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1,1-Di-*p*-hydroxyphenyl-2,2-diethyl-ethylene, a New Isomer of Stilbestrol

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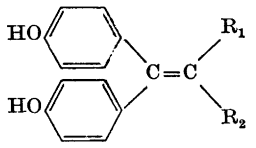
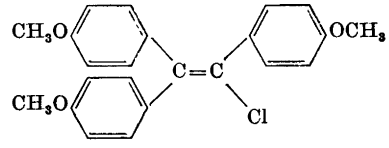
Interchanging one of the ethyl groups of diethylstilbestrol with one of the *para*-hydroxyphenyl groups gives a substance, 1,1-di-*p*-hydroxyphenyl-2,2-diethyl-ethylene, which is 50—100 times less estrogenic than diethyl-stilbestrol and is able to interfere with the vaginal estrus reaction if given intravaginally to spayed rats receiving estrogen systemically. The synthesis is made through the *p*-hydroxy-2-ethyl-butyrophenone or directly through the dimethyl ether obtained by an abnormal Friedel-Crafts reaction. The demethylation of the phenolic methoxyl groups must be effected with potassium hydroxide in triethyleneglycol. The demethylated compound decomposes on warming or in acidic media. The U.V. absorption of the new compound has been determined in different solvents.

In connection with work concerning the antagonism between natural or synthetic estrogens and related substances [1], the 2-alkylderivatives of 1,1-di-*p*-hydroxyphenyl-ethylene (I) became of interest. These substances are related to the substituted polyarylethylenes and particularly to TACE (trianisyl-chloroethylene) (II)



