4-hydroxyphenyl)-ethane, in common with hexestrol, are geometrically related to estradiol but, in contrast, have no estrogenic activity.

2. The amino analog of hexestrol, 3,4-bis-(*p*-aminophenyl)-hexane, is inactive.

3. Replacement of the *p*-hydroxyphenyl groups of hexestrol with 3,4-dihydroxyphenyl or *p*-hydroxybenzyl results in decreased estrogenic activity.

PEARL RIVER, N. Y. RECEIVED APRIL 20, 1943

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SCHIEFFELIN & CO.]

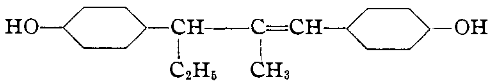
Synthetic Estrogenic Compounds. I. Monosubstituted Derivatives of 1,3-Di-(*p*-hydroxyphenyl)-propane

BY ALFRED H. STUART AND RALPH C. TALLMAN

The high estrogenic activity of di-*p*-hydroxy-1,2-diethylstilbene, or diethylstilbestrol has focused attention on this class of phenols. In connection with their development of diethylstilbestrol, Dodds and co-workers[1] have reported many other stilbene and diphenylethane derivatives. Dodds and Lawson[2] have also prepared various derivatives of di-(*p*-hydroxyphenyl)-methane, a series which was later investigated very thoroughly by Campbell.[3] With few exceptions, some estrogenic activity was reported throughout the series, although diethylstilbestrol remained by far the most potent.

The estrogenic effectiveness of derivatives of 1,3-di-(*p*-hydroxyphenyl)-propane has not been reported extensively. The parent substance was listed by Dodds and Lawson[2] as producing 100% estrus in ovariectomized rats in a dose of 100 mg. (We find the minimum effective dose to be 10 mg.) Di-anol (I), obtained as a gum from the demethylation of di-anethole, was reported by Campbell, Dodds and Lawson[4] as showing activity in doses of 50 to 100 γ, although they later found[5] the minimum effective dose of the hydrogenated product to be 1 mg. As part of a study of the relation of structure to estrogenic activity, there have been prepared in this Laboratory a number of compounds which can be considered as derivatives of di-(*p*-hydroxyphenyl)-propane, and in this paper are reported some of the simpler members of the series—namely, those containing one additional substituent in the 1- or 2-position.

Starting material for the first group (IV, R = H) was the known di-*p*-methoxychalcone (II). 1,4-Addition of various Grignard reagents produced the ketones (III), which were reduced, either by the Clemmensen method, or catalytically over copper–chromium oxide catalyst. The resulting ethers (IV, R = CH_3) were hydrolyzed and the phenols obtained as clear resins, some of which crystallized on long standing. The following R_1 groups were thus introduced: methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *n*-amyl, phenyl and benzyl.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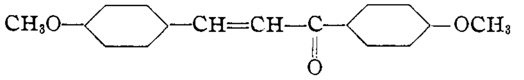
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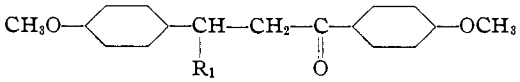
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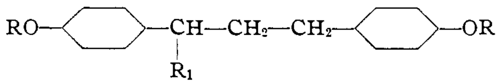
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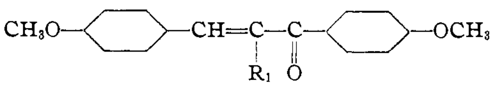
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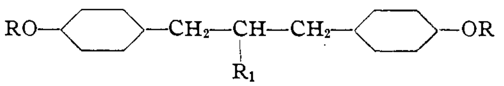
VI

The α-alkyl-di-*p*-methoxychalcones (V, R_1 = CH_3, C_2H_5, or *n*-C_3H_7) were prepared by condensation of anisaldehyde with various *p*-acylanisoles, dry hydrogen chloride being the most effective condensing agent. Reduction to the ethers (VI, R = CH_3) was effected in one step by high pressure hydrogenation over copper–chromium oxide catalyst at 220–230°. After hydrolysis, the phenols of this group were readily obtained in crystalline form. Campbell[6] has recently obtained 1,3-di-(*p*-methoxyphenyl)-2-methylpropane by the bimolecular condensation of anethole

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[1] Dodds, Golberg, Lawson and Robinson, *Proc. Roy. Soc.* (London), **B127**, 140 (1939).

[2] Dodds and Lawson, *ibid.*, **B125**, 222 (1938).

[3] Campbell, *ibid.*, **B129**, 528 (1940).

[4] Campbell, Dodds and Lawson, *Nature*, **141**, 78 (1938).

[5] Campbell, Dodds and Lawson, *Proc. Roy. Soc.* (London), **B128**, 253 (1940).

[6] Campbell, *J. Chem. Soc.*, 672 (1941).

