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

2,8-Dihydroxy-5,6,11,12-tetrahydrochrysene

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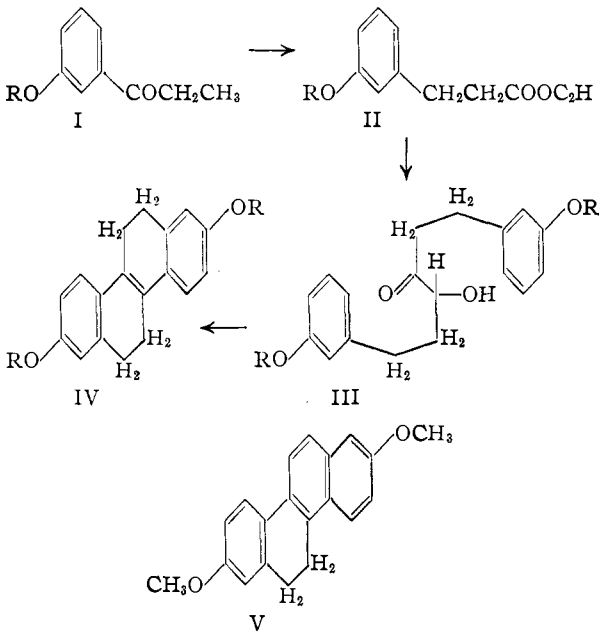
2,8-Dihydroxy-5,6,11,12-tetrahydrochrysene (IV, R = H), the closed ring analog of diethylstilbestrol, has been synthesized from *m*-hydroxypropiophenone as follows. Conversion to the methyl ether followed by a Willgerodt reaction and esterification gave ethyl β-*m*-methoxyphenylpropionate (II, R = CH_3). Treatment of this ester with sodium gave the acyloin III (R = CH_3) which was cyclodehydrated to the dimethoxy compound IV (R = CH_3). Demethylation with methylmagnesium iodide followed by acetylation yielded the diacetate IV (R = $COCH_3$), the structure of which was confirmed by ultraviolet spectroscopy and by dehydrogenation experiments. This compound did not exhibit the high estrogenic activity previously reported by Salzer.[2] Acid-catalyzed alcoholysis of IV (R = $COCH_3$) gave the free dihydroxy compound IV (R = H) which also exhibited weak estrogenic properties.

2,8-Dihydroxy-5,6,11,12-tetrahydrochrysene IV (R = H) is of particular interest because it represents the closed-ring analog of *trans*-diethylstilbestrol. Salzer[2] has recorded a synthesis of this substance *via* 6-methoxy-2-tetralone, and has reported that the diacetate IV (R = $COCH_3$) is active at a level of 10 γ in rats.



We have devised a 5-step synthesis of the dimethoxy compound IV (R = CH_3) from commercially available *m*-hydroxypropiophenone, I (R = H). Methylation with dimethyl sulfate and alkali followed by a Willgerodt reaction and esterification gave ethyl β-*m*-methoxyphenylpropionate, II (R = CH_3) in 40% over-all yield. Condensation of this ester with sodium gave the acyloin III (R = CH_3) which without purification was cyclodehydrated to IV (R = CH_3).[3] Anhydrous hydrogen fluoride was employed for the cyclization, and the product consisted of a mixture of the desired tetrahydrochrysene IV (R = CH_3) and the dihydro compound V, the latter presumably arising either by disproportionation of the former, or from α-diketone, which may have been present as an oxidative contaminant[4] in the acyloin. Although the best conditions for separating the mixture have not been ascertained, 10% of pure IV (R = CH_3) was easily isolated. Our product melted at 165.1–166.4° which is in good agreement with the m.p. of 164° reported by Salzer.[2] Birch and Smith,[3] on the other hand, found the m.p. 172–173°. Either the compound exhibits polymorphism or the English workers were dealing with a specimen contaminated with some of the higher melting (203°) dihydro compound (V) which is extremely difficult to remove by crystallization and when present in certain proportions raises the m.p. of IV (R = CH_3). The structure of our substance was confirmed by ultraviolet absorption spectroscopy and by dehydrogenation of the diacetate (see below). Dehydrogenation of the dihydro compound (V) over palladium-on-carbon gave 1 mole of hydrogen (per mole of V) and presumably 2,8-dimethoxychrysene.

