[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

CYCLIC ANALOGS OF HEXESTROL IN THE CHRYSENE SERIES

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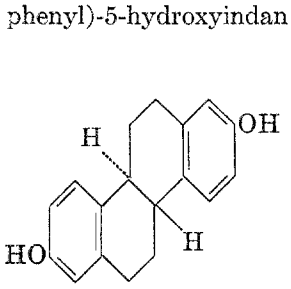
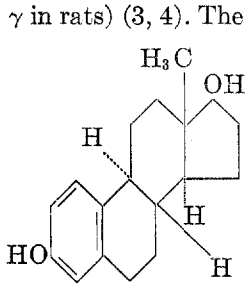
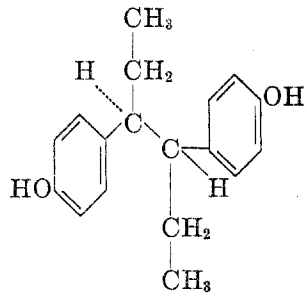
To one considering the relation between structure and activity of the synthetic estrogens, 2,8-dihydroxyhexahydrochrysene (I) presents an anomaly. Although it is intermediate in structure between estradiol (II) and *meso*-hexestrol (III), which have approximately the same estrogenic activity (0.1 γ and 0.2 γ in rats, respectively), the chrysene derivative is reported to have an estrogenic potency (1000 γ in rats) less than one-thousandth that of hexestrol (1, 2). This very low activity for I contrasts with the higher potencies reported for the closely related 2,8-dihydroxy-5,6,11,12-tetrahydrochrysene analog of diethylstilbestrol (10 γ in rats)[2] and certain indene and indan analogs, such as 1-isopropyl-2-(*p*-hydroxyphenyl)-5-hydroxyindan (0.7 γ in rats) (3, 4). The low activity of I is comparable



I



II



III

to that of DL-hexestrol (1000 γ in rats), although by analogy to results in the desoxy series this isomer of I was presumed to have the *trans* configuration comparable to *meso*-hexestrol and estradiol.

In an attempt to clarify this situation, we have reinvestigated I, preparing both *cis*- and *trans*-isomers and establishing the configurations unequivocally. The procedures for preparing I have been improved, making this interesting compound available as an intermediate for synthesizing other compounds related to the steroid hormones.

The most convenient synthesis of hexahydrochrysene derivatives of this type is that of von Braun and Irmisch (5) *via* cyclization of β,γ-diaryladipic acids (*e.g.* VIII). The latter have been prepared by bimolecular reduction of a cinnamic ester derivative (6, 7) or by means of a double Reformatsky reaction with a benzil derivative and ethyl bromoacetate followed by a reduction step

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[2] However, the considerably lower activity found by Solmssen and Wenis (4) for 2-(*p*-hydroxyphenyl)-3-methyl-6-hydroxyindene and its diacetate than that reported by Salzer may also throw some doubt on the potency of the tetrahydrochrysene analog.

(8). Ramage and Robinson (9), who first prepared the methoxy derivative VIa, employed the former method. Since they found the bimolecular reduction of methyl *p*-methoxycinnamate with aluminum amalgam to give quite low yields of the isomeric adipic acid derivatives IVa (14% and 6%), we first investigated the approach from anisil.

Cook and Lawson (10) were able to isolate one isomer of diethyl β,γ-dihydroxy-β,γ-dianisyladipate (XII) in 15% yield from the Reformatsky reaction of anisil with ethyl bromoacetate. In this laboratory, Mr. Walter Polovina (11) obtained yields as high as 47% of this *meso*-isomer (XII), together with 20% of the doubly unsaturated acid (XIII) after saponification of the residues, although the results in other runs were variable. Selective hydrogenolysis of the ester XII over a copper chromium oxide catalyst at 210° gave a low yield (*ca.* 4%) of the *meso* ester of IVa, although in the desoxy series (XII, R = H) the yield of *meso* ester corresponding to VIII was considerably higher (30%). Hydrogenation over Raney nickel of the dimethyl ester of the unsaturated acid XIII[3] gave somewhat better results, since 20–25% of the *meso* ester of IVa was isolated together with about 30% of lower-melting material probably containing the DL-isomer. Nevertheless, these results made it seem probable that the approach *via* the cinnamic ester would be preferable.[4] The recent work of Badger confirms this view (12).[5]

On reinvestigating the bimolecular reduction of methyl *p*-methoxycinnamate with aluminum amalgam it was possible approximately to double the previous yields, and obtain 24% of the *meso* dimethyl ester and 18% of the DL ester corresponding to IVa, together with 30% of methyl *p*-methoxyhydrocinnamate. This makes the approach feasible even on a moderately large scale, in view of the accessibility of the starting material and the excellent yields on subsequent steps.