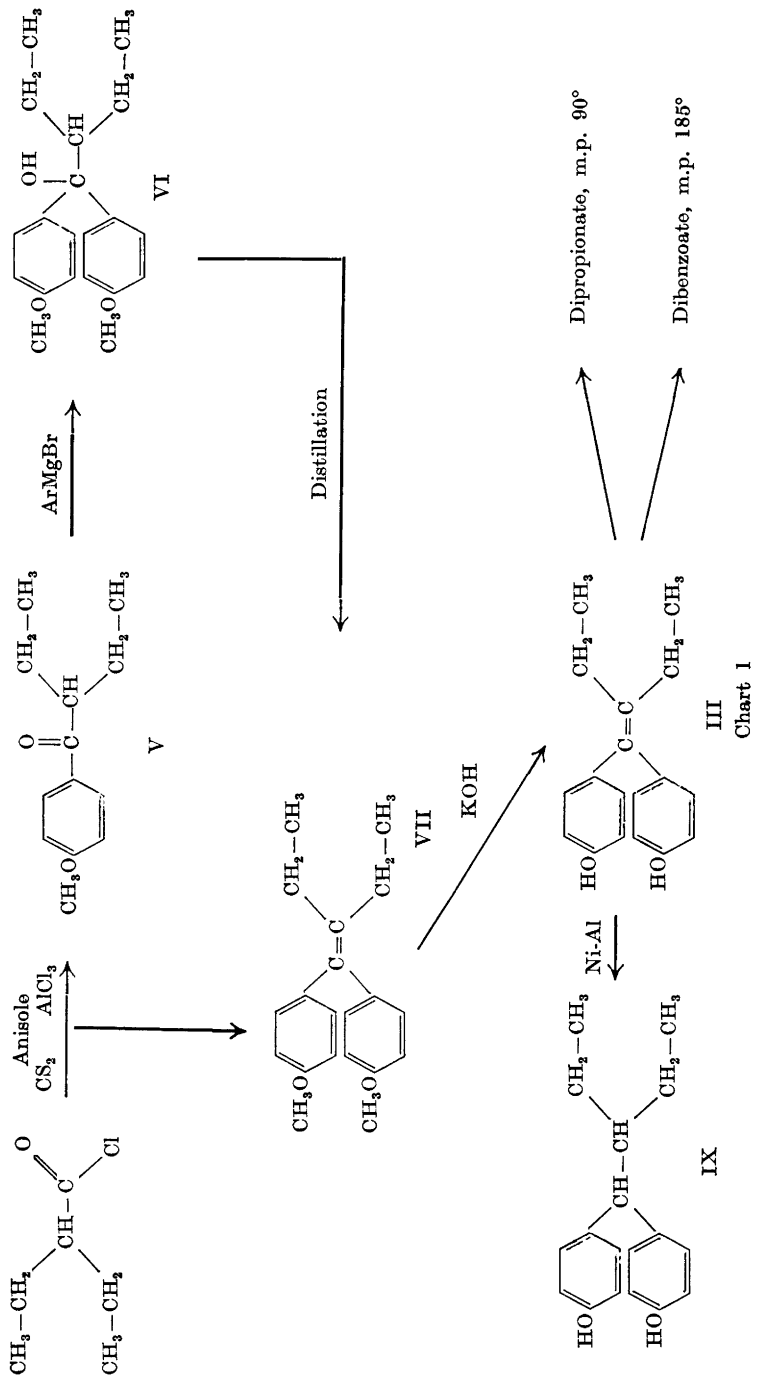
I



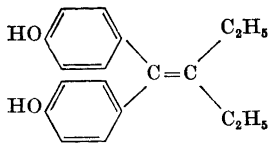
II

No alkyl-derivatives of I are described in the literature except 1,1-di-*p*-hydroxyphenyl-propylene which was prepared by Wessely [2]. He found the diacetate to give 66 % estrus response in 100 μg per rat. Later Lacassagne *et al.*[3] showed that the free compound has a very weak estrogenic activity, giving 66 % response at 15 mg/rat.

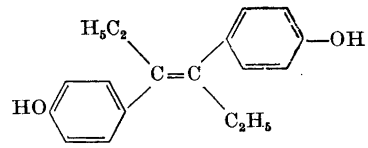
We have prepared several of the 2-alkyl and 2,2-dialkyl derivatives but the present report is concerned only with compound III: 1,1-di-*p*-hydroxy-


Anisole
CS_2 $AlCl_3$
ArMgBr
Distillation
KOH
Ni-Al
Dipropionate, m.p. 90°
Dibenzoate, m.p. 185°
V
VI
VII
III
IX
Chart 1

phenyl-2,2-diethyl-ethylene (*aa*DE for brevity). This compound is an isomer of diethyl-stilbestrol (IV) the difference being the transposition of an ethyl group and an aromatic group. Hence *aa*DE represents an interesting connection between diethyl-stilbestrol and the triphenyl-ethylene series.



III



IV

In a similar way Campbell [4] has studied the same transposition in the hexestrol series, where it causes a 50 000 fold drop in activity. In the case of the present compound the transposition has much less effect, the activity of *aa*DE is only 50 to 100 times less than that of diethyl-stilbestrol. Tested according to the technique of Bárány *et al.*[1], it interferes with the vaginal estrus reaction. Under the same conditions diethyl-stilbestrol is inactive. Further biological data will be reported elsewhere.

*aa*DE is prepared by a Grignard reaction of *p*-bromo-anisole with the *p*-methoxy-2-ethyl-butyrophenone (V). The carbinol (VI) so obtained dehydrates spontaneously during the distillation to give 1,1-di-*p*-methoxyphenyl-2,2-diethyl-ethylene (VII) which is then demethylated (Chart I).

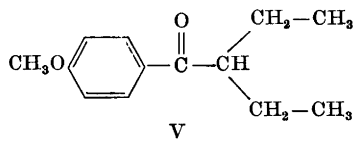
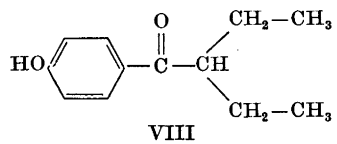
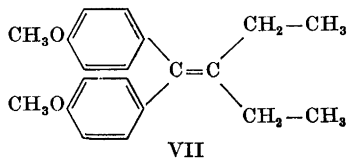
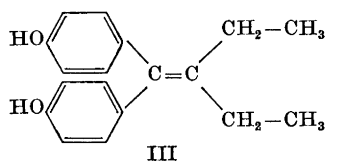
The new ketone (V) is prepared with good yields:
a) (74 % from the acid) by methylation of the *p*-hydroxy-2-ethyl-butyrophenone (VIII) obtained by the action of BF_3 on a mixture of diethyl-acetic acid and phenol;
b) (70 % from the acid) by a Friedel-Crafts reaction between diethyl-acetyl chloride and anisole in carbon disulfide.