TABLE I

1,3-DI-*p*-METHOXYPHENYL KETONES (III)

R_1	Yield[a]	M. p., °C.	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found	Semicarbazones m. p., °C.
CH_3	45	72	76.03	75.94	7.09	7.19	142–143
C_2H_5	80	70	76.13	76.36	7.40	7.70	127–128
n-C_3H_7	80	78–79	76.89	76.83	7.74	7.78	126–127
i-C_3H_7	75	51–52	76.89	77.20	7.74	7.67	166–168
n-C_4H_9	70	59	77.27	77.05	8.03	8.27	125–127
n-C_5H_{11}	75	70	77.59	77.75	8.29	8.22	
C_6H_5	75	88	79.72	80.02	6.41	6.55	
Benzyl	70	102	79.95	79.76	6.72	6.61	146
Anisyl	70	83–84	76.55	76.73	6.43	6.28	161–162.5

[a] Use of a smaller excess of Grignard reagent or higher reaction temperatures tends to increase the amount of by-products, which were not investigated. *Cf.* Kharasch and Sayles, THIS JOURNAL, **64**, 2972 (1942).

and also by an independent synthesis which establishes its structure. We repeated his synthesis and found the ether and phenol thus produced identical in every respect with the compounds obtained from reduction of di-*p*-methoxy-α-methylchalcone. The ethyl and *n*-propyl derivatives have not been reported previously.

The phenols of both series (IV and VI) were assayed for estrogenic activity by Dr. E. W. Blanchard of this Laboratory; all showed some potency, although of a comparatively low order. In the first group the phenols in which the substituent R_1 was phenyl or benzyl were even less active than the unsubstituted di-(*p*-hydroxyphenyl)-propane—the minimum effective Allen–Doisy rat unit being 15 to 20 mg. The rat unit for all the alkyl derivatives of both series seems to lie between 5 and 10 mg. In the first group (IV), a maximum appears to be reached when R_1 is *n*-propyl; the 2-ethyl compound (VI, R = H, $R_1 = C_2H_5$) is somewhat more effective than its homologs. In both series the differences are too slight to be of significance. Thus, introduction of a simple alkyl or aryl substituent into the chain of 1,3-di-(*p*-hydroxyphenyl)-propane does not materially affect the estrogenic activity. Much greater changes appear in more highly substituted derivatives, some of which will be reported in later papers.

Experimental[7]

Grignard Reactions.—Solid *p,p'*-dimethoxychalcone[8] was added in small portions to ether solutions of three molecular equivalents of the appropriate Grignard reagents (bromides being used in every instance except methyl iodide and benzyl chloride) maintained at −5 to −10°. After addition was complete, the cooling bath was removed, stirring continued for two to three hours and the mixtures worked up in the usual manner. The products were purified by distillation in an oil-pump vacuum and crystallization from ethanol.

Reduction.—The lower molecular weight ketones (III, R = CH_3, C_2H_5, C_3H_7) were reduced by the Martin modification of the Clemmensen method.[9] However, even in these instances, the reaction was incomplete, the difficulty increasing with ascending molecular weight. Catalytic hydrogenation was much more satisfactory. Ten grams of each ketone, in 50 cc. of ethanol, with 1 g. of copper–chromium oxide catalyst (prepared as described by Adkins[10]) was reduced completely within two to three hours at 200° and approximately 150 atm. pressures. Yields were nearly quantitative. Those ethers in which R_1 was aromatic were crystalline and could be purified by recrystallization from ethanol. Others were fractionally distilled under oil-pump vacuum.

Hydrolysis.—Two grams of each ether (IV, R = CH_3) was hydrolyzed by four hours of refluxing with a mixture of 20 cc. of 57% hydriodic acid and 10 cc. of glacial acetic acid. The hydrolysis could be effected also by heating the ethers with 2 parts of potassium hydroxide and 4 parts of ethanol for sixteen to eighteen hours at 200° in a rocking autoclave (*cf.* ref. 1). Those phenols in which R_1 was phenyl or benzyl readily solidified and were recrystallized from benzene. The tri-phenol (R_1 = *p*-HOC_6H_4) likewise solidified, but was so insoluble in ordinary solvents that no adequate purification was effected and no physiological assay could be obtained. The alkyl derivatives distilled to thick, clear resins; those which eventually solidified were crystallized from benzene–petroleum ether mixtures.

***p*-Methoxybutyrophenone.**—The yield reported by Skraup and Nieten[11] was considerably improved by use of the following procedure. To 650 cc. of petroleum ether (b. p. 45–55°), well stirred at 0°, was added 105 g. of reagent aluminum chloride, followed by 105 g. of anisole. After addition of 10 cc. of butyryl chloride, the mixture was warmed to 15–20° until hydrogen chloride evolution began, then cooled again and held at 0° while 90 cc. of butyryl chloride was dropped in. The mixture was allowed to warm to 15–20° with constant stirring, over the course of two hours, decomposed and worked up in the

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(7) Microanalyses by Dr. Carl Tiedcke, New York.

(8) Straus, *Ann.*, **374**, 139 (1910); Tognazzi, *Gazz. chim. ital.*, **54**, 699 (1924).

(9) Martin, THIS JOURNAL, **58**, 1440 (1936).

(10) Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wis., 1937, p. 13.

(11) Skraup and Nieten, *Ber.*, **57**, 1300 (1924).