By analogy to the desoxy derivatives VIII, the reasonable assumption had been made by previous workers (9) that the higher-melting, less soluble ester and acid had the *meso* configuration. This has now been established by resolving the lower-melting acid IVa as the brucine salt, using the method employed by Oommen and Vogel in the desoxy series VIII (7).

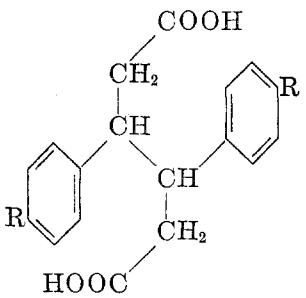
For ring-closure the inverse Friedel-Crafts procedure of Johnson and Glenn (13) was employed to advantage. In this way the *meso* acid IVa was cyclized as the acid chloride to the *trans*-diketone V in 87% yield and the DL-acid IVa to the *cis*-diketone in 86% yield.

[3] β,γ-Di-*p*-anisylmuconic acid (XIII), m.p. 204–205° (gas) (from acetic acid-ethyl acetate). *Anal.* Calc'd for $C_{20}H_{18}O_6$: C, 67.80; H, 5.12; Found: C, 67.42; H, 5.16. Methyl ester, m.p. 156–157° (from methanol-benzene); *Anal.* Calc'd for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80. Found: C, 69.22; H, 6.05.

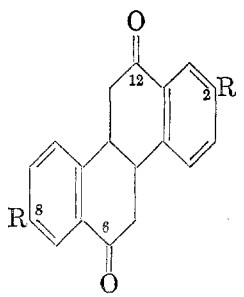
[4] Experiments aimed at preparing the acids VIII and IVa from stilbene dibromide, stilbene dichloride, or *p,p'*-dimethoxystilbene dichloride using sodiomalonic ester were unpromising.

[5] Badger developed a two-stage process in the desoxy and methoxy series for reducing these Reformatsky esters chemically to VIII and IVa through an intermediate dihydromuconic acid derivative. In the methoxy series only the *meso* isomer of IVa was prepared and in low over-all yield (39% from XII, for which the yield was unspecified).

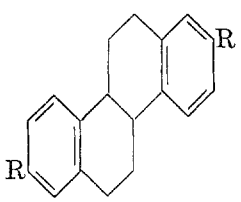
Previously the Clemmensen or Huang-Minlon procedures have been used to reduce these diketones. In the present work the method of Rosenmund and Karg as developed by Kindler and Kwok (14) proved to be excellent (15). Hydrogenation of the *trans*-diketone V with a palladium catalyst in acetic acid containing a small amount of perchloric acid gave the desired *trans*-dimethoxy derivative VIa in 90% yield. Similarly the *cis*-diether VIa was prepared in excellent yield. These were smoothly demethylated with hydrobromic and acetic acids to *trans*-



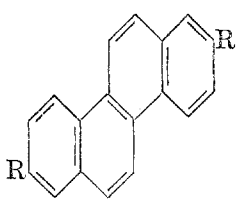
IVa, R = OCH_3
IVb, R = OH
VIII, R = H



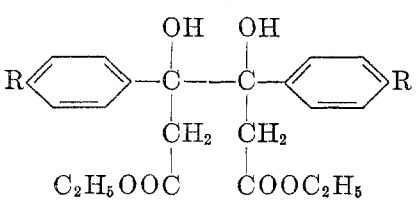
V, R = OCH_3
IX, R = H



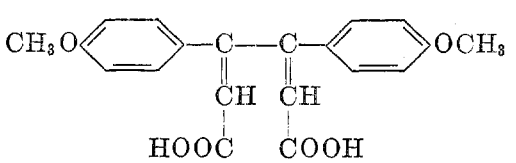
VIa, R = OCH_3
VIb, R = OH
X, R = H



VIIa, R = OCH_3
VIIb, R = OH
XI, R = H



XII, R = OCH_3



XIII

2,8-dihydroxyhexahydrochrysene (I), m.p. 269–271°, and the *cis*-isomer, m.p. 224–224.5°.

