tained; heating was then continued two hours, the reaction mixture was allowed to stand overnight and heating was resumed for three hours more. After attaching a condenser, the phosphorus oxychloride was distilled off from an oil-bath, heating being continued until the temperature of the vapor reached 140°. The residual dark acid chloride was transferred to a 50-cc. Claisen flask and distilled at 14 mm., the portion boiling at 80–90° being collected. This material was added, with cooling, to 50 cc. of absolute ethanol. In order to remove most of the hydrogen chloride formed, carbon dioxide was bubbled through the reaction mixture for several hours. Then the excess alcohol was removed on the steam-bath, and the residual oil distilled *in vacuo*. The fraction, b. p. 135–142° (15 mm.) weighed 31 g. (59%) and was substantially pure **ethyl chlorofumarate.**

1-Methyl-1,2-dicarbethoxy-Δ^2-cyclohexanedione-4,6 (enol).—In preparing this substance, the method of Ruhemann and Wolf[1] was followed closely. The crude product was washed thoroughly with benzene, recrystallized once from this solvent, and then thrice from aqueous alcohol; it then had m. p. 137–138° and weighed (from 0.078 mole of the reactants) 4.5 g. The absorption spectrum was observed in absolute ethanol: $\lambda_{max.}$ 326 mμ, log ϵ = 3.68, infl. ~250 mμ, log ϵ ~3.4.

Cresorsellinic Acid.—One gram of the condensation product (VI) was heated under reflux for two hours with 9 cc. of concentrated hydrochloric acid. The crystalline material which separated on cooling was collected and combined with a second crop obtained on further evaporation of the filtrate. The combined material (0.4–0.5 g.), on recrystallization from water (decolorizing charcoal), separated in large clear crystals which became opaque on drying at 100°, m. p. 245–246°, mixed with an authentic sample, m. p. 245–246°. (Since the fusion in this case is accompanied by some browning at *ca.* 230°, and extensive decomposition at the melting point, the mixed melting point is probably of no great significance.)

2,4,6,8-Tetrahydroxy-1,5-dimethylanthraquinone Tetraacetate.[4]—The hydrolysis product (0.2 g.) was dissolved in 2 g. of concentrated sulfuric acid by heating on the steam bath for ten to fifteen minutes. The resultant deep red solution was poured into 15 cc. of water; the flocculent orange precipitate was collected, washed well with water, dissolved in saturated baryta, and reprecipitated by hydrochloric acid. After filtration and washing, the product was dissolved in hot alcohol (*ca.* 15 cc.). On cooling, the orange microcrystalline quinone separated (*ca.* 0.1 g.), m. p. >300°. This material was boiled for two hours with 2 cc. of acetic anhydride and 0.3 g. of anhydrous sodium acetate. The reaction mixture was poured into water, the precipitated yellow product was collected, washed with water, and recrystallized first from alcohol and then from benzene: fine yellow needles, m. p. 231–232°, mixed with a sample prepared similarly from authentic cresorsellinic acid, m. p. 231–232°.

Summary

The condensation of ethyl α-acetylpropionate with ethyl chlorofumarate gives 1-methyl-1,2-dicarbethoxy-Δ^2-cyclohexanedione-4,6. The latter, on hydrolysis, is converted into cresorsellinic acid.

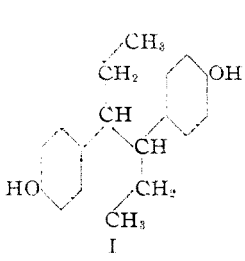
CAMBRIDGE, MASSACHUSETTS RECEIVED APRIL 12, 1943

[CONTRIBUTION FROM THE LEDERLE LABORATORIES]

