  $172^\circ$  respectively are practically identical and quite unlike that of the alkenylsuccinic acid II ( $R = H$ ) melting at  $166^\circ$ . The curve for the molecular compound, moreover, is almost identical with that calculated from the spectra of the  $154^\circ$  acid and of the  $127\text{--}134^\circ$  dihydro acid III ( $R = H$ ) on the basis of an equimolar mixture of the two (Fig. 4).

A discovery of particular interest was the fact that the  $154^\circ$  unsaturated acid VII ( $R = H$ ) on treatment with anhydrous hydrogen fluoride gave the same lactone X that was formed from the  $172^\circ$  unsaturated acid XI ( $R = H$ ), but in significantly lower yield. This abnormal ring



closure must be induced by the 6-methoxy group, since such cyclization of an analog of VII ( $R = H$ ) lacking this substituent gave the expected phenanthrolcarboxylic acid in good (82%) yield and none of the benzindone lactone.<sup>19</sup> This behavior is reasonable on theoretical grounds, the acid-catalyzed nature of the reaction suggesting a carbonium ion mechanism. A significant contribution of the form XV to the electronic state of the ion would destroy the stereoselectivity of the reaction, and with all other factors equal, five- would probably take precedence over six-

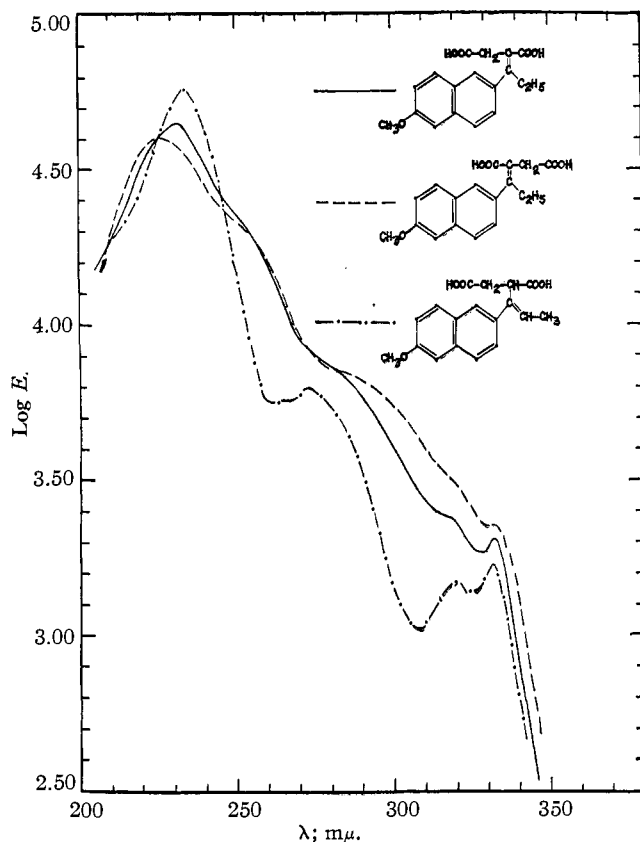


Fig. 3. —, VII (R = H); - - - - - , XI (R = H); - · - · - · , II (R = H).

membered ring closure under acidic conditions as demonstrated in the diphenylitaconic acid series.<sup>20</sup> A decision with regard to the exact course of the conversion of the 154° acid to the lactone X cannot be made on the existing evidence. The two more obvious hypotheses involve (1) intermediary conversion of the 154 into the 172° acid, or (2) lactonization preceding cyclization.

#### Experimental Part<sup>22,23</sup>

2-Propionyl-6-methoxynaphthalene was prepared by the procedure of Haworth and Sheldrick<sup>6</sup> with some modifications. A solution of 212.2 g. of  $\beta$ -methoxynaphthalene,<sup>24</sup> m. p. 72–73°, in 336 ml. of dry nitrobenzene was added dropwise with stirring to a chilled (0–2°) solution of 224 g. of anhydrous aluminum chloride in 1 l. of nitrobenzene. This mixture was then maintained at –3° while 143 g. of propionyl chloride was added dropwise with stirring, and the resulting dark brown solution was kept at 0° for ninety-six hours. This mixture which had turned to a dark green color was poured onto 4 kg. of ice and 450 ml. of concentrated hydrochloric acid, and steam distilled to remove the nitrobenzene. The organic residue was taken up in benzene and washed thoroughly first with

(22) Unless otherwise stated, all melting points were determined on a micro-melting point block and are corrected for stem exposure.

(23) We are indebted to Virginia D. Miller and Richard H. Hunt for many of the microanalyses reported herein.

(24) Prepared from  $\beta$ -naphthol either by the action of dimethyl sulfate and alkali or by the method of Stork, THIS JOURNAL, 69, 576 (1947).

5% sodium hydroxide, then with 6 N hydrochloric acid, followed by water and finally dried over anhydrous sodium sulfate. Evaporation of the solvent and distillation in a two-bulb flask gave 259.5 g. of pale yellow distillate, b. p. 145–162° (0.05–0.06 mm.), which crystallized on standing, m. p. 97.5–107° with softening at 94°. A single crystallization from methanol gave 189 g. (66%) of colorless needles, m. p. 110.5–111.5° (reported,<sup>6</sup> 109°). An additional 11.3 g. of satisfactory material could be obtained from the mother liquor, raising the yield to 70%.

When the aqueous acidic layer was separated from the nitrobenzene solution and discarded before steam distillation, the yield dropped to 43% of material melting at 109–111°.

**The Stobbe Condensation with 2-Propionyl-6-methoxynaphthalene.**—To a solution of 42.5 g. of potassium in 1100 ml. of dry *t*-butyl alcohol was added 244 g. of diethyl succinate and 201.5 g. of the ketone.<sup>8</sup> The mixture was boiled under reflux in an atmosphere of nitrogen for forty minutes, cooled, 610 ml. of 2 N hydrochloric acid added and most of the alcohol removed by distillation at reduced pressure. The residue was extracted with ether, and the ether extracts washed with six 200-ml. portions of 5% sodium carbonate solution. These aqueous solutions were combined, acidified, and the liberated oily half-ester taken up in ether and dried over anhydrous sodium sulfate. Evaporation of the ether gave 321.5 g. (practically quantitative yield, but probably containing some solvent) of viscous yellow-brown oily half-ester mixture which was employed without purification for the remaining steps of the synthesis.

Further extraction of the original ether solution with 5% sodium carbonate yielded an additional 15.3 g. of crude oil which gave an intense color with ferric chloride characteristic of diethyl 1,4-cyclohexanedi-one-2,5-dicarboxylate, the self-condensation product of diethyl succinate. This small fraction was not investigated further.