The hydroxyketone (VIII) is a colourless and microcrystalline substance, the methoxy compound is a pleasantly smelling pale yellow oil which can be demethoxylated easily by pyridine hydrochloride.

Following earlier work on the U.V. absorption of hydroxyarylketones [5] we have now studied the absorption of compounds V and VIII in different solvents. Both show the characteristic band of the *para*-acetophenones. After solution in equal volumes of ethanol and 0.1 N NaOH, the bathochromic effect for the paramethoxy group is weak even for the stronger band, the maximum being 265 mμ in *cyclo*hexane, 273 mμ in ethanol and 277 mμ in the alkaline solution. For the parahydroxyketone the shift is from 280 mμ in ethanol to 328 mμ in alkaline solution and the intensity increase from log $\varepsilon = 4.17$ to log $\varepsilon = 4.41$. The first band shows in this case a shift from 221 mμ to 238 mμ (Fig. 1).

The dimethoxy derivative (VII) can be directly obtained in competition with the methoxyketone (VI) by an interesting modification of the Friedel-Crafts reaction, using more drastic conditions of temperature and the anisole in large excess. This reaction described for the first time by Gattermann [6], who obtained 1,1-di-*p*-methoxyphenyl-propene in addition to *p*-methoxy-propiophenone, has lately been studied by Mentzer and Xuong [7] and extended

Table 1.

	*Cyclo*hexane		Ethanol		50% Ethanol 50% HCl, 0.1 N		50% Ethanol 50% NaOH, 0.1 N	
	λ_{M-m}	log ε	λ_{M-m}	log ε	λ_{M-m}	log ε	λ_{M-m}	log ε
 V	—		—		210	3.92	—	
	215	4.19	220	4.10	219	4.04	219	4.08
	230	3.10	235	3.07	236	3.03	236	3.14
	265	4.27	273	4.24	277	4.21	277	4.26
 VIII	—		—		210	4.00	223	3.67
	—		221	4.00	220	4.10	238	3.86
	230	3.34	237	2.80	238	3.25	260	3.09
	261	4.19	280	4.17	280	4.23	328	4.46
 VII			222	4.07				
			241	4.29				
 III								
	221	4.12	221	4.31			230	4.16
	237	4.23	239	4.42			256	4.39

to the preparation of the triphenyl-ethylene derivatives by Xuong and Buu-Hoï [8]. We have previously determined the proportions of such 1,1-diaryl-ethylenes in the simultaneous preparation of *ortho*- and *para*-hydroxy-aryl-ketones[9]. Now yields of the ethylene derivative are varying from 12 to 20 % and at the same time 44—55 % of the ketones, calculated from the acid chloride used.

By chromic oxidation of the ethylene derivative (VII) *p,p'*-dimethoxy-benzophenone is formed in good yield. Demethylation of VII cannot be done by hydrobromic acid or other acidic agents which have little activity and produce polymerisation of the hydroxy compound formed. The best demethylation results are obtained with potassium or sodium hydroxide in boiling triethylene glycol.

The compound *αα*DE is a colourless microcrystalline substance. The melting point is 163° (instantaneous m.p.). It is soluble in ethanol, acetone,

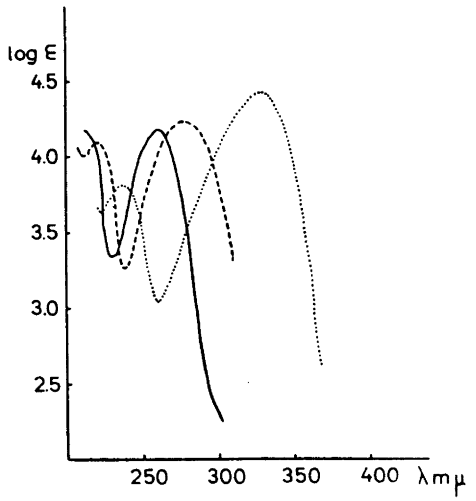


Fig. 1. —— *p*-hydroxy-2-ethyl-butyrophenone (VIII) in *cyclo*hexane. ------ compound VIII in ethanol 50 %, HCl 0.1 N 50 %. ····· compound VIII in ethanol 50 %, NaOH 0.1 N 50 %.

less soluble in benzene. It can be recrystallized from ligroin (100—125°), *cyclo*hexane, or a mixture: methanol 70 %, water 30 %. It is stable under alkaline and neutral conditions but very quickly formes coloured resins in acidic media. It gives a dipropionate, m.p. 89° and a dibenzoate, m.p. 184°. By reduction with nickel-aluminium alloy it forms compound IX which has previously been prepared by Campbell [4] by the action of diethyl-acetaldehyde on phenol.