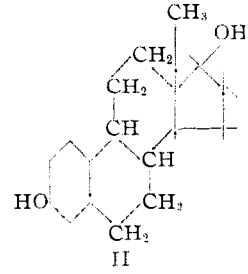
Some Analogs of Hexestrol

BY B. R. BAKER

It has been postulated[1] that hexestrol (I) owes its estrogenic activity to its geometrical relationship to estradiol (II). To test this theory 1,6-bis-(*p*-hydroxyphenyl)-hexane (III),[2] 1,3-bis-(*p*-hydroxyphenyl)-hexane (IV), and 1,2-bis-(2-ethyl-4-hydroxyphenyl)-ethane (V) were synthesized



I



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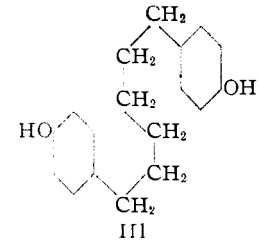
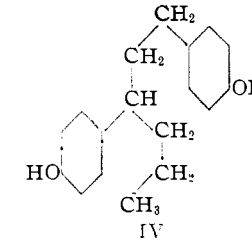
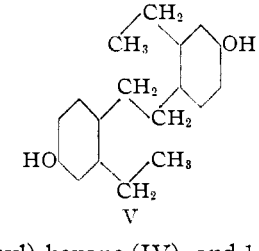


III



IV



V

(1) Dodds, Golberg, Lawson and Robertson, *Proc. Roy. Soc.* (London), **127**, 140 (1939); Dodds, *Lancet*, **2**, 953 (1939); Golberg, *J. S. African Chem. Inst.*, **23**, No. 2, 41 (1940); Plentl and Bogert, THIS JOURNAL, **63**, 989 (1941).

(2) Prepared by modifications of the method of Richardson and Reid, THIS JOURNAL, **62**, 413 (1940).

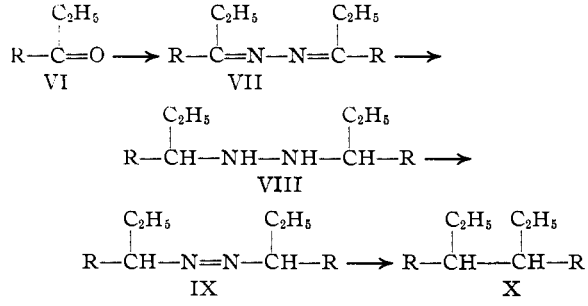
in which the ring system of estradiol was ruptured in other positions. However, the theory proved invalid in these cases, as all three compounds had little if any estrogenic activity.

The amino analog of hexestrol, 3,4-bis-(*p*-aminophenyl)-hexane, also had no activity in either the *meso* or *racemic* form.

Replacement of the *p*-hydroxyphenyl groups of hexestrol with 3,4-dihydroxyphenyl resulted in a fifty-fold decrease in estrogenic activity, while substitution with a *p*-hydroxybenzyl group destroyed the activity to a greater extent.

1,3-Dianisyl-1-propanone, obtained by hydrogenation of 4,4′-dimethoxychalcone with Raney nickel catalyst, when treated with *n*-propylmagnesium halide gave 1,3-dianisyl-3-hexanol, which was dehydrated to the corresponding hexene by distillation from potassium acid sulfate. Catalytic reduction of the double bond followed by demethylation resulted in the formation of 1,3-bis-(*p*-hydroxyphenyl)-hexane (IV).

Propioveratrone (VI, R = 3,4-dimethoxyphenyl-) after conversion to the azine (VII) was



hydrogenated in the presence of palladium to the tetrahydroazine (VIII), then oxidized with air to the dihydroazine (IX). Elimination of nitrogen[3] by refluxing a xylene solution of the dihydroazine gave the substituted hexane (X). The latter was demethylated to 3,4-bis-(3,4-dihydroxyphenyl)-hexane with hydrobromic acid.

In a similar manner *p*-propiopropionanilide was converted to *meso* and *racemic* 3,4-bis-(*p*-aminophenyl)-hexane. The higher melting *meso* isomer was identified by conversion to the *meso* form of hexestrol.