**Hydrogenation of the Half-Ester Mixture.**—The crude oily condensation product (258.7 g.) described

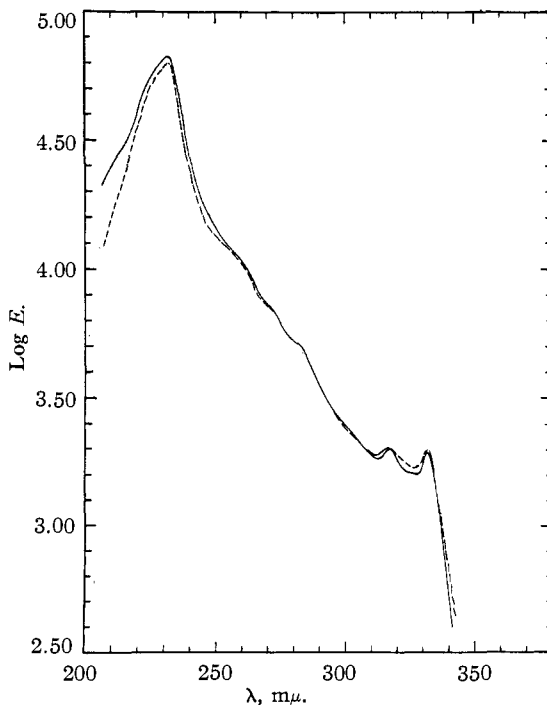


Fig. 4.—172° Molecular compound: —, observed; - - - - -, calculated.

above was hydrogenated in alcohol in three approximately equal portions, about 120 ml. of solvent and 1.0 g. of platinum oxide being used for each batch. Shaking was started at about 32 p. s. i. and the absorption of hydrogen stopped after about nine hours at room temperature, with an uptake of 75–80% of the calculated amount of gas. The combined oily residues obtained upon filtration and evaporation of the alcohol were treated with 1800 ml. of 10% sodium hydroxide. After heating on the steam-bath with stirring for five hours the mixture was cooled and the insoluble salt, which had begun to precipitate during the saponification, was separated by filtration and washed with two 150-ml. portions of cold water. This product amounted to 89 g. and represented the colorless crystalline sodium salt of the molecular compound which is considered below.

The filtrate and washings from the sodium salt were acidified with hydrochloric acid, and the brown oily mixture of organic acids was isolated by ether extraction and after drying (over anhydrous sodium sulfate) was crystallized from ethyl acetate-petroleum ether (60–68°) giving 104.7 g. (44% yield) of 3-carboxy-4-(6-methoxy-2-naphthyl)-caproic acid (III, R = H) as light buff-colored needles, m. p. 163–165° (evolution of gas) with softening at 160°. An additional 11.9 g. of material m. p. 159–161° was obtained from the mother liquor making the total yield 49%. A sample of this acid purified by repeated recrystallization from dilute alcohol was obtained in the form of colorless needles, m. p. 163–165° (evolution of gas).

*Anal.* Calcd. for  $C_{18}H_{20}O_5$ : C, 68.34; H, 6.37. Found: C, 68.30; H, 6.30.

The anhydride prepared by the action of boiling acetyl chloride on the dibasic acid was obtained as a pale yellow glassy oil, b. p. 210–220° (0.05 mm.).

*Anal.* Calcd. for  $C_{18}H_{18}O_4$ : C, 72.47; H, 6.08. Found: C, 72.55; H, 6.36.

**Cyclization of 3-Carboxy-4-(6-methoxy-2-naphthyl)-caproic Acid.** (a) *With Aluminum Chloride in Nitromethane.*—A 50.0-g. sample of the acid III (R = H) was heated under reflux for five hours with 120 ml. of acetyl chloride, and the excess acetyl chloride removed by co-distillation with four 120-ml. portions of dry benzene. The residual anhydride was dissolved in 200 ml. of dry nitromethane and added dropwise with stirring over a period of three and three-quarter hours to a solution of 48.5 g. of aluminum chloride in 200 ml. of nitromethane which was maintained at –16 to –15° throughout the addition with an ice-salt-bath. After stirring for six hours in the cold, the mixture was stored in an ice-salt mixture at –18 to –15° for four days. The mixture was then poured onto 1 kg. of ice and 250 ml. of concentrated hydrochloric acid, about 400 ml. each of ether and ethyl acetate were added to dissolve precipitated material, and the aqueous layer separated and extracted with ether. The combined organic layers were washed with water, and then with three 250-ml. portions of 5% sodium carbonate solution. The combined alkaline extracts were acidified with hydrochloric acid, and the precipitated organic material taken up in chloroform-ethyl acetate. After drying over sodium sulfate the solution was concentrated to about 150 ml. until crystalline material began to separate. The mixture was cooled to room temperature and the tan granular precipitate separated and, without drying, recrystallized directly from alcohol to give 8.09 g. of 1-ethyl-4-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene-2-carboxylic acid (IV, R = H) as pale buff-colored prisms, m. p. 211.5–216.5° with softening at 198°. Additional material amounting to 1.37 g., m. p. 187–214°, was isolated from the two mother liquors as described below, making the total yield 20%. The conversion of this material into  $\alpha$ -bisdehydrodoisynolic acid is described below. Repeated recrystallization from alcohol gave colorless prisms, m. p. 215.5–216.5°.

*Anal.* Calcd. for  $C_{18}H_{18}O_4$ : C, 72.47; H, 6.08. Found: C, 72.31; H, 6.03.

The semicarbazone was obtained in 73% yield by treatment of the keto acid with semicarbazide hydrochloride and pyridine in boiling ethanol for one hour. The derivative was obtained as sparingly soluble buff-colored prisms; and no suitable solvent for recrystallization was found. After washing thoroughly with warm water, it melted at 265–269° (dec.) (uncor.) when placed on hot stage at 258° or at 274–276° (dec.) (uncor.) in a capillary tube when introduced in bath at 250°.

*Anal.* Calcd. for  $C_{18}H_{21}O_4N_3$ : C, 64.21; H, 5.96. Found: C, 64.31; H, 5.92.

The methyl ester obtained with diazomethane was obtained from ether-petroleum ether (60–68°) as colorless prisms, m. p. 129–130°.

*Anal.* Calcd. for  $C_{19}H_{20}O_4$ : C, 73.06; H, 6.45. Found: C, 73.26; H, 6.71.

The original brown filtrate from which the first crystalline product was isolated (see above) was treated with 50 ml. of 60–68° petroleum ether and on standing 25.78 g. (55% yield) of crude 3-ethyl-2'-methoxy-6,7-benz-1-hydrindone-2-acetic acid (VIII, R = H) separated as dark needles, m. p. 143–151° with previous softening. The brown oily residue A obtained by evaporation of the mother liquor amounted to 9.55 g. The crude benzhydrindoneacetic acid was treated with 75 ml. of hot ethyl acetate and all but 1.19 g. of buff-colored granular material dissolved. This insoluble portion (1.19 g.) was combined with the residues (2.44 g.) from the alcohol recrystallization of the isomeric keto acid IV (R = H) (see above) and recrystallized from alcohol to give the additional 1.37 g. of IV (R = H) mentioned above. Evaporation of the mother liquor left a brown oily residue B amounting to 2.29 g.

The pure keto acid VIII (R = H) was obtained in the form of colorless prismatic needles, m. p. 150.5–151.5° after evaporative distillation at 185–195° (0.06 mm.) followed by repeated recrystallization from ethyl acetate-petroleum ether (60–68°).

*Anal.* Calcd. for  $C_{18}H_{18}O_4$ : C, 72.47; H, 6.08. Found: C, 72.67; H, 5.96.

The methyl ester, prepared with diazomethane, was obtained by repeated recrystallization from ether as colorless prisms, m. p. 104–105°.

*Anal.* Calcd. for  $C_{19}H_{20}O_4$ : C, 73.06; H, 6.45. Found: C, 73.03; H, 6.49.

The benzhydrindoneacetic acid was quite resistant to semicarbazone formation, the derivative being obtained in only 8% yield after a heating period of nine hours with semicarbazide hydrochloride and pyridine in ethanol. The crude product consisted of buff-colored prisms, m. p. 213.5–217.5° (dec.) placed on hot stage at 200°, and could not be satisfactorily purified for analysis due to its sparing solubility.