Each isomer of the dimethoxyhexahydrochrysene (VIa) was readily dehydrogenated with palladium to the same 2,8-dimethoxychrysene, a fact which also confirmed the direction of cyclization of the adipic acids IVa. This compound and the corresponding 2,8-dihydroxy derivative apparently have not been reported previously.

Similar reactions have been applied in the desoxy series to the *meso* and DL acids (VIII)[6] obtained by bimolecular reduction of methyl cinnamate. The cyclization steps to the *cis*- and *trans*-diketones (IX), reduction to the *cis*- and *trans*-hexahydrochrysenes (X), and dehydrogenation to chrysene (XI) all were carried out in excellent yields. Thus, in spite of the relatively low yields on the bimolecular reduction step (*ca.* 25% each of *meso* and DL VIII), this nevertheless provides an excellent approach to symmetrical derivatives of chrysene, particularly if the fully aromatic products are desired.

We are indebted to Drs. R. K. Meyer and Elva G. Shipley of the Department of Zoology for the estrogenic assays. In preliminary tests the level of activity of the *trans*-dihydroxyhexahydrochrysene (I) was such that one rat unit (50% response) is between 350 γ (which resulted in a 60% borderline response) and 500 γ (90%) while for the *cis*-isomer it is slightly over 500 γ (40%). On the other hand with the corresponding diacetates, the *cis*-isomer was slightly favored, one rat unit lying below 400 γ (80%), and with the *trans*-diacetate below 500 γ (77%). Clearly, there is little significant difference between these stereoisomers, in striking contrast to the thousand-fold difference between *meso* and DL hexestrol, and the stereoisomers of equilenin and estrone differing in C:D ring configuration.[7]

From these results we would infer that the failure to find high activity for the *trans*-isomer of I may be discounted in the general picture relating structure to activity. To us the most satisfactory working hypothesis at present is that the over-all size and shape of the synthetic molecule, as compared to the natural hormone, with its appropriate although not always essential functional groups, is of foremost importance in determining activity (18); this "intrinsic activity" due to the structure is modified markedly, however, by other factors such as solubility and partition coefficient, ease of inactivation or excretion by the test animal, etc.

EXPERIMENTAL[8, 9]

SYNTHESES IN THE METHOXY SERIES

meso- and DL-*Methyl* β,γ-*di-p-anisyladipate.* The following modification of the procedure of Ramage and Robinson (9a) gave higher yields of the bimolecular reduction products. First, 100 g. of 8-mesh aluminum granules[10] and 11 g. of aluminum foil in small strips were treated with 100 ml. of 5% sodium hydroxide for three minutes, washed thoroughly with water by decantation, then amalgamated by swirling with 100 ml. of 26% mercuric chloride

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[6] Recently Fierz-David, Blangey, and Uhlig (16) have prepared *p,p'*-substituted diphenyladipic acids including the *meso* dihydroxy derivative through nitration of VIII.

[7] It is interesting to note that the 8-isoestrone of Serini and Logemann (17), believed to differ from estrone only in having a B:C *cis*-configuration, was reported to be nearly one-half as potent as estrone.

[8] All melting points below 275° are corrected; above this temperature they are uncorrected, taken in an aluminum block. Those marked vac. were determined in sealed Pyrex capillary tubes evacuated to at least 0.5 mm.

[9] Microanalyses by Virginia Miller, Richard Hunt, Gerald Gilbert, and John Belew.