2-Ethyl-4-methoxybenzaldehyde was prepared from *m*-ethylanisole by the Gatterman[4] reaction. To prove that the aldehyde group entered *para* to the methoxyl, *m*-ethylphenol was converted to a mixture of 2-ethyl-4-hydroxybenzaldehyde and 2-hydroxy-4-ethylbenzaldehyde, which were separated by steam distillation. The non-volatile 2-ethyl-4-hydroxybenzaldehyde, after methylation, was treated with hydrazine and the product was identical with the aldazine obtained from *m*-ethylanisole. The latter was converted to 1,2-bis-(2-ethyl-4-hydroxyphenyl)-ethane (V) via the dihydroazine synthesis.

1-Anisyl-2-nitro-1-butene (XI), from the condensation of anisaldehyde with 1-nitropropane, was reduced with iron and hydrochloric acid in dilute ethanol to 1-anisyl-2-butanone (XII). The latter, when treated with ethyl cyanoacetate yielded the unsaturated cyano ester (XIII)[5] which was hydrogenated to ethyl α-cyano-β-(*p*-methoxybenzyl)-valerate (XIV). Ethylation of XIV followed by saponification and decarboxylation gave α-ethyl-β-(*p*-methoxybenzyl)-valeronitrile (XVI)[6] readily convertible by the action of *p*-anisylmagnesium bromide to the ketone (XVII), yielding 3,4-bis-(*p*-methoxybenzyl)-hexane (XVIII) by Clemmensen–Martin reduction. This compound

TABLE I

BIOASSAYS

Compound	No. rats[a]	Dose in γ	Response, %
3,4-Bis-(3,4-dihydroxyphenyl)-hexane	4	50	100
	7	20	29
	6	10	0
1,6-Bis-(*p*-hydroxyphenyl)-hexane	3	100	0
1,3-Bis-(*p*-hydroxyphenyl)-hexane	6	100	0
1,2-Bis-(2-ethyl-4-hydroxyphenyl)-ethane	6	100	0
3,4-Bis-(*p*-aminophenyl)-hexane			
(a) *racemic*	7	200	0[b]
(b) *meso*	4	200	0
3,4-Bis-(*p*-hydroxybenzyl)-hexane	4	50	0

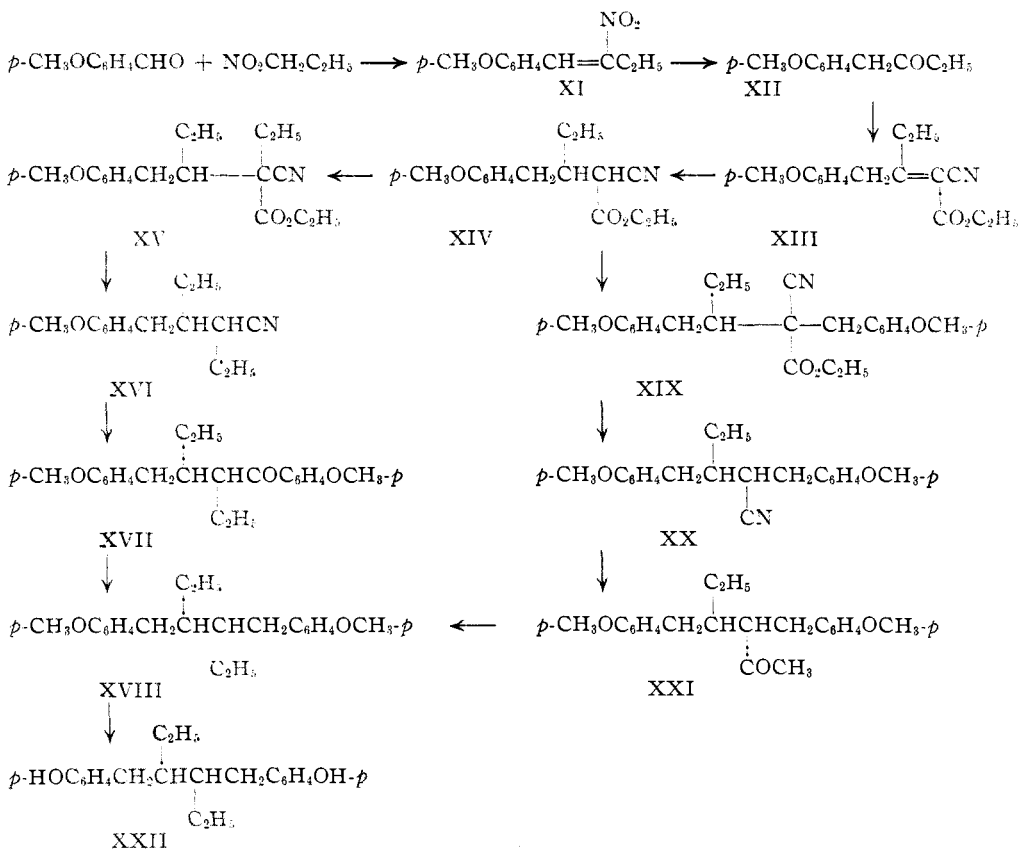
[a] Ovariectomized rats of 200–250 g. weight were given subcutaneous injections (0.1 cc.) of the substance to be tested in butyl succinate. Vaginal smears were taken at twenty-four, forty-eight and seventy-two hours. Complete disappearance of leucocytes was used as the criterion of full activity. All rats were "normal" in that they gave positive responses when injected with 1 microgram of diethylstilbestrol in butyl succinate. [b] At this level as well as at 50 micrograms about half of the rats had cornified cells present in the vaginal smear, but in no case was there complete disappearance of all the leucocytes.