*Anal.* Calcd. for  $C_{18}H_{21}O_4N_3$ : C, 64.21; H, 5.96. Found: C, 62.41; H, 6.03.

The product XII of linear cyclization was isolated from the oily residues A (9.55 g.) and B (2.29 g.) which were combined and treated with 4.425 g. of semicarbazide hydrochloride and 5 ml. of pyridine in 200 ml. of ethanol. After refluxing for one hour the mixture yielded, after concentration, a total of 4.36 g. of crude semicarbazone which was hydrolyzed with concentrated hydrochloric acid at room temperature for twelve hours. The product was treated with excess diazomethane to give 1.92 g. of a crude oily mixture of methyl esters which was adsorbed in benzene solution on a column of activated alumina<sup>25</sup> and eluted with dry benzene followed by benzene containing 15% ether. Examination of the column with ultraviolet light revealed the development of two main bands which were roughly separated in the elution process. The more weakly adsorbed fraction amounted to 0.842 g. of colorless oil which on crystallization from ether-petroleum ether (60–68°) gave 0.672 g. of IV (R = CH<sub>3</sub>) as colorless

(25) A special acid-washed product kindly furnished by Merck and Co., Inc.

prisms, m. p. 127.5–129° with softening at 125.5°, undepressed on admixture with the ester prepared from the pure keto acid described above.

The more strongly adsorbed fraction (0.948 g.) was crystallized from ether–petroleum ether (60–68°) giving 0.651 g. of methyl 1-ethyl-4-keto-6-methoxy-1,2,3,4-tetrahydroanthracene-2-carboxylate (XII, R = CH<sub>3</sub>) as colorless plates, m. p. 127–128°. Repeated recrystallization from the same solvent pair raised the m. p. to 128.3–129.3°. On admixture with the angular isomer IV (R = CH<sub>3</sub>) the m. p. was depressed to 101–120°.

*Anal.* Calcd. for C<sub>19</sub>H<sub>20</sub>O<sub>4</sub>: C, 73.06; H, 6.45. Found: C, 72.96; H, 6.30.

The free acid, 1-ethyl-4-keto-6-methoxy-1,2,3,4-tetrahydroanthracene-2-carboxylic acid (XII, R = H), was prepared directly from the acid mixture obtained by a hydrolysis of the crude semicarbazone fraction isolated as described above. Evaporative distillation at 190–195° (0.02 mm.) followed by repeated recrystallization from ethyl acetate–petroleum ether (60–68°) gave colorless blades, m. p. 199–200°.

*Anal.* Calcd. for C<sub>18</sub>H<sub>18</sub>O<sub>4</sub>: C, 72.47; H, 6.08. Found: C, 72.60; H, 6.09.

The semicarbazone, prepared as described for the angular isomer IV (R = H), was obtained in 97% yield as colorless plates, m. p. 253–256° (dec.) (uncor.) with softening at 250°, when placed on hot stage at 217°. Due to its sparing solubility it was analyzed without recrystallization.

*Anal.* Calcd. for C<sub>19</sub>H<sub>21</sub>O<sub>4</sub>N<sub>3</sub>: C, 64.21; H, 5.96. Found: C, 63.43; H, 6.18.

(b) *With Sulfuric Acid.*—A 0.50-g. sample of the acid III (R = H) was treated with a solution of 5.0 ml. of concentrated sulfuric acid in 1.33 ml. of water as described by Robinson and Thompson.<sup>14</sup> After heating for thirty minutes at steam-bath temperature the mixture was treated with 30 g. of crushed ice and the organic material separated by ether extraction. Evaporation of the ether left 0.330 g. of red-brown oil from which 0.055 g. (12% yield) of crude keto acid IV (R = H), m. p. 201–209° with softening at 170°, was obtained by crystallization from alcohol. Two recrystallizations gave material with the m. p. 215.5–216.5°, undepressed on admixture with the sample of this keto acid described above, part a.

(c) *With Hydrogen Fluoride.*—This reagent did not effect cyclization at room temperature, but when 2.00 g. of the acid III (R = H) was treated with about 75 ml. of anhydrous hydrogen fluoride in a steel bomb at 80° for one and one-half hours, a complex mixture of acids was produced which could not be purified directly. Crystallization of the methyl esters, prepared with diazomethane, from ether gave a first crop of 0.763 g. (39% yield) of the methyl benzhydrindoneacetate, m. p. 103–104°, and a second crop of 0.139 g. (7% yield) of the methyl keto-tetrahydrophenanthrenecarboxylate, m. p. 127.5–129.5°. The identity of these products was confirmed by mixed melting point determination with materials prepared as described above, part a.

(d) *By Other Methods.*—When nitrobenzene was employed in place of nitromethane (part a) with aluminum chloride at 0–5° the crude ketotetrahydrophenanthrenecarboxylic acid was obtained in 8–16% yields, and the benzhydrindoneacetic acid in about 40% yield.

Attempts to effect cyclization of the anhydride with aluminum chloride in carbon disulfide or in ether at 0° failed. The use of boron trifluoride etherate in ether on the anhydride or of phosphorus pentoxide in benzene on the dibasic acid was also unsuccessful.

**Hydrogenation of 1-Ethyl-4-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene-2-carboxylic Acid.**—A suspension of 2.500 g. of pure keto acid IV (R = H), and 0.350 g. of 30% palladium-charcoal<sup>26</sup> in 50 ml. of acetic acid containing 2.0 ml. of 60% perchloric acid,<sup>17</sup> was stirred in the presence of hydrogen at room temperature and atmospheric pressure for eight hours during which the calcu-

lated amount of gas was absorbed. At the end of this period the hydrogenation was slow, but had not stopped completely. Ethyl acetate (30 ml.) was added and the mixture heated to boiling on the steam-bath to dissolve the crystalline suspension. The hot solution was filtered, the catalyst washed with hot ethyl acetate, and the filtrate evaporated in a current of air, water being added to maintain a volume of at least 10–15 ml. After most of the acetic acid was thus removed, the residue was diluted with water and extracted with ethyl acetate. The organic layer was washed thoroughly with water, followed by saturated salt solution, and dried over anhydrous magnesium sulfate. The semi-crystalline residue was recrystallized from acetone to give 1.545 g. of 1-ethyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-2-carboxylic acid (V, R = H) as colorless prisms, m. p. 205–206.5° with softening at 204.5°. An additional 0.479 g. of material, m. p. 201.5–205° with softening at 198°, was obtained from the mother liquor making the total yield 85%. Two additional recrystallizations of the first crop from acetone raised the m. p. to 204–207°.

*Anal.* Calcd. for C<sub>18</sub>H<sub>20</sub>O<sub>3</sub>: C, 76.03; H, 7.09. Found: C, 76.04; H, 6.82.

The methyl ester V (R = CH<sub>3</sub>) was prepared both by the action of diazomethane on the free acid V (R = H) and by catalytic hydrogenation of the methyl keto ester IV (R = H) according to the procedure described above. Material which had been evaporatively distilled at 125–135° (0.02 mm.) and repeatedly recrystallized from ether petroleum ether (60–68°) was obtained as colorless plates, m. p. 101–102°.