[10] Inferior results were obtained using pure aluminum turnings, considerable amounts of unreduced cinnamic ester being recovered.

solution for three minutes, and finally washed three times with distilled water. Immediately 50 g. of methyl *p*-methoxycinnamate (m.p. 88–89°)(9a) in 450 ml. of moist ether (previously shaken with water) was added and gentle refluxing was maintained for 24 hours, first by the heat of reaction and later using a steam-bath. Small portions of water were added from time to time, the total amounting to 25 ml. Ether was added as necessary to maintain a layer over the aluminum sludge. At the end of the reaction the ether layer was decanted and the aluminum sludge was dissolved in 500 ml. of 18% hydrochloric acid and extracted with three 200-ml. portions of benzene. The combined ether-benzene extracts were washed, concentrated, and the product crystallized from methanol-benzene affording 6.5 g. of *meso*-dimethyl β,γ-dianisyladipate, m.p. 153–154°, and an additional 5.55 g. of lower-melting material for a total yield of 24% for this isomer. Recrystallization from methanol gave pure *meso*-ester melting at 154.5–155.5° [Ramage and Robinson (9a) obtained this isomer in 14% yield, m.p. 153°].

Distillation of the material in the filtrate gave 15.1 g. (30%) of methyl *p*-methoxyhydrocinnamate, b.p. 75–78° at 0.3 mm. (m.p. 31–33°), and 17.4 g. of a colorless higher-boiling fraction, b.p. 235–250° (0.8–1.0 mm.). Crystallization of the latter from methanol gave 6.1 g., m.p. 62–64°, and 3.0 g., m.p. 59–62°, of the DL-isomer for a total of 18%. Further recrystallization from methanol gave the DL-dimethyl β,γ-dianisyladipate as colorless needles, m.p. 63.5–64.5° [Lewis, Ramage and Robinson (9b) obtained this isomer in 6% yield, m.p. 67°].

meso-β,γ-Di-p-anisyladipic acid (IVa). Hydrolysis of the *meso*-dimethyl ester with 10% sodium hydroxide in methanol-water gave the acid in essentially quantitative yield, m.p. 250–255°. Recrystallization from acetic acid gave the pure *meso*-acid, m.p. 258.5–259.5° [reported (9, 12) m.p. 250°, 255–257°].

Anal. Calc'd for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19.

Found: C, 66.97; H, 6.45.

DL-*β,γ-Di-p-anisyladipic acid* (IVa). After alkaline hydrolysis of the DL-dimethyl ester, the mixture was acidified and extracted with ether. Evaporation of the extract afforded the acid in quantitative yield, m.p. 183–185°. The purified acid exhibited a double melting point; material recrystallized from methanol melted at 185.5–186.5°, resolidified and remelted at 193–193.5° [reported (9b) m.p. 180°]. Some of the higher-melting form was obtained by recrystallization from ethyl acetate, m.p. 192–193°.

Anal. Calc'd for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19.

Found: C, 66.90; H, 6.53.

Resolution of DL-*β,γ-di-p-anisyladipic acid.* Following the procedure of Oommen and Vogel for DL-β,γ-diphenyladipic acid (7), 1.0 g. of DL-β,γ-dianisyladipic acid (m.p. 185–186°) and 2.19 g. of *l*-brucine were dissolved in 400 ml. of hot water, then the clear solution was allowed to cool slowly to room temperature, seeding with the brucine salt of the *d*-acid from a previous run. (Some difficulty was first encountered in obtaining a crystalline salt, which did result, however, using aqueous acetone as the solvent.) By further recrystallization of the first crop (1.32 g.; $[\alpha]_D^{25}$ −22°) the brucine salt of the *d*-acid was obtained with the constant $[\alpha]_D^{25}$ −19° (50 mg. in 5 ml. of 95% alcohol). By warming 310 mg. of the salt with 10 ml. of 5% hydrochloric acid until a clear solution resulted, then extracting with ether and crystallizing the acid from benzene containing a few drops of ether, 54 mg. of *d*-acid was obtained, m.p. 104–110°, $[\alpha]_D^{25}$ +47° (50 mg. in 5 ml. of 95% alcohol). Further recrystallization yielded acid of m.p. 108–110°; the product contained benzene of crystallization. After vacuum-drying it melted at 124–126.5° with previous softening.

By concentrating the original filtrate from the brucine salt of the *d*-acid to one-half its volume and seeding with the salt of the *l*-acid from a previous run, 1.41 g. of crystals slowly separated, $[\alpha]_D^{25}$ −35° (50 mg. in 5 ml. of 95% alcohol). Further recrystallization from water gave the brucine salt of the *l*-acid with the constant $[\alpha]_D^{25}$ −41°. Decomposition of the salt with 5% hydrochloric acid as above gave the crude *l*-acid, $[\alpha]_D^{25}$ −42° (50 mg. in 5 ml. of 95% alcohol); after several recrystallizations from benzene the melting point of the acid containing benzene of crystallization was 106–110°. The solvent-free acid was obtained after drying 35 hours at 100° and 0.05 mm., m.p. 127–129°.