(3) These transformations are based on a synthesis of hexestrol by Foldi and Fodor, *Ber.*, **74**, 590 (1941).

(4) The method of Adams and Montgomery, THIS JOURNAL, **46**, 1520 (1924), for the preparation of 2-methyl-4-methoxybenzaldehyde was employed.

(5) The excellent method of Cope, Hofmann, Wyckoff and Hardenbergh, THIS JOURNAL, **63**, 3452 (1941), was used.

(6) This nitrile was resistant to both alkaline and acid hydrolyses, little if any of the corresponding acid being formed. An attempt to prepare this acid by Clemmensen reduction of α-ethyl-β-anisoylvaleric acid, obtained by the action of α,β-diethylsuccinic anhydride and aluminum chloride on anisole, resulted in a good yield of α,β-diethyl-γ-anisylbutyrolactone.



was also synthesized, though less readily, by *p*-methoxybenzylation of the cyano ester (XIV) followed by saponification, decarboxylation, conversion of the α,β-bis-(*p*-methoxybenzyl)-valeronitrile (XX) to the ketone (XXI) with methylmagnesium iodide and finally Wolf–Kishner reduction.

1-Anisyl-2-butanone could be converted to the dihydroazine, but pyrolysis failed to give the desired hexane derivative (XVIII).

Acknowledgment.—The author is indebted to Drs. G. H. Carlson and Y. SubbaRow for their many helpful suggestions, to Dr. L. W. McElroy for the bioassays and Messrs. Louis Brancone, Philip Weiss and Louis Dorfman for the microanalyses.

Experimental

1,3-Dianisyl-1-propanone.—A mixture of 55 g. of 4,4'-dimethoxychalcone[7] and 200 cc. of ethanol was shaken with hydrogen at 2–3 atmospheres and 55° in the presence of Raney nickel, one mole equivalent of hydrogen being absorbed in thirty minutes. The filtered solution was combined with a similar reduction and kept in the refrigerator overnight. The product was collected on a filter, white crystals, m. p. 40–42°; yield, 88 g. By concentration of the filtrate an additional 6 g. (total 85%), m. p. 40–42°,[8] was obtained.