*Anal.* Calcd. for C<sub>19</sub>H<sub>22</sub>O<sub>3</sub>: C, 76.48; H, 7.43. Found: C, 76.66; H, 7.59.

**Methylation of Methyl 1-Ethyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-2-carboxylate. The Bisdehydrodoisynolic Acid Methyl Ethers.**—A 1.629-g. sample of the above ester V (R = CH<sub>3</sub>), prepared from 1.545 g. of the acid V (R = H) with diazomethane, was dissolved in 60 ml. of dry ether and treated (nitrogen atmosphere) with 25.5 ml. of 0.428 N sodium triphenylmethyl solution in ether.<sup>27</sup> After thirty minutes at room temperature 5 ml. of methyl iodide was added whereupon the red color of the solution was immediately dispelled and heat was evolved causing the solution to boil gently. Water was then added, and the organic layer was separated, washed with water and the washings were extracted with ether. The yellow oil (5.24 g.) obtained on evaporation of the combined ether solutions was heated under reflux with a solution of 2.5 g. of potassium hydroxide in 50 ml. of alcohol and 2.5 ml. of water for twelve hours. The alcohol was then evaporated in a current of air, and water and ether were added to the semi-crystalline residue. The aqueous layer was separated and the ether layer washed thoroughly with water. The combined aqueous layers were acidified, and the precipitated organic acid taken up in ether and dried over anhydrous magnesium sulfate. Evaporation of the ether gave 1.184 g. of buff-colored granular crystalline solid, m. p. 222.5–224.5° with softening at 135°. The unsaponified material remaining in the ether layer (see above) amounted to 3.98 g. of yellow oil which was re-treated with 60 ml. of 5% alcoholic potassium hydroxide as described above. Additional crude acid amounting to 0.235 g. was thus obtained as colorless granular crystals.

From the combined crude acid fractions a total of 0.905 g. (56% yield) of pure racemic  $\alpha$ -bisdehydrodoisynolic acid methyl ether was obtained as colorless prisms, m. p. 230.5–231.5° (reported,<sup>3</sup> 228–230°), by crystallization from acetone, and evaporative distillation at 175° (0.02 mm.) of the oily residues remaining after no more crystalline crops were obtainable, final purification being effected by recrystallization from acetone. The total yield of material of fair purity, m. p. of all crops above 226°, was 1.04 g. (64%).

The pure acid showed no depression of m. p. on admixture with an authentic specimen of racemic  $\alpha$ -bisdehydro-

(26) Linstead and Thomas, *J. Chem. Soc.*, 1130 (1940).

(27) "Org. Syn.," Coll. Vol. II, 607 (1943).

doisynolic acid methyl ether prepared by the Swiss method. The methyl esters prepared from both samples with diazomethane had the same m. p. (75–76.5°) separately or on admixture.

Evaporative distillation at 175° (0.02 mm.) and repeated recrystallization from ether–petroleum ether of the oily residue from isolation of the  $\alpha$ -isomer, gave in poor yield (about 7%) what appeared to be racemic  $\beta$ -bisdehydroisynolic acid methyl ether, m. p. 203.5–204.3° (reported,<sup>8</sup> 204–206°).

*Anal.* Calcd. for  $C_{19}H_{22}O_3$ : C, 76.48; H, 7.43. Found: C, 76.68; H, 7.53.

In the above methylation experiment the molar ratio of methyl ester to sodium triphenylmethyl was about 1 to 2. When this was changed to a 1 to 1 ratio, the yield fell off markedly: only about 10% of the  $\alpha$ -racemate was isolated and as much as 18% of starting acid was recovered.

**Hydrogenation of Methyl 1-Ethyl-4-keto-6-methoxy-1,2,3,4-tetrahydroanthracene-2-carboxylate.**—A 0.250-g. sample of the ester (described above) was hydrogenated in 15 ml. of acetic acid with 0.100 g. of 30% palladium-charcoal<sup>28</sup> and 0.20 ml. of 60% perchloric acid<sup>17</sup> as described above for the hydrogenation of IV (R = H). The calculated amount of gas was absorbed in two hours, and the neutral brown oily product was purified by evaporative distillation at 135–142° (0.1 mm.) followed by crystallization from ether–petroleum ether (60–68°). A total of 0.172 g. (72% yield) of colorless needles, m. p. 87.5–88.5°, was thus obtained. A single recrystallization from the same solvent pair gave pure methyl 1-ethyl-6-methoxy-1,2,3,4-tetrahydroanthracene-2-carboxylate, m. p. 88.5–89°.

*Anal.* Calcd. for  $C_{19}H_{22}O_3$ : C, 76.48; H, 7.43. Found: C, 76.47; H, 7.51.

**1-Ethyl-2-methyl-6-methoxy-1,2,3,4-tetrahydroanthracene-2-carboxylic Acid (XIII).**—A solution of 0.142 g. of the above ester in 8 ml. of ether was treated with 3.0 ml. of 0.32 *N* sodium triphenylmethyl solution in ether, followed by 1.0 ml. of methyl iodide just as described above for the angular isomer. Saponification of the crude neutral oil (0.557 g.) with 10 ml. of 5% alcoholic potassium hydroxide gave 0.139 g. of colorless oily acid from which a total of 0.068 g. (48% yield) of crude XIII, m. p. 211–214°, was obtained by crystallization from acetone. Recrystallization from acetone gave colorless prisms, m. p. 212.5–215°. The m. p. was depressed to 169–202° on admixture with  $\beta$ -bisdehydroisynolic acid methyl ether.

*Anal.* Calcd. for  $C_{19}H_{22}O_3$ : C, 76.48; H, 7.43. Found: C, 76.48; H, 7.43.

**3-Ethyl-2'-methoxy-6,7-benzhydrindane-2-acetic Acid.**—The hydrogenation of 1.265 g. of the keto acid VIII (R = H) in 30 ml. of acetic acid with 0.402 g. of 30% palladium-charcoal<sup>28</sup> and 1.0 ml. of 60% perchloric acid<sup>17</sup> was carried out as described above for the phenanthrene derivative IV (R = H). The reaction was interrupted after the absorption of the calculated amount of hydrogen, and the crude semi-crystalline product (1.279 g.) was crystallized from acetone giving 0.821 g. (68% yield) of colorless needles, m. p. 182.5–185° with softening at 177.5°. Repeated recrystallization from acetone raised the m. p. to 185–186.3°.

*Anal.* Calcd. for  $C_{18}H_{20}O_3$ : C, 76.03; H, 7.09. Found: C, 75.98; H, 7.16.

The methyl ester, prepared with diazomethane, was obtained from ether–petroleum ether (40–60°) as colorless needles, m. p. 83–83.8°.

*Anal.* Calcd. for  $C_{19}H_{22}O_3$ : C, 76.48; H, 7.43. Found: C, 76.25; H, 7.63.

When the keto ester VIII (R = CH<sub>3</sub>) was hydrogenated as described above for the free acid VIII (R = H), the product was mainly 3-ethyl-2'-methoxy-6,7-benzhydrindane-2-acetic acid instead of the methyl ester. The ester group, therefore, must have hydrolyzed during the process, and this behavior is consistent with the less hindered nature of the carbomethoxy group of formula VIII

(R = CH<sub>3</sub>) as compared with that of formula IV (R = CH<sub>3</sub>) and XII (R = CH<sub>3</sub>).