Anal. Calc'd for $C_{20}H_{22}O_6 + C_6H_6$: C, 71.54; H, 6.47.
Found: C, 71.30; H, 6.56.
Calc'd for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19.
Found: C, 66.92; H, 6.29.

trans-6,12-Diketo-2,8-dimethoxy-4b,5,6,10b,11,12-hexahydrochrysene (V). The *meso* acid (m.p. 250–255°) (2 g.) was converted into the acid chloride by heating two hours in 10 ml. of dry benzene with 10 ml. of purified (19) thionyl chloride and a trace (*ca.* 1 mg.) of pyridine. The benzene and excess reagent were removed under reduced pressure, followed by addition and similar removal of two portions of benzene. A solution of the solid acid chloride in 75 ml. of dry benzene was then added during one-half minute to a stirred suspension of 6 g. of powdered aluminum chloride in 50 ml. of benzene at 20°. The reaction mixture was stirred four hours, cooled to 10° and hydrolyzed with 25 ml. of 5% hydrochloric acid. The solid diketone was filtered and, together with the solid obtained by evaporation of the benzene layer, was triturated with acetone. The resulting pale yellow solid, 1.58 g. (88%), m.p. 304–305° (dec.), gave a negative phenol test with the Folin-Dennis reagent.[11] Recrystallization from dioxane gave the *trans*-diketone (V) as a pale cream-colored powder, m.p. 310–311° (vac., uncorr.); reported (9) m.p. 285°.

Anal. Calc'd for $C_{20}H_{18}O_4$: C, 74.53; H, 5.63.
Found: C, 74.01; H, 5.53.

cis-6,12-Diketo-2,8-dimethoxy-4b,5,6,10b,11,12-hexahydrochrysene (V). The DL-acid (IVa) (1 g.) was cyclized as described above for the *meso*-acid, except the temperature of addition to the aluminum chloride was 10°. After stirring at room temperature for four hours, hydrolyzing, and extracting with ether-benzene, there was obtained 855 mg. of product, m.p. 228–230°, and 43 mg., m.p. 225–228°, for a total yield of 99%. Two recrystallizations from acetone raised the m.p. of the colorless prisms to 232–233° (vac.) [Lewis, Ramage, and Robinson (9b) obtained the *cis*-diketone in 70% yield, m.p. 220°]. When the sample was inserted in a bath preheated to 220–228° it melted immediately and resolidified, remelting at 230–231°, indicating polymorphism for the compound. At temperatures below 207° this transition was not observed.

Anal. Calc'd for $C_{20}H_{18}O_4$: C, 74.53; H, 5.63.
Found: C, 74.42; H, 5.33.

trans-2,8-Dimethoxy-4b,5,6,10b,11,12-hexahydrochyrsene (VIa). A suspension of 1.19 g. of the *trans*-diketone (V) (m.p. 304–305°) and 500 mg. of 30% palladium-on-carbon catalyst (20) in 80 ml. of redistilled acetic acid containing 0.2 ml. of 60% perchloric acid (14, 15) was stirred with hydrogen at atmospheric pressure and room temperature until the hydrogen uptake had ceased (31 hours). The catalyst was filtered and washed thoroughly with hot benzene and the diluted filtrate was extracted with three 100-ml. portions of benzene, washing the latter with dilute sodium hydroxide and water. The product was crystallized from methanol resulting in 878 mg., m.p. 183–185°, and 100 mg., m.p. 180–182°, for a total of 90%. The purest sample of the *meso* derivative melted at 187–188° [reported (9) m.p. 185°].