1,3-Dianisyl-2-hexene.—To the Grignard reagent from 55 cc. of *n*-propyl bromide and 14.4 g. of magnesium in 150 cc. of dry ether was added over a period of twenty minutes a solution of 81 g. of 1,3-dianisyl-1-propanone in 200 cc. of dry ether. After being refluxed for two hours, the mixture was decomposed with iced ammonium chloride, the separated ether layer washed twice with water and solvent removed. The residue was distilled from 3 g. of potassium acid sulfate *in vacuo*. At 100–120° water was split out from the carbinol, then the hexene distilled as a colorless oil, b. p. 188–190° (1 mm.), $n^{25}D$ 1.5687; yield, 78 g. (88%).

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.1; H, 8.2. Found: C, 80.7; H, 7.9.

The same yield was obtained using *n*-propylmagnesium iodide.

1,3-Dianisylhexane.—A solution of 38 g. of 1,3-dianisyl-2-hexene in 150 cc. of ethanol was shaken with hydrogen at 55° and 2–3 atmospheres in the presence of Raney nickel, reduction being complete in eight hours. The product was a colorless viscous oil, b. p. 178–180° (1 mm.), $n^{25}D$ 1.5485; yield, 37 g. (97%).

(7) Prepared in 87% yield by a modification of the procedure of Tognazzi, *Gazz. chim. ital.*, **54**, 697 (1924).

(8) Straus and Grundel (*Ann.*, **439**, 296 (1924)) give the m. p. as 42–43° using a platinum black catalyst. Their yield was considerably inferior and the product difficult to purify due to some reduction of the carbonyl.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.5; H, 8.8. Found: C, 80.4; H, 8.8.

1,3-Bis-(*p*-hydroxyphenyl)-hexane.—A mixture of 15 g. of 1,3-dianisylhexane, 27 cc. of 48% hydrobromic acid and 85 cc. of acetic acid was refluxed for five hours, diluted with water and the oil extracted with ether. The ether extract was in turn extracted with 10% aqueous sodium hydroxide, acidified and the separated oil taken up in ether. After removal of the solvent, the residue was distilled, b. p. 190–195° (1 mm.), and the distillate (11.3 g.) crystallized twice from ethylene dichloride to give a 61% yield of white crystals, m. p. 101.5–103° after drying at 70°.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.9; H, 8.2. Found: C, 79.8; H, 7.8.

After seed crystals were obtained, the dimethylation mixture could be diluted with water and the oil crystallized. Recrystallization from benzene–heptane gave an 81% yield of white crystals, m. p. 99–101°.

The bis-*p*-nitrobenzoate formed cream colored crystals from an acetic acid–alcohol mixture, m. p. 114–116°.

Anal. Calcd. for $C_{32}H_{28}N_2O_8$: C, 67.7; H, 5.0; N, 4.9. Found: C, 67.7; H, 5.4; N, 5.2.

1,6-Dianisylhexane.—A mixture of 11.3 g. of 1,4-dianisoylbutane,[9] 5.5 cc. of 85% hydrazine hydrate and 100 cc. of alcohol was refluxed three hours, solvent evaporated and the residue heated in an oil-bath with 16 g. of powdered potassium hydroxide. At 140° a copious evolution of gas took place. After ten minutes at 200°, the cooled mixture was diluted with water, the separated product extracted with ether, and washed with water. The residual oil after removal of the solvent was crystallized from alcohol yielding 8.4 g. (82%) of product, m. p. 64–67°,[2] suitable for demethylation. This method was found more convenient than Clemmensen reduction[2] which is reported to give a 62% yield.

3,4-Dimethoxypropiophenone Azine.—To a hot solution of 30.4 g. of 3,4-dimethoxypropiophenone[10] in 30 cc. of alcohol and 10 cc. of acetic acid was added 5 g. of 85% hydrazine hydrate in 10 cc. of alcohol. The mixture was refluxed for ten minutes, during which time the azine began to separate; yellow crystals, from benzene, m. p. 151–153°; yield, 24.5 g. (81%).