**Oxidation of 2-Ethyl-2'-methoxy-6,7-benz-1-hydrindone-2-acetic Acid.**—A mixture of 0.50 g. of the keto acid, 1.5 ml. of water and 2.0 ml. of concentrated nitric acid was heated in a sealed tube at 195–205° for sixteen hours and the mixture worked up as described by Campbell, Soffer and Steadman<sup>28</sup> to give 0.203 g. of colorless solid. A portion recrystallized from concentrated nitric acid gave colorless prisms, m. p. 240–243° (dec.) in a sealed capillary when placed in bath at 230°. The reported m. p. for benzene-1,2,3,4-tetracarboxylic acid is 236–238°.<sup>29</sup> The tetramethyl ester, prepared with diazomethane, was obtained after three recrystallizations from methanol as colorless needles, m. p. 129–130° (reported,<sup>29</sup> 131–133°), undepressed on admixture with an authentic specimen of tetramethyl benzene-1,2,3,4-tetracarboxylate, m. p. 127.5–129.5°, kindly furnished by Dr. A. L. Wilds.

**The Products of the Stobbe Condensation.**—The crude oily mixture of half-esters (11.93 g.), produced as described at the beginning of the experimental section, was saponified with 33.1 g. of barium hydroxide octahydrate in 150 ml. each of alcohol and water. The mixture was boiled under reflux for six hours, agitation being achieved by admitting a stream of nitrogen near the bottom of the mixture, thus preventing bumping as the heavy precipitate of barium salts accumulated. These salts were separated from the cooled solution by filtration, and washed with 50% alcohol. The filtrate upon acidification yielded only 0.418 g. of intractable brown gum which was not investigated. Decomposition of the barium salts with dilute hydrochloric acid gave 10.2 g. (93% yield) of an oily mixture of dibasic acids. Crystallization from ethyl acetate–petroleum ether (60–68°) gave a first crop amounting to 5.48 g. (50% yield) of colorless crystals, m. p. 164–167° (with slow evolution of gas) with softening at 162°. This product represented nearly pure 3-carboxy-4-(6-methoxy-2-naphthyl)-4-hexenoic acid (II, R = H). Repeated recrystallization from the same solvent gave colorless prisms, m. p. 164–166° (evolution of gas).

*Anal.* Calcd. for  $C_{18}H_{18}O_3$ : C, 68.78; H, 5.77; neut. equiv., 157. Found: C, 68.40; H, 5.83; neut. equiv., 158.

The second and third crops isolated from the original mother liquor amounted to 0.111 g. (m. p. 132.5–133.5°) and 0.425 g. (m. p. 146–147.5°), and represented crude *trans*-3-carboxy-4-(6-methoxy-2-naphthyl)-3-hexenoic acid (VII, R = H), recrystallization from ethyl acetate–petroleum ether (60–68°) yielding nearly pure material, m. p. 152.5–154° (evolution of gas). The major portion of this isomer remained in the mother liquor from the third crop, and was isolated by evaporation of the solvent and treatment of the oily residue with 50 ml. of warm 10% sodium hydroxide. The sparingly soluble sodium salt which precipitated was separated by filtration, washed sparingly with water, then decomposed with dilute hydrochloric acid. The oily acidic material (1.84 g.) which was liberated was crystallized from ethyl acetate–petroleum ether (60–68°) and thus 1.355 g. of the *trans* isomer was obtained, m. p. 153–154° (evolution of gas) with softening at 151°, making the total yield 17%. Repeated recrystallization of a sample gave colorless prisms, m. p. 152.5–154.5° (evolution of gas).

*Anal.* Calcd. for  $C_{18}H_{18}O_3$ : C, 68.78; H, 5.77; neut. equiv., 157. Found: C, 68.80; H, 5.56; neut. equiv., 163.

Acidification of the aqueous filtrate from the separation of the sodium salt gave 2.311 g. of oily acidic material which on crystallization from ethyl acetate–petroleum ether (60–68°) afforded 0.741 g. (7% yield) of colorless crystals of crude *cis*-3-carboxy-4-(6-methoxy-2-naphthyl)-3-hexenoic acid (XI, R = H), m. p. 164.5–168° (evolution of gas) with previous softening. A single recrystalliza-

(28) Campbell, Soffer and Steadman, *THIS JOURNAL*, **64**, 425 (1942).

(29) Smith and Carlson, *ibid.*, **61**, 288 (1939).



tion gave 0.702 g. of nearly pure material as colorless needles, m. p. 169.5–171° (evolution of gas) with softening at 162°. Repeated recrystallization raised the m. p. to 169–172° (evolution of gas).

*Anal.* Calcd. for  $C_{18}H_{18}O_5$ : C, 68.78; H, 5.77; neut. equiv., 157. Found: C, 68.82; H, 5.89; neut. equiv., 158.

**Cyclization by the Sodium Acetate Method.** (a) *Of trans-3-Carbomethoxy-4-(6-methoxy-2-naphthyl)-3-hexenoic Acid (VII, R = CH<sub>3</sub>).*—The half-ester VII ( $R = CH_3$ ) was prepared from the 154° dibasic acid (0.748 g.) by treatment with excess diazomethane and partial saponification of the resulting dimethyl ester with 0.374 g. of barium hydroxide octahydrate in 15 ml. of alcohol and 10 ml. of water. After refluxing for six hours the mixture was filtered to remove 0.258 g. of insoluble barium salt (corresponding to dibasic acid), and the filtrate concentrated at reduced pressure to remove the alcohol. The remaining aqueous solution was acidified with dilute hydrochloric acid and extracted with ether. The half-ester was then extracted from the ether solution with 5% sodium bicarbonate solution, 14 portions being required for complete extraction. Acidification of these extracts gave 0.356 g. of colorless oily product (separated by extraction) which was cyclized as described below without further purification. Dimethyl ester amounting to 0.226 g. remained in the ether layer.

The 0.356 g. of half-ester was treated with 0.100 g. of anhydrous sodium acetate in 3.0 ml. each of acetic acid and acetic anhydride. After refluxing for three hours, the light yellow solution was evaporated in a current of air and the semi-crystalline residue treated with 10 ml. of 5% sodium carbonate solution. The organic material was taken up in ether, washed with 5% sodium carbonate solution and dried over anhydrous magnesium sulfate. Evaporation of the ether gave 0.350 g. (92% yield) of crude methyl 1-ethyl-4-acetoxy-7-methoxyphenanthrene-2-carboxylate (XIV,  $R^1 = COCH_3$ ,  $R^2 = CH_3$ ), m. p. 129.5–134.5° with previous softening. Recrystallization from ethyl acetate-petroleum ether (60–68°) gave (in two crops) a total of 0.320 g. (84% yield) of colorless prisms, m. p. 135–137°. Further recrystallization raised the m. p. to 136–137°.

*Anal.* Calcd. for  $C_{22}H_{20}O_5$ : C, 71.58; H, 5.72. Found: C, 71.78; H, 5.84.

Saponification of a sample of XIV ( $R^1 = COCH_3$ ,  $R^2 = CH_3$ ) yielded material identical (by mixed m. p. determinations) with the phenanthrolcarboxylic acid XIV ( $R^1 = R^2 = H$ ) described below.