TABLE II

1,3-DI-(*p*-METHOXYPHENYL)-PROPANES (IV, R = CH_3)

R_1	M. p., °C.	B. p., °C.	Mm.	d^{20}_4	n^{20}_D	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found
CH_3		152–154	1	1.0616	1.5579	79.95	79.35	8.21	7.65
C_2H_5		161–163	1	1.0398	1.5488	80.24	80.05	8.51	8.60
n-C_3H_7		198–200	3	1.0238	1.5447	80.49	80.27	8.78	9.00
i-C_3H_7		178–179	2			80.49	80.08	8.78	8.76
n-C_4H_9		201–203	3	1.0123	1.5437	80.73	80.64	9.03	8.79
n-C_5H_{11}		194–195	2	1.0096	1.5403	80.94	80.93	9.25	9.27
C_6H_5	63					83.10	83.00	7.28	7.28
Benzyl	36–38					83.20	83.22	7.56	7.53
Anisyl	62–63					79.52	79.43	7.23	6.91

TABLE III

1,3-DI-(*p*-HYDROXYPHENYL)-PROPANES (IV, R = H)

R_1	M. p., °C.	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found
CH_3	Resin	79.31	79.47	7.49	7.26
C_2H_5	99–100	79.65	80.06	7.87	7.71
n-C_3H_7	101	79.96	80.25	8.20	8.21
i-C_3H_7	Resin	79.96	79.77	8.20	8.20
n-C_4H_9	Resin	80.24	79.55	8.51	8.86
n-C_5H_{11}	Resin	80.49	79.60	8.78	8.94
C_6H_5	105–106	82.87	82.84	6.62	6.74
Benzyl	108–110	82.98	83.10	6.97	7.09

usual manner. The yield, after distillation, was 136 grams (85%).

***p*-Methoxyvalerophenone** was prepared in 80% yield by a procedure which differed from the above only in that the mixture was refluxed for fifteen minutes before decomposition.

Preparation of Di-*p*-methoxy-α-alkylchalcones.—The method employed was similar to that of Bogert and Davidson[12] for methyl (α-alkyl)-styryl ketones. A mixture of 1 mole of anisaldehyde and 1.5 moles of *p*-methoxypropiophenone, *p*-methoxybutyrophenone, or *p*-methoxyvalerophenone was cooled to about 15° and stirred or shaken while dry hydrogen chloride was passed in until one mole had been absorbed. This was usually close to saturation. Stirring or shaking was continued until the mass thickened or solidified. After standing overnight, it was taken up in benzene, dried, the solvent removed, the residue heated at 150° until hydrogen chloride evolution ceased, and finally distilled at 1–2 mm. About 0.5 mole of impure ketone was recovered in each run, followed by the much higher boiling product. Average yields based on anisaldehyde were 85–90%.

Di-*p*-methoxy-α-methylchalcone crystallized from ethanol in almost colorless needles, m. p. 60°.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.68; H, 6.25.

Di-*p*-methoxy-α-ethylchalcone was a pale yellow sirup, b. p. 200–203° at 1.5 mm.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.09; H, 6.71.

Di-*p*-methoxy-α-*n*-propylchalcone was a pale yellow sirup, b. p. 207–208° at 2 mm.

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 79.96; H, 8.20. Found: C, 80.25; H, 8.21.

Hydrogenation of α-Alkylchalcones.—A mixture of 10 to 15 g. of each chalcone with 1.5 g. of copper–chromium oxide catalyst[10] and 50 cc. of absolute alcohol was hydrogenated at 150–160 atm. and 220–230° for five hours. Initial hydrogen absorption appeared to set in at about 150°, but complete reduction was not obtained at temperatures below 220°. Yields were nearly quantitative.

Hydrolysis of the ethers was carried out as described above. The phenols were crystalline and could be purified by sublimation and by crystallization from benzene.

1,3-Di-(*p*-methoxyphenyl)-2-methylpropane, from hydrogenation of the methylchalcone, melted at 68–69° and showed no depression on mixed m. p. with a sample prepared from *p*-methoxy-α-methylcinnamic acid by the method of Campbell.[6] Hydrolysis of a sample of ether from each source with hydriodic–acetic acid mixture gave a phenol of m. p. 130°, the two showing no depression on mixed m. p. determination.

1,3-Di-(*p*-methoxyphenyl)-2-ethylpropane was recrystallized from ethanol, m. p. 43°.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.33; H, 8.46.

1,3-Di-(*p*-hydroxyphenyl)-2-ethylpropane, m. p. 102°.

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.87. Found: C, 80.07; H, 7.83.

1,3-Di-(*p*-methoxyphenyl)-2-*n*-propylpropane, colorless oil, b. p. 181° at 2 mm.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.70; H, 8.64.

1,3-Di-(*p*-hydroxyphenyl)-2-*n*-propylpropane, m. p. 118–119°.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.25; H, 8.03.

Summary

Alkyl and aryl derivatives of 1,3-di-(*p*-hydroxyphenyl)-propane have been prepared and tested for estrogenic activity.

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[12] Bogert and Davidson, THIS JOURNAL, **54**, 334 (1932); *cf.* also Abell, *J. Chem. Soc.*, **79**, 929 (1901).