EXPERIMENTAL

p-Hydroxy-2-ethyl-butyrophenone (VIII)

a) 12.6 g of diethyl-acetic acid and 12 g of phenol were slowly saturated during 2 h with BF_3. The temperature was then slowly elevated to 60—80° and kept there during one hour. The reaction product was poured into water, the ketone distilled easily under pressure 175°/1 mm. The ketone was dissolved at 25° in *cyclo*hexane and then recrystallized in the icebox as shiny soft colourless needles, m. p. 70°, yield 15.75 g (82 %).

b) 5 g of the methoxy derivative was refluxed with 5 g of pyridine hydrochloride for 20 min, then poured into water and extracted with ether. The organic layer was washed with water, dried, the ether distilled off and the ketone distilled. B. p. 175°/1 mm, yield 3.2 g (68 %). (Found: C 75.03; H 8.44. Calc. for $C_{12}H_{16}O_2$ (192.25): C 74.97; H 8.39).

Semicarbazone, colourless needles, m. p. 191° (from diluted ethanol). (Found: N 16.70. Calc. for $C_{13}H_{21}O_2N_3$ (251.32): N 16.72).

p-Methoxy-2-ethyl-butyrophenone (V)

13.5 g (0.1 mole) of diethyl-acetyl chloride [10] was mixed with 12 g anisole (0.1 mole + 10 %) in 80 ml of carbon disulfide, the mixture was cooled to 0° and 15 g of aluminium chloride added, the temperature being kept under 5°. After 24 h the mixture was refluxed one hour and poured into dilute cold hydrochloric acid. The organic layer taken up with ether was washed with 10 % aqueous sodium hydroxide, with water, then dried (Na_2SO_4) and the solvent removed by distillation. The distillation at 16 mm and 150—178° gave a yield of 16 g (78 %). A rectification at 16 mm and 172° afforded nearly colourless oil. n_D^{24} 1.5280 (Found: C 75.55; H 8.72. Calc. for $C_{13}H_{18}O_2$ (206.27) C 75.69; H 8.80).

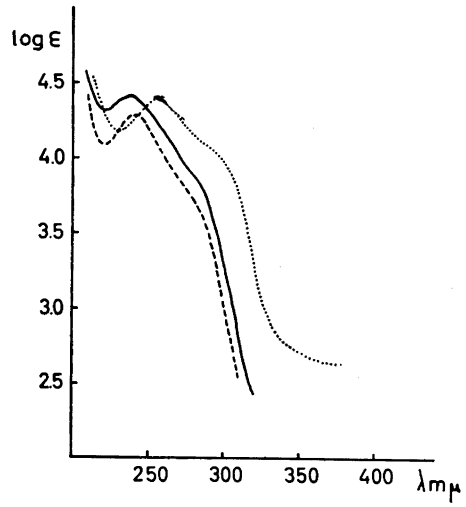


Fig. 2. ——— *aa*DE (III) in ethanol. ------ dimethylether *aa*DE (VII) in ethanol. ..... *aa*DE (III) in ethanol 50 %, NaOH 0.1 N 50 %.

Synthesis of a mixture of ketone (V) and ethylene (VIII)

13.5 (0.1 mole) of diethyl-acetyl chloride, 50 g anisole and 13 g aluminium chloride were mixed with good stirring keeping the temperature between 20 and 30°. After 24 h the mixture was refluxed during one hour and left at room temperature for 72 h. After normal decomposition and treatment, the red oil was distilled. The ketone distilled first under water pump pressure between 170° and 175°. When the temperature rose to 180° the oil pump was used and the ethylene (VIII) distilled at 195—200° under 1 mm Hg. After two recrystallizations from ethanol the ethylene melted at 90—91°.