The dimethoxy compound IV (R = CH_3) was demethylated with methylmagnesium iodide as described by Salzer,[2] and the crude phenol was converted to the diacetate IV (R = $COCH_3$). Our product melted at 210.6–211.8° as compared with the previously reported m.p. of 187°.[2] The structure of our material was confirmed by the ultraviolet absorption spectrum (see below) and by dehydrogenation over palladium-on-carbon which gave 2 moles of hydrogen (per mole of compound) and 2,8-diacetoxychrysene, compared by mixed m.p. determination with material prepared by an independent synthesis.[5]

The ultraviolet spectra of the dimethoxy and the diacetoxy compound IV (R = CH_3, and $COCH_3$) are very similar and except for the expected bathochromic shift due to the additional alkyl substituent in the aromatic rings, resemble closely those of 4,4′-dimethoxy- and 4,4′-diacetoxystilbene, respectively (see Figs. 1 and 2). It is of particular interest to note the striking difference between the spectra of IV (R = CH_3, and $COCH_3$) and the corresponding stilbestrol derivatives (Figs. 1 and 2). This observation may be considered as strong evidence in favor of the non-coplanarity of the latter substances,[6] since the tetracyclic compounds must represent the coplanar analogs.

The diacetate IV (R = $COCH_3$) was tested for

(1) Wisconsin Alumni Research Foundation Research Assistant, 1950–.

(2) W. Salzer, *Z. physiol. chem.*, **274**, 39 (1942).

(3) A. J. Birch and H. Smith, *J. Chem. Soc.*, 1882 (1951) have recently reported a similar study on the steps II → III → IV (R = CH_3). Our work, which has given somewhat different results, was completed in 1950; M.S. dissertation of C. A. Erickson, University of Wisconsin, 1950.

(4) *Cf.* M. Stoll and J. Hulstkamp, *Helv. Chim. Acta*, **30**, 1815 (1947).

(5) A. L. Wilds and R. E. Sutton, *J. Org. Chem.*, **16**, 1371 (1951).

(6) See R. N. Jones, THIS JOURNAL, **65**, 1818 (1943), and G. A. Jeffrey, H. P. Koch and S. C. Nyburg, *J. Chem. Soc.*, 1118 (1948).

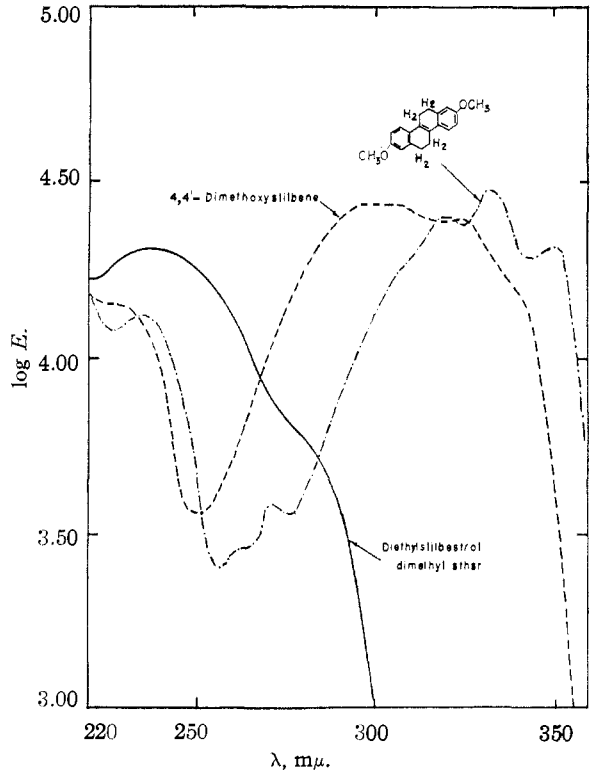


Fig. 1.