Anal. Calc'd for $C_{20}H_{22}O_2$: C, 81.59; H, 7.53.
Found: C, 81.58; H, 7.43.

cis-2,8-Dimethoxy-4b,5,6,10b,11,12-hexahydrochrysene (VIa). Similar hydrogenation of 597 mg. of the *cis*-diketone (V) in 30 ml. of acetic acid with 0.2 ml. of 60% perchloric acid and 300 mg. of the palladium catalyst was complete in 14 hours. Evaporative distillation at 150° (0.1 mm.) of the crude product (532 mg., m.p. 134–141°) gave 520 mg. (95%), m.p. 138–141°, which was recrystallized from acetone affording material of m.p. 145.5–146.5° in 70–75% recovery. The purest sample, obtained as colorless needles from acetone, melted at 147–148° [reported (9b) in 42% yield, m.p. 140–141°].

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[11] Folin and Dennis, *J. Biol. Chem.*, **12**, 239 (1912). The material to be tested was triturated well with a small amount of 5% potassium hydroxide and the reagent then added dropwise, a blue color indicating a positive test.

Anal. Calc'd for $C_{20}H_{22}O_2$: C, 81.59; H, 7.53.
Found: C, 81.73; H, 7.60.

trans-2,8-Dihydroxy-4b,5,6,10b,11,12-hexahydrochrysene (VIb). Demethylation of 878 mg. of the *trans*-dimethoxy derivative (VIa) by heating overnight under nitrogen with 6 ml. of 48% hydrobromic acid and 50 ml. of acetic acid resulted, after diluting and filtering the reaction mixture, in 745 mg. (94%) of crude phenol, m.p. 262–267°, readily purified except for a trace of color by recrystallization from methanol. The analytical sample was obtained by sublimation at 185–200° (0.001 mm.) and recrystallization from methanol, m.p. 269–271° vac. [reported (1) m.p. 263–264°].

Anal. Calc'd for $C_{18}H_{18}O_2$: C, 81.18; H, 6.81.
Found: C, 81.19; H, 6.94.

The *trans-diacetate*, prepared in 75% yield by refluxing a solution of the crude phenol in acetic anhydride containing a drop of pyridine, was recrystallized from ethyl acetate, m.p. 201–202°.

Anal. Calc'd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33.
Found: C, 75.47; H, 6.47.

cis-2,8-Dihydroxy-4b,5,6,10b,11,12-hexahydrochrysene (VIb). Similar demethylation of the *cis*-dimethoxy derivative gave 91% of the crude phenol, m.p. 217–221°. The analytical sample, after sublimation at 180–200° (0.001 mm.) and recrystallization from methanol, was obtained as a colorless powder, m.p. 223.8–224.6° (vac.).

Anal. Calc'd for $C_{18}H_{18}O_2$: C, 81.18; H, 6.81.
Found: C, 80.80; H, 6.96.

The *cis-diacetate*, prepared in 80% yield, was recrystallized from ethyl acetate, m.p. 213–214°.

Anal. Calc'd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33.
Found: C, 75.48; H, 6.38.

2,8-Dimethoxychrysene (VIIa). A mixture of 100 mg. of the *trans*-hexahydro derivative (VIa) and 100 mg. of 30% palladium-on-carbon catalyst (20) was heated under nitrogen to 320° for 30 minutes. Digestion of the catalyst with hot benzene and crystallization of the product from the same solvent afforded a total of 85 mg. (87%), m.p. 276–279° (uncorr.). Further recrystallization gave material melting at 282–283° (uncorr.).

Anal. Calc'd for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59.
Found: C, 83.74; H, 5.70.

Similar dehydrogenation of the *cis*-hexahydro derivative afforded the same compound in similar yield, m.p. and mixed m.p. 282–283° (uncorr.).

2,8-Dihydroxychrysene (VIIb). Dehydrogenation of 100 mg. of the *trans*-dihydroxy hexahydro derivative (VIb) was carried out with 30 mg. of the palladium catalyst at 300°, and the product extracted from the catalyst with acetone was a gray solid. Sublimation at 260–280° (0.05 mm.) gave 90 mg. (92%) of material tinged with a blue color, m.p. 349–351° (vac., uncorr.). Recrystallization from acetone gave samples melting over a two-degree range as high as 386–388° (vac., uncorr.). Material purified through the diacetate and recrystallized from ethyl acetate-alcohol melted at 362–365° (vac., uncorr.), but evidently was still not completely pure.

Anal. Calc'd for $C_{18}H_{12}O_2$: C, 83.05; H, 4.65.
Found: C, 83.55; H, 5.35.