The proportion of ketone and ethylene seems to depend on the time of contact between the reactants: with a time of 48 h the yield was an average of 61 % ketone and 8 % ethylene, with a time of 96 h the yield came to 42 % ketone and 8 % ethylene. (Found for the ethylene: C 80.93; H 8.12. Calc. for $C_{20}H_{24}O_2$ (296.39) C 81.04; H 8.16).

1,1-Di-*p*-methoxy-phenyl-2,2-diethyl-ethylene by Grignard reaction

11 g of *p*-bromo-anisole were slowly added to 3 g of magnesium-turnings in 80 ml anhydrous ether. After the end of the reaction the mixture was refluxed half an hour, then ice-cooled and 10 g of the ketone (VI), dissolved in 30 ml dried ether, slowly added. After the classical treatment and distillation the orange yellow oil crystallized spontaneously and gave after two recrystallizations in ethanol 10.7 g (72.4 %) of colourless microcrystalline substance. Melting point 90—91°. A mixture of crystals with those obtained by the abnormal Friedel-Crafts reaction gave the same melting point. (Found: C 80.96; H 8.24. Calc. for $C_{20}H_{24}O_2$ (296.39) C 81.04; H 8.16). Péteri[11] who obtained this substance as by-product in a synthesis of diethylstilbestrol gives a melting point of 86-88°.

Oxidation of 1,1-di-*p*-methoxy-phenyl-2,2-diethyl-ethylene

The preceding ethylene (2.5 g) treated with chromic acid (2 g) in acetic acid gave an exothermic reaction: the green solution was then poured into water. The solid precipitate was filtered and recrystallized from ethanol, m. p. 143—144°. The literature [12] gives the same melting point for *p,p'*-dimethoxy-benzophenone. (Found: C 74.28; H 5.76. Calc. for $C_{15}H_{14}O_3$ (242.26) C 74.36; H 5.83).

1,1-Di-*p*-hydroxyphenyl-2,2-diethyl-ethylene (*aa*DE) (III)

5 g of the ethylenic derivative (VIII) was refluxed with 5 g of potassium hydroxide in triethylene glycol with good stirring during 3 h. The mixture was then poured into 60 ml cold water, extracted with ether then acidified to pH 3 under ether. The ether layer was carefully washed with water until pH 6.6, dried with Na_2SO_4 and the ether distilled off. The oily precipitate crystallized on standing; after several recrystallizations from methanol (70 %) and water (30 %) long, colourless, soft needles were obtained, m. p. 163° (instantaneous m. p.), yield 3.2 g (76 %). (Found: C 80.37; H 7.61. Calc. for $C_{18}H_{20}O_2$ (268.34): C 80.56; H 7.51).

The dipropionate was obtained easily by refluxing the crude product with propionic anhydride in pyridine. After 30 min the mixture was poured into water, warmed to decompose the excess of anhydride and slightly acidified with hydrochloric acid, the dipropionate extracted with ether, the ether layer washed with a carbonate solution, with water, and dried (Na_2SO_4). The dipropionate recrystallized from ethanol as a colourless microcrystalline substance, m. p. 89—90°. (Found: C 75.74; H 7.42. Calc. for $C_{24}H_{28}O_4$ (380.46): C 75.76; H 7.42).

The dibenzoate was obtained by action of benzoyl chloride on an alkaline solution of *aa*DE. It recrystallized from ethanol and melted at 183—185°. (Found: C 80.60; H 5.84. Calc. for $C_{32}H_{28}O_4$ (476.54): C 80.64; H 5.92).

1,1-*p*-Hydroxy-phenyl-2,2-diethyl-ethane (IX)

1 g of *aa*DE was dissolved in 30 ml of 10 % NaOH and warmed to 90°. 2.5 g of nickel aluminium alloy was added in small portions with stirring, the mixture was then refluxed during one hour, filtered, the residue washed with hot water and the filtrate poured into hydrochloric acid. The precipitate was extracted with ether which was washed with water, dried and distilled off. The crystals mixed with oil were recrystallized from benzene, m. p. 168°. Campbell [4] who has prepared this compound by condensation of the diethylacetaldehyde with phenol, gives the same melting point.

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