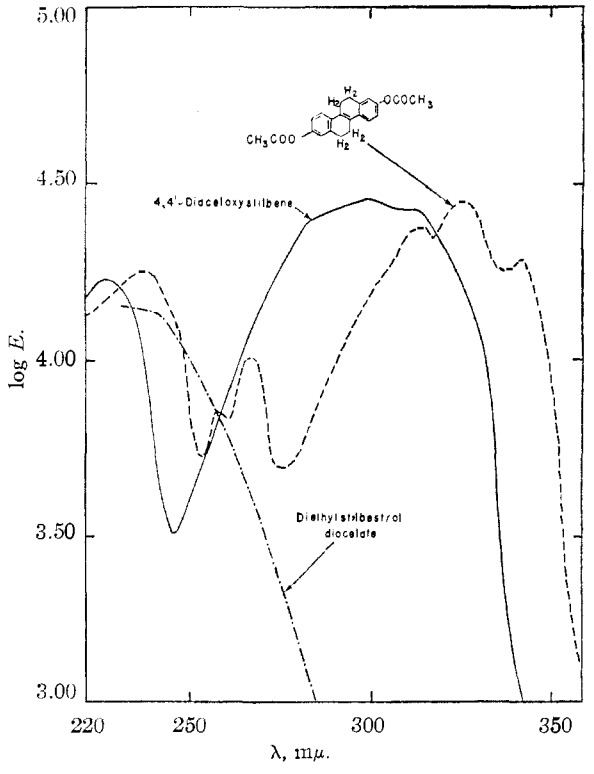


Fig. 2.

estrogenic activity by subcutaneous administration in ovariectomized rats (vaginal smear technique). Instead of the high activity (10γ) reported by Salzer,[2] this compound exhibited relatively weak estrogenic properties: 40–50% positive response at 100 γ level. It is perhaps significant that Solmssen and Wenis[7] similarly found considerably lower activity for 2-(*p*-hydroxyphenyl)-3-methyl-6-hydroxyindene and its diacetate than was reported by Salzer.[2]

The dihydroxy compound IV (R = H), m.p. 255–257°, was obtained by cleavage of the diacetate IV (R = $COCH_3$) with alcoholic hydrogen chloride. It was even less active than the diacetate showing no estrogenic response at 100 γ.

The low estrogenic activity of IV (R = H) and of IV (R = $COCH_3$) as compared with that of *trans*-diethylstilbestrol and its diacetate leads to the interesting suggestion that the molecule of a synthetic model of a steroid must have a thickness significantly greater than that of the benzenoid hydrocarbons in order to possess high activity. This "thickness" is presumably achieved in the case of diethylstilbestrol by its non-coplanarity The premise is further supported by the relatively low reactivity of the closed chain analogs in the hexestrol series.[5]

Acknowledgment.—We wish to thank the Sterling–Winthrop Research Institute for a generous supply of *m*-hydroxypropiophenone. We are also indebted to Drs. R. K. Meyer and E. G. Shipley of the University of Wisconsin Zoology Department for performing the physiological tests.

Experimental[8]

***m*-Methoxypropiophenone.**—A solution of 225 g. of *m*-hydroxypropiophenone (as obtained from alcohol by one recrystallization of material manufactured by Hilton–Davis Chemical Co.) in 500 ml. of 15% potassium hydroxide solution was methylated by adding with stirring 189 g. of dimethyl sulfate at 60–65°. While the temperature was maintained at 60°, an additional 250 ml. of 15% potassium hydroxide and 95 g. of dimethyl sulfate were then added alternately in six approximately equal portions. Finally 150 g. of 85% potassium hydroxide in 400 ml. of water was added, and the mixture heated for 1 hour on the steam-bath. The product was isolated by ether extraction in the usual way and on distillation yielded 213 g. (87% yield) of pale yellow product, b.p. 124–125° (10 mm.). The reported b.p. is 129° (14 mm.).[9] A sample redistilled through a 19-inch Fenske column packed with glass helices was obtained as a colorless liquid, $n^{25}D$ 1.5325.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.23; H, 7.33.

The 2,4-dinitrophenylhydrazone was obtained from ethanol–ethyl acetate as red needles, m.p. 189–191°.

Anal. Calcd. for $C_{16}H_{16}O_5N_4$: C, 55.81; H, 4.68. Found: C, 55.73; H, 4.69.

Ethyl β-*m*-Methoxyphenylpropionate.—The Willgerodt reaction was carried out according to the modification of Schwenk and Papa.[10] A mixture of 82 g. of once-distilled (yellowish) *m*-methoxypropiophenone, 25.6 g. of sulfur and 75 ml. of morpholine was boiled under reflux for 8 hours; then 500 ml. of 10% alcoholic sodium hydroxide was added and refluxing continued for an additional 6 hours. After adding 250 ml. of water, the alcohol was evaporated. The cooled solution was acidified with hydrochloric acid, extracted with ether, and the ether solution extracted thoroughly with saturated sodium bicarbonate solution. Acidification of the bicarbonate extracts gave an oil which was separated by ether extraction. The crude product (71–80 g.) obtained on evaporation of the ether solution was esterified by refluxing with 400 ml. of benzene, 70 ml. of alcohol and 3 ml. of concentrated sulfuric acid until no more

(7) U. V. Solmssen and E. Wenis, THIS JOURNAL, **70**, 4197 (1948).