(b) *Of cis-3-Carbomethoxy-4-(6-methoxy-2-naphthyl)-3-hexenoic Acid (XI, R = CH<sub>3</sub>).*—A 0.149-g. sample of the 172° dibasic acid XI ( $R = H$ ) was converted to the dimethyl ester with diazomethane and partially saponified with 0.076 g. of barium hydroxide octahydrate in 6 ml. of alcohol and 4 ml. of water just as described above, part a. The crude oily half-ester thus obtained amounted to 0.139 g. It was treated with 0.040 g. of sodium acetate and 1.5 ml. each of acetic acid and acetic anhydride as described in part (a) to give only 7 mg. of neutral oily material. The recovered acidic material amounted to 0.127 g. indicating that essentially no cyclization had occurred.

(c) *Of the Crude Stobbe Condensation Product.*—A solution of 13.5 g. of the crude mixture of half-esters, prepared as described at the beginning of the experimental section, and 3.38 g. of anhydrous sodium acetate in 42.2 ml. of acetic acid and 63.3 ml. of acetic anhydride was heated under reflux for four hours. After evaporation of the solvents the residue was treated with 100 ml. of 5% sodium carbonate solution and 50–60 ml. of ether. On shaking, buff-colored needles separated at the interface of the layers. This product was removed by filtration and amounted to 4.89 g. (34% yield) of ethyl 1-ethyl-4-acetoxy-7-methoxyphenanthrene-2-carboxylate (XIV,  $R^1 = COCH_3$ ,  $R^2 = C_2H_5$ ), m. p. 146–148°. Repeated recrystallization from ethyl acetate-petroleum ether (60–68°) gave colorless prismatic needles, m. p. 150–151°.

*Anal.* Calcd. for  $C_{22}H_{22}O_5$ : C, 72.11; H, 6.05. Found: C, 72.09; H, 6.08.

**1-Ethyl-4-hydroxy-7-methoxyphenanthrene-2-carboxylic acid (XIV,  $R^1 = R^2 = H$ )** was obtained by hydrolysis of 1.92 g. of the above ester with 75 ml. of 10% sodium hydroxide solution and 50 ml. of alcohol. After five and one-half hours of refluxing, the solution was evaporated to remove the alcohol. Acidification with dilute hydrochloric acid gave 1.506 g. (97% yield) of crude phenolic acid, m. p. (capillary) 262–265° (dec.) (uncor.) with softening and darkening at 235°. Two recrystallizations from ethyl acetate gave colorless plates, m. p. (in evacuated capillary) 265–269° (dec.) (uncor.); m. p. (hot stage) 255–258° when placed on stage at 235°. The pure material gave a reddish-brown color with dilute alcoholic ferric chloride.

*Anal.* Calcd. for  $C_{18}H_{16}O_4$ : C, 72.96; H, 5.44. Found: C, 72.91; H, 5.57.

**Ethyl 4-hydroxy-7-methoxyphenanthrene-2-carboxylate (XIV,  $R^1 = H$ ,  $R^2 = C_2H_5$ )** was prepared by alcoholysis of 0.050 g. of the acetoxy compound XIV ( $R^1 = COCH_3$ ,  $R^2 = C_2H_5$ ) with 6.5 ml. of ethanol saturated with hydrogen chloride. After refluxing for three hours, the solution was evaporated in a current of air and the residue crystallized five times from alcohol; yield 0.018 g. (41%) of pale yellow needles, m. p. 191–192°. This product gave no color with ferric chloride.

*Anal.* Calcd. for  $C_{20}H_{20}O_4$ : C, 74.05; H, 6.22. Found: C, 74.24; H, 6.17.

**Hydrogenation of Ethyl 1-Ethyl-4-acetoxy-7-methoxyphenanthrene-2-carboxylate.**—In preliminary experiments of the hydrogenation of this substance over platinum oxide in acetic acid the only homogeneous product which was isolated by crystallization was a dihydro compound probably ethyl 1-ethyl-4-acetoxy-7-methoxy-9,10-dihydrophenanthrene-2-carboxylate. It crystallized from ethyl acetate-petroleum ether (60–68°) to give colorless prisms, m. p. 137.5–138°.

*Anal.* Calcd. for  $C_{22}H_{24}O_5$ : C, 71.72; H, 6.57. Found: C, 71.85; H, 6.46.

**Cyclization by Hydrogen Fluoride.** (a) *Of the 154° Acid: trans-3-Carboxy-4-(6-methoxy-2-naphthyl)-3-hexenoic Acid (VII, R = H).*—A solution of 0.106 g. of the acid, m. p. 150.5–152.5° (evolution of gas), in about 20 ml. of anhydrous hydrogen fluoride was allowed to stand in a platinum vessel at room temperature for four hours. After removal of the reagent in a current of air, the residue was taken up in ether and washed with 5% sodium carbonate solution. Acidification of the aqueous extracts gave 0.035 g. of reddish-yellow oil which could not be crystallized. Evaporation of the dried ether solution gave 0.070 g. of colorless oil which on crystallization from ethyl acetate-petroleum ether (60–68°) gave the lactone X of 3-ethyl-3-hydroxy-2'-methoxy-6,7-benz-1-hydrindone-2-acetic acid in two crops, 0.027 g. melting at 172–173° and 0.027 g. melting at 170.5–172.5° representing a total yield of 54%. A sample purified by repeated recrystallization from alcohol was obtained as colorless plates, m. p. 172–173°.

*Anal.* Calcd. for  $C_{18}H_{16}O_4$ : C, 72.96; H, 5.44. Found: C, 72.77; H, 5.48.

(b) *Of the 172° Acid: cis-3-Carboxy-4-(6-methoxy-2-naphthyl)-3-hexenoic Acid (XI, R = H).*—A 0.100-g. sample of the acid was treated just as the stereoisomer described above. The reddish oily acidic fraction, thus obtained, amounted to 0.016 g., and the colorless neutral fraction, 0.081 g. Crystallization of the latter from ethyl acetate-petroleum ether (60–68°) gave the lactone X in two crops, 0.055 g. melting at 171.8–172.8° and 0.020 g. melting at 168–169.5°, representing a total yield of 80%.

**Cyclization of the Crude Stobbe Condensation Product by the Zinc Chloride Method.**—A solution of 2.77 g. of the crude half-ester mixture in 28 ml. of acetic anhydride and 14 ml. of 2% fused zinc chloride in acetic acid was heated under reflux for fifteen minutes. The deep red solution was evaporated in a current of air and the residue treated with 25 ml. each of ether and 5% sodium carbonate solution. From the small amount of insoluble material there was ob-

tained by trituration with hot ethyl acetate and recrystallization of the soluble portion from ethyl acetate-petroleum ether (60–68°), 0.180 g. of ethyl 1-ethyl-4-acetoxy-7-methoxyphenanthrene-2-carboxylate, m. p. 147–149°, undepressed on admixture with the sample of this substance described above.

The red ether layer was washed thoroughly with 5% sodium carbonate solution and dried over anhydrous magnesium sulfate. Evaporation of the ether gave 2.48 g. of red oil which was adsorbed on a column of activated alumina<sup>25</sup> and eluted with 50% ether-benzene which brought through a bright red band. Evaporation of the eluate gave 0.168 g. of crude ethyl 3-ethyl-2'-methoxy-6,7-benz-1-indone-2-acetate (IX, R = C<sub>2</sub>H<sub>5</sub>) as a red oil which on recrystallization twice from 60–68° petroleum ether was obtained as bright red needles, m. p. 115–117° with softening at 105°. Further recrystallization raised the m. p. to 117–118°.