The *diacetate* was prepared in 68% yield from the crude sublimed phenol (m.p. 349–351°) by heating ten hours with acetic anhydride containing a small amount of pyridine. Recrystallization of the crude product (m.p. 270–272°) from benzene-acetone and finally acetone gave the pure diacetate as a colorless powder, m.p. 279–280° (vac.).

Anal. Calc'd for $C_{22}H_{16}O_4$: C, 76.74; H, 4.68.
Found: C, 76.67; H, 4.70.

SYNTHESES IN THE DESOXY SERIES

meso- and DL-*Methyl β,γ-diphenyladipate.* Following the procedure of Oommen and Vogel (7) as modified above in the methoxy series, 50 g. of methyl cinnamate in 200 ml.

of moist ether was reduced with 100 g. of amalgamated 8-mesh aluminum, maintaining a gentle reflux for 24 hours, adding ether as required and a total of 25 ml. of water. Working up as in the methoxy series, and crystallizing the product from methanol gave a total of 11.6–11.9 g. (23–24%) of the *meso*-ester, m.p. 172–176°. Recrystallization from methanol gave colorless needles, m.p. 177–177.5° (Oommen and Vogel obtained this isomer in 22–23% yield, m.p. 175°). Distillation of the filtrate resulted in 15.5 g. (31%) of methyl hydrocinnamate, b.p. 82–86° (0.3 mm.) and a higher fraction, 13.6 g., b.p. 165–185° (0.5 mm.), which afforded on crystallization from methanol 7.3 g. of the DL-ester, m.p. 71–72°, together with additional material melting at 61–66° to bring the total of this isomer to 20–25%. The pure DL-ester melted at 73–74° [reported (7) 16% yield, m.p. 73–74°].

meso- and DL-*β,γ-Diphenyladipic acid* (VIII). Alkaline hydrolysis of the *meso*-ester gave nearly pure *meso*-acid in 99% yield. After recrystallization from *n*-butyl alcohol it melted at 274–275° [reported (7, 12) m.p. 270–271° and 274.5–276.5°].

The DL-ester similarly afforded the DL-acid in 99% yield. This compound, colorless needles from methanol, melted at 185–186°; a sample inserted at 180° melted immediately, resolidified and remelted at 185–186°, indicating polymorphism [reported (7, 12) m.p. 184–186°, 185–186°].

cis- and trans-6,12-Diketo-4b,5,6,10b,11,12-hexahydrochrysene (IX). Cyclization of the *meso*-acid *via* the acid chloride as described in the methoxy series (*meso*) afforded 87% of diketone, m.p. 292–295°. Recrystallization from dioxane gave the *meso*-diketone, m.p. 303–304°, vac., uncorr. [reported (9) m.p. 293°].

Anal. Calc'd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38.

Found: C, 82.30; H, 5.61.

Cyclization of the DL-acid as described for the isomer in the methoxy series gave the diketone in 89% yield, m.p. 177–180°. Recrystallization from methanol raised the m.p. of the *cis*-diketone to 185–186° [reported (9) 184°].

cis- and trans-4b,5,6,10b,11,12-Hexahydrochrysene (X). Hydrogenation of 500 mg. of the *trans*-diketone in the presence of perchloric acid as described for the methoxy derivative was complete in three hours. The product was evaporatively distilled at 150–175° (0.1 mm.), giving 440 mg. (98%), m.p. 110–113°. Recrystallization from methanol gave material melting at 113–116° in 85% recovery, with the purest sample melting at 115–116° [reported (9) 115°].

Similar hydrogenation of the *cis*-diketone (five hours) gave the *cis*-hexahydrochrysene derivative in 70% yield; colorless crystals from methanol, m.p. 77–78° [reported (9, 12) 74–75°].

Both the *cis*- and *trans*-hexahydrochrysenes (40–50 mg.) gave chrysene (XI) on dehydrogenation with palladium-on-carbon at 300°; m.p. 252–253°, yield 82% and 75%, respectively.

SUMMARY

Improved procedures have been developed for the synthesis of *cis*- and *trans*-2,8-dihydroxyhexahydrochrysene and their configurations have been established. Estrogenic tests showed both isomers to have about the same activity. 2,8-Dihydroxychrysene and derivatives were prepared.

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