(8) All melting points are corrected for stem exposure. The absorption spectra were determined in 95% ethanol solution on a Beckman quartz spectrophotometer.

(9) P. Grammaticakis, *Bull. soc. chim.*, [5] **7**, 540 (1940).

(10) E. Schwenk and D. Papa, *J. Org. Chem.*, **11**, 798 (1946).

water was liberated in an attached Cope water separator. Most of the benzene and alcohol were removed by distillation, and the residue was washed with cold 5% sodium hydroxide solution, then with water, dilute acid and finally water. Distillation gave 55–61 g. of pale yellow ester, b.p. 140–160° (10 mm.). In order to further purify this product and to remove sulfur impurities, it was refluxed with about 3 g. of Raney nickel in 150 ml. of alcohol for 3 hours. After filtration and removal of the alcohol by distillation, the residue was fractionated through a 19-inch Fenske column packed with glass helices. The colorless fraction of $n^{25}D$ 1.5023–1.5028 (mainly 1.5025) amounted to 43.2–48.4 g. (41.5–46.5% yield). A sample of ethyl β-*m*-methoxyphenylpropionate prepared by the sequence *m*-$O_2NC_6H_4CHO$ → *m*-$O_2NC_6H_4CH{=}CHCOOH$ → *m*-$H_2NC_6H_4CH{=}CHCOOH$ → *m*-$HOC_6H_4CH{=}CHCOOH$ → *m*-$HOC_6H_4CH_2CH_2COOH$ → II (R = CH_3), boiled at 183–184° (17 mm.), and had $n^{25}D$ 1.5022. Robinson and Walker[11] report the b.p. 145–146° (10.5 mm.).

The identity of the product from the Willgerodt reaction was confirmed by saponification of a sample of the purified ester to the well-known crystalline β-*m*-methoxyphenylpropionic acid, m.p. 44–46°. After recrystallization from petroleum ether (60–68°), the m.p. was not depressed on admixture with a specimen of the acid prepared by the alternate route (see above). The amides, prepared from both specimens of the acids, melted at 53.5–55.5° separately or when admixed. It is reported to melt at 56°.[12]

2,8-Dimethoxy-5,6,11,12-tetrahydrochrysene.—According to the general procedure of Hansley[13] 4.00 g. of ethyl β-*m*-methoxyphenylpropionate in 50 ml. of dry xylene was added dropwise with stirring over a period of 30 minutes to a hot (105–110°) suspension of 0.88 g. of sodium in 50 ml. of xylene. The reaction was carried out in an atmosphere of nitrogen. After heating with stirring for an additional 30 minutes the mixture was cooled, a little methanol was added to decompose excess sodium, and then the solution was washed thoroughly with water. The xylene was removed by steam distillation, and the residue was extracted with ether. The ether solution was dried over anhydrous sodium sulfate and concentrated. The residual yellow oil (2.2 g.) which could not be induced to crystallize was treated directly with about 150 ml. of anhydrous hydrogen fluoride. After standing overnight, the hydrogen fluoride had evaporated and the residual reddish gum was dried, dissolved in carbon tetrachloride and chromatographed on a 1.6 × 30 cm. wet-packed column of −80 mesh activated alumina. After a small oily fraction, a total of 0.352 g. of colorless crystalline fractions were eluted ranging in m.p. from 158–165° to 163–166°. This represented crude IV (R = CH_3) and by recrystallization from benzene a total of 0.281 g. of material of good quality melting above 163° was obtained. Repeated recrystallization gave colorless rhombohedra, m.p. 165.1–166.4°, λ_{max} 237 mμ (log *E* 4.13), 271 (3.59), 318 (4.41), 332 (4.89), 348 (4.33).

Anal. Calcd. for $C_{20}H_{20}O_2$: C, 82.16; H, 6.90. Found: C, 82.29; H, 6.93.

Further elution of the chromatographic column yielded a total of 0.207 g. of colorless crystalline fractions ranging in m.p. from 166–167° to 185–201°. Repeated recrystallization of the combined higher melting fractions from ethyl methyl ketone yielded **2,8-dimethoxy-5,6-dihydrochrysene** (V), as colorless needles, m.p. 202.1–203.4° (cloudy melt which became clear at 216°).

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.84; H, 6.26.