*Anal.* Calcd. for C<sub>20</sub>H<sub>20</sub>O<sub>4</sub>: C, 74.05; H, 6.22. Found: C, 74.07; H, 6.30.

**Hydrogenation of Ethyl 3-Ethyl-2'-methoxy-6,7-benz-1-indone-2-acetate.**—A solution of 0.063 g. of the above benzindoneacetic ester IX (R = C<sub>2</sub>H<sub>5</sub>) in 15 ml. of ethyl acetate was hydrogenated over 0.020 g. of 30% palladium-charcoal.<sup>26</sup> The absorption of hydrogen was complete in seven minutes, and evaporation of the filtered solution gave a colorless oil which was saponified with 5 ml. of 2% alcoholic sodium hydroxide solution. After refluxing for forty-five minutes, 0.058 g. of colorless oily acidic material was obtained. Crystallization from ethyl acetate-petroleum ether (60–68°) gave 0.023 g. of 3-ethyl-2-methoxy-6,7-benz-1-hydrindone-2-acetic acid (VIII, R = H) as colorless needles, m. p. 149–151°, undepressed on admixture with the specimen of this ketone obtained by cyclization of the saturated acid described above.

**Lactonization of Ethyl 3-Ethyl-2'-methoxy-6,7-benz-1-indone-2-acetate.**—A solution of 0.120 g. of crude benzindoneacetic ester in 10 ml. of 33% alcoholic hydrogen chloride was heated under reflux for thirty minutes. The solution which had turned from deep red to a yellow color was evaporated in a current of air, and the oily residue taken up in ether and washed with 2% sodium hydroxide solution. Evaporation of the ether layer gave a light brown oil which after three recrystallizations from ethyl acetate-petroleum ether (60–68°) gave colorless prisms, m. p. 171–172°, undepressed on admixture with the sample obtained by hydrogen fluoride cyclization described above.

**Hydrogenation Experiments.** (a) *With the 166° Acid: 3-Carboxy-4-(6-methoxy-2-naphthyl)-4-hexenoic Acid (II, R = H).*—A solution of 0.152 g. of the pure acid in 15 ml. of ethyl acetate was hydrogenated at room temperature in the presence of 0.024 g. of platinum oxide. After about four hours gas absorption had ceased, and the mixture was filtered. The oily residue obtained on evaporation of the filtrate was recrystallized three times with ethyl acetate-petroleum ether (60–68°) giving 0.116 g. (76% yield) of the dihydro acid III (R = H), as colorless needles, m. p. 161–165° (evolution of gas), undepressed on admixture with the sample prepared by hydrogenation of the crude mixture of half-esters described above.

In another run a product m. p. 156–158° (evolution of gas) was obtained in 89% yield.

(b) *With the 154° Acid: trans-3-Carboxy-4-(6-methoxy-2-naphthyl)-3-hexenoic Acid (VII, R = H).*—This acid was resistant to catalytic hydrogenation under the conditions described above, part a. No evident gas absorption was observed after two hours, and the starting material was largely recovered. A trace of material, m. p. 156.5–163° (evolution of gas) with softening at 149° was isolated, which may correspond to the 165° dihydro acid III (R = H).

(c) *With the 172° Acid: cis-3-Carboxy-4-(6-methoxy-2-naphthyl)-3-hexenoic Acid (XI, R = H).*—This acid was also resistant to hydrogenation, but did react slowly. Gas absorption stopped after twelve hours with a 0.314-g. sample of the acid in 25 ml. of ethyl acetate and 0.075 g. of platinum oxide. Two recrystallizations of the crude oily

product from ethyl acetate-petroleum ether (60–68°) gave 0.250 g. (79% yield) of colorless plates, m. p. 127.5–133° (evolution of gas) with softening at 124.5°. The m. p. of this product, which probably corresponds to the second racemic modification of III (R = H), was not depressed on admixture with the dihydro acid isolated from the molecular compound (see below).

**The Molecular Compound.** (a) *Isolation.*—The 89 g. of crystalline sodium salt isolated from the hydrogenation of the half-ester mixture described at the beginning of the experimental section was treated with dilute hydrochloric acid, and the oily mixture of acids was recrystallized from ethyl acetate. A total of 62.5 g. of colorless granular crystals, m. p. 167–169° (evolution of gas), was thus obtained, representing a yield of 27% based upon the crude half-ester mixture. Repeated recrystallization from ethyl acetate gave a microcrystalline powder melting at 171–172.5° (evolution of gas) after drying at 100–105° (0.02 mm.) for twenty hours.

*Anal.* Calcd. for C<sub>18</sub>H<sub>20</sub>O<sub>6</sub>·C<sub>18</sub>H<sub>18</sub>O<sub>5</sub>: C, 68.56; H, 6.07. Found: C, 68.73; H, 6.09.

(b) *Cyclization by the Sodium Acetate Method and Isolation of the Low-Melting Dihydro Acid (III, R = H) Component.*—A 1,000-g. sample of the molecular compound was converted to the half-ester, by treatment with excess diazomethane followed by partial saponification of 1,006 g. of the resulting di-ester with 0.464 g. of barium hydroxide octahydrate in 45 ml. of alcohol and 30 ml. of water, as described above for the cyclization of VII (R = CH<sub>3</sub>). The dibasic acid fraction obtained from the insoluble barium salt amounted to 0.125 g. after recrystallization from ethyl acetate-petroleum ether (60–68°) and melted at 163.5–167° (evolution of gas) alone or on admixture with the original molecular compound. The dimethyl ester fraction amounted to 0.132 g., and the yield of oily half-ester fraction was 0.730 g. This last fraction was treated with 0.200 g. of sodium acetate in 7 ml. each of acetic acid and acetic anhydride just as described above for the cyclization of VII (R = CH<sub>3</sub>). The neutral product amounted to 0.413 g. of pale yellow semi-crystalline material from which a total of 0.285 g. (36.5% yield based on total half-ester mixture) of the acetoxyphenanthrenecarboxylate XIV (R<sup>1</sup> = COCH<sub>3</sub>, R<sup>2</sup> = CH<sub>3</sub>), all crops melting between 133.5–135° and 135.5–136.7°.

The oily acidic (uncyclized) fraction amounted to 0.378 g., and a portion (0.217 g.) was saponified with barium hydroxide to give 0.201 g. of oily dibasic acid. Crystallization from ethyl acetate-petroleum ether (60–68°) gave 0.128 g. of the low-melting dihydro acid (probably III, R = H), m. p. 127–134° (evolution of gas). Repeated recrystallization from the same solvent pair gave thin colorless plates, m. p. 127.5–134.5° (evolution of gas).

*Anal.* Calcd. for C<sub>18</sub>H<sub>20</sub>O<sub>5</sub>: C, 68.34; H, 6.37. Found: C, 68.21; H, 6.66.

(c) *Cyclization with Hydrogen Fluoride.*—A 1.00-g. sample of the molecular compound was treated with hydrogen fluoride as described above for the 154° acid. The pale yellow neutral oil amounted to 0.423 g. which on crystallization from ethyl acetate-petroleum ether (60–68°) gave the lactone X: 0.209 g., m. p. 171–172° and 0.086 g., m. p. 167.5–170°, making the total yield 31%.

(d) *Reformation of the Molecular Compound.*—When a mixture of equal amounts of the 154° unsaturated dibasic acid VII (R = H) and the low-melting dihydro acid isolated either from the molecular compound (part b above) or from the hydrogenation of the 172° unsaturated acid described above was recrystallized from ethyl acetate-petroleum ether (60–68°), the molecular compound, m. p. 168–170° (evolution of gas) was formed in good yield. The m. p. was not depressed on admixture with the original specimen.

(e) *Reduction with Nickel and Alkali.*—A 5.0-g. sample of the molecular compound in 200 ml. of 10% sodium hydroxide solution was treated with 20 g. of nickel-aluminum alloy according to the procedure described by Papa, Schwenk and Whitman.<sup>10</sup> Even at the end of the reaction period, considerable insoluble sodium salt remained

indicating that reduction was not complete. The hot mixture was filtered, the insoluble portion washed with hot water, and the filtrate and washings were acidified with hydrochloric acid giving 4.5 g. of colorless oily acidic material. This product was treated with 50 ml. of 10% sodium hydroxide, and the insoluble sodium salt (3.13 g.) was separated by filtration. Acidification of the filtrate gave an oily product from which 1.56 g. (31% yield) of colorless needles, m. p. 155–161.5° (evolution of gas) was obtained by crystallization from ethyl acetate–petroleum ether (60–68°). The m. p. was not depressed on admixture with the high-melting dihydro acid III (R = H) produced by catalytic hydrogenation of the half-ester mixture (see above).

Decomposition of the insoluble sodium salt with dilute hydrochloric acid gave an oily acid which after two recrystallizations from ethyl acetate afforded 1.15 g. of the molecular compound, m. p. 170–172° (evolution of gas) with previous softening, undepressed on admixture with the original material.

The molecular compound, thus, affords a source of additional III (R = H) for the synthesis of bisdehydrodisynolic acid. It seems probable that modification of the reduction conditions will give improved yields. A study of the cyclization of the low-melting dihydro acid III (R = H) would also be interesting.

**Ultraviolet Absorption Spectra.**—All determinations were made on the analytical specimens described above in 95% alcohol solution. A Beckman ultraviolet spectrophotometer was employed.

**trans-3-Carboxy-4-(6-methoxy-2-naphthyl)-3-hexenoic Acid (VII, R = H).**— $\lambda$  max 231.0 (log *E* 4.648), 332.0 (3.308). **cis-3-Carboxy-4-(6-methoxy-2-naphthyl)-3-hexenoic Acid (XI, R = H).**— $\lambda$  max. 225.5 (log *E* 4.604), 330.5 (3.356) (plateau). **3-Carboxy-4-(6-methoxy-2-naphthyl)-4-hexenoic Acid (II, R = H).**— $\lambda$  max. 234.0 (log *E* 4.763), 266.0 (3.760) (plateau), 272.5 (3.791), 320.0 (3.158), 331.0 (3.225). **High-Melting 3-Carboxy-4-(6-methoxy-2-naphthyl)-caproic Acid (III, R = H).**— $\lambda$  max. 232.0 (log *E* 4.917), 252.5 (3.647), 262.0 (3.732), 271.5 (3.722), 317.0 (3.242), 331.0 (3.325). **Low-Melting 3-Carboxy-4-(6-methoxy-2-naphthyl)-caproic Acid (III, R = H).**— $\lambda$  max. 232.0 (log *E* 4.913), 253.0 (3.620), 262.0 (3.720), 271.0 (3.715), 317.0 (3.214), 325 (3.172), (plateau), 331.0 (3.292). **172° Molecular Compound.**— $\lambda$  max. 232.0 (log *E* 4.827), 317.5 (3.303), 331.5 (3.283). **Calculated for Equimolecular Mixture of the trans Hexenoic Acid VII (R = H) and the Low-Melting Dihydro Acid (III, R = H).**— $\lambda$  max. 232.0 (log *E* 4.800), 316.5 (3.306), 332.0 (3.300). **Methyl 1-Ethyl-4-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene-2-carboxylate (IV, R = CH<sub>3</sub>).**— $\lambda$  max. 220.0 (log *E* 4.832), 247.0 (4.531), 315.5 (3.944), 345.0 (3.684) (plateau). **Methyl 3-Ethyl-2'-methoxy-6,7-benz-1-hydrindone-2-acetate (VIII, R = CH<sub>3</sub>).**— $\lambda$  max. 213.5 (log *E* 4.780), 245.5 (4.651), 306.5 (3.977), 351.5 (3.667). **Methyl 1-Ethyl-4-keto-6-methoxy-1,2,3,4-tetrahydroanthracene-2-carboxylate (XII, R = CH<sub>3</sub>).**— $\lambda$  max. 210.0 (log *E* 4.585), 252.0 (4.871), 300.0 (4.286), 372.5 (3.489).

### Summary

Racemic  $\alpha$ - and  $\beta$ -bisdehydrodisynolic acid methyl ether have been synthesized from  $\beta$ -methoxynaphthalene. Friedel-Crafts acylation with propionyl chloride gave the previously known 2-propionyl-6-methoxynaphthalene, which was employed in a Stobbe condensation with diethyl succinate. Hydrogenation of the resulting mixture gave mainly one racemic form of the substituted succinic acid which on cyclization *via* the anhydride with aluminum chloride in nitromethane afforded, in addition to products of abnormal cyclization, the desired 1-ethyl-4-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene-2-carboxylic acid. Reduction of the keto group of this substance, followed by methylation of the ester with sodium triphenylmethyl and methyl iodide gave, after saponification, the mixture of  $\alpha$ - and  $\beta$ -bisdehydrodisynolic acid methyl ether, mainly the former.

Evidence for the structure of the abnormal products of cyclization (see above) has been obtained, and a linear (anthracene) analog of bisdehydrodisynolic acid was prepared and shown to have estrogenic activity.

The mixture of isomers produced in the Stobbe condensation has been separated, and structures and configurations of the components have been assigned on the basis of ultraviolet absorption studies and chemical behavior.

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## Studies in Decarboxylation and Lacto-Enoic Tautomerism. IV.<sup>1</sup> Paraconic Acids<sup>2</sup>

BY WILLIAM S. JOHNSON AND RICHARD H. HUNT<sup>3</sup>

From the work of Fittig and his collaborators, it is well known that paraconic acids (I) lose carbon dioxide readily on heating, generally giving a mixture of an unsaturated acid and a lactone.<sup>4</sup> Although there is, in most of the cases, little or no evidence for the intimate structure of these prod-

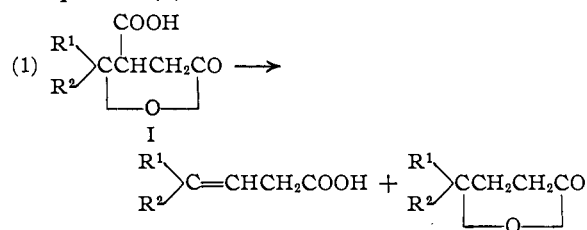
(1) Paper III, Johnson and Müller, *THIS JOURNAL*, **72**, 511 (1950).

(2) Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

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(4) Richter-Anschütz, "Chimie der Kohlenstoffverbindungen," Vol. I, 12th edition, Akademische Verlagsgesellschaft m. b. H., Leipzig, 1928, pp. 678–679.

ucts, the most likely presumption is that they are  $\beta$ , $\gamma$ -unsaturated acids and  $\gamma$ -lactones as indicated in equation (1).



When R<sup>1</sup> = alkyl and R<sup>2</sup> = H (equation 1) the unsaturated acid is the main product, while with