2,8-Diacetoxy-5,6,11,12-tetrahydrochrysene.—The crude dimethoxy compound was demethylated according to the method of Salzer[2] by heating 0.187 g. of the crude ether (m.p. 164–169°) with methylmagnesium iodide (from 0.060 g. of magnesium) at 160–180° until no more gas was evolved. The residue was cooled, treated with cold dilute hydrochloric acid and the solid organic material was taken up in ethyl acetate. On shaking the organic layer with 10% sodium hydroxide containing a little sodium hydrosulfite an insoluble sodium salt formed which was separated and decomposed with dilute hydrochloric acid. The phenol which was liberated was acetylated by treating with 1.5 ml. of acetic anhydride and 3 ml. of pyridine. After heating to boiling, then standing for 2 hours at room temperature, the mixture was diluted with water and the crude diacetate separated as colorless crystals, m.p. 205.5–210°; yield 0.173 g. Repeated recrystallization from acetic acid gave colorless plates, m.p. 210.6–211.8°, λ_{max} 236.5 mμ (log *E* 4.27), 257.5 (3.87), 266.5 (4.01), 313 (4.39), 341.5 (4.29).

Anal. Calcd. for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.91; H, 5.80.

2,8-Dihydroxy-5,6,11,12-tetrahydrochrysene.—A solution of 0.125 g. of the above diacetate in 10 ml. of ethanol saturated with hydrogen chloride was refluxed for 1.5 hours. The residue obtained on evaporation of the solvent was recrystallized from acetic acid to give 0.034 g. of pink crystals m.p. 248–253° (vac.), and 0.034 g. of tan crystals, m.p. 247–253° (vac.). Two recrystallizations of the first crop from acetic acid gave slightly pink crystals of the dihydroxy compound, m.p. 255–257° (vac.).

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.40; H, 6.20.

Dehydrogenation (a) of 2,8-Dimethoxy-5,6-dihydrochrysene.—A mixture of 0.040 g. (0.00014 mole) of the dimethoxy compound and 0.050 g. of 30% palladium-on-carbon[14] was heated in the Heymann type of apparatus[15] at 210° for 40 minutes during which 0.00015 mole of hydrogen was evolved. On raising the temperature to 290°, the product sublimed. Two recrystallizations from benzene gave colorless plates of what was probably impure 2,8-dimethoxychrysene, m.p. 270–276° (reported 273–275°,[3] 282–283°[5]). Sufficient material was not available for further purification.

Of **2,8-Diacetoxy-5,6,11,12-tetrahydrochrysene.**—A 0.047-g. (0.000135 mole) sample of the diacetate was dehydrogenated as described above over 0.049 g. of catalyst at 230–250° for 1 hour. A total of 0.00028 mole of hydrogen was evolved. The product was isolated in the customary manner, and recrystallized several times from acetic acid. It melted at 278–279° (vac.) alone or when admixed with an authentic specimen,[5] m.p. 279–280° (vac.), kindly furnished by Dr. A. L. Wilds.

4,4′-Diacetoxystilbene was prepared from 4,4′-dimethoxystilbene,[16] m.p. 214.5–215°—λ_{max} 227.5 mμ (log *E* 4.16), 299 (4.3), 302.5 (4.43), 324 (4.39)—by demethylation with methylmagnesium iodide followed by acetylation as described above for the preparation of IV (R = $COCH_3$). Repeated recrystallization from acetic anhydride gave colorless crystals, m.p. 215–218° (reported,[17] 213°), λ_{max} 226.5–228 mμ (log *E* 4.23), 298 (4.46), 311 (4.44).

The spectrum for diethylstilbestrol dimethyl ether (Fig. 1) was taken from Kharasch and Kleiman,[18] and that for diethylstilbestrol diacetate (Fig. 2) was taken from Solmssen.[19]

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(11) R. Robinson and J. Walker, *J. Chem. Soc.*, 192 (1936).

(12) L. Helfer, *Helv. Chim. Acta*, **7**, 945 (1924).

(13) V. L. Hansley, THIS JOURNAL, **57**, 2303 (1935).

(14) R. P. Linstead and S. L. S. Thomas, *J. Chem. Soc.*, 1127 (1940).

(15) L. F. Fieser, "Experiments in Organic Chemistry," 2nd edition, D. C. Heath and Co., Boston, Mass., 1941, p. 461.

(16) Prepared by the method of C. B. Frankforter and W. Kritchevsky, THIS JOURNAL, **36**, 1511 (1914).

(17) Edm. ter Meer, *Ber.*, **7**, 1200 (1874).

(18) M. S. Kharasch and M. Kleiman, THIS JOURNAL, **65**, 11 (1943).

(19) U. V. Solmssen, *ibid.*, **65**, 2370 (1943).