Anal. Calcd. for $C_{22}H_{28}O_4N_2$: C, 68.8; H, 7.3; N, 7.3. Found: C, 69.2; H, 7.2; N, 7.5.

3,4-Bis-(3,4-dimethoxyphenyl)-hexane.—A mixture of 14.3 g. of 3,4-dimethoxypropiophenone azine, 1 g. of palladium chloride, 30 cc. of acetic acid and 100 cc. of methanol was shaken with hydrogen at 2–3 atmospheres until solution of the azine was complete (about fifteen hours). After evaporation of the filtered solution to dryness *in vacuo* (bath 40°), the oily tetrahydroazine was dissolved in alcohol, treated with 3 cc. of 10% sodium hydroxide and 1 cc. of 10% copper sulfate, then aerated for two hours. Addition of water precipitated the semi-solid dihydroazine which was removed by filtration, dissolved in 100 cc. of xylene, dried over anhydrous sodium sulfate, then refluxed one hour. The solvent was removed *in vacuo* and the residue crystallized from alcohol, white crystals, m. p. 102–105°, which solidified and re-melted at 129–131°; yield 2.6 g. (19.5%). The pure product was obtained by recrystallization from alcohol by seeding with the higher melting form, m. p. 133–133.5°.

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.7; H, 8.4. Found: C, 73.7; H, 8.8.

3,4-Bis-(3,4-dihydroxyphenyl)-hexane.—A mixture of 0.30 g. of 3,4-bis-(3,4-dimethoxyphenyl)-hexane, 3 cc. of acetic acid and 3 cc. of 48% hydrobromic acid was refluxed four and one-half hours. Dilution with water gave 0.23 g. (91%) of white crystals, m. p. 231–235° which was unchanged by recrystallization from 50% acetic acid.

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.6; H, 7.4. Found: C, 71.5; H, 7.4.

***p*-Propiopropionanilide Azine.**—From 5 g. of *p*-propiopropionanilide,[11] 0.8 g. of 85% hydrazine hydrate and 5 cc. of acetic acid in 10 cc. of boiling alcohol was obtained 5 g. of product, m. p. 270–275°. Recrystallization from pyridine gave yellow crystals, m. p. 276–280°.

Anal. Calcd. for $C_{24}H_{30}N_4O_2$: C, 70.8; H, 7.4; N, 13.8. Found: C, 70.5; H, 7.5; N, 14.1.

***p*-Propiopropionanilide Dihydroazine.**—A mixture of 8 g. of *p*-propiopropionanilide azine, 90 cc. of methanol, 10 cc. of acetic acid and 0.5 g. of palladium chloride was shaken with hydrogen at one atmosphere, two more additions of catalyst (0.5 g.) being added to complete the reduction. After aeration of the ethanol solution of the tetrahydroazine in the presence of 2 cc. each of 10% sodium hydroxide and copper sulfate, the product was precipitated by the addition of water, yield 1.4 g. (18%). Recrystallization from ethanol gave white crystals gradually melting over 160° with decomposition.

Anal. Calcd. for $C_{24}H_{32}O_2N_4$: C, 70.7; H, 7.9; N, 13.7. Found: C, 71.1; H, 7.5; N, 13.5.

3,4-Bis-(*p*-propionaminophenyl)-hexane.—*p*-Propiopropionanilide dihydroazine (1.8 g.) was placed in a bath at 180°, fusion taking place with the evolution of gas which was completed by heating rapidly to 240°. The cooled product was recrystallized from hot acetic acid by dilution with water to incipient crystallization. After several hours at 5°, the *meso* form (0.65 g., m. p. 252–257°) was removed by filtration and recrystallized from dilute acetic acid, white needles, m. p. 261–264°. Dilution of the first filtrate with water gave white leaflets of the *racemic* form (0.53 g., m. p. 200–212°). One recrystallization from dilute acetic acid raised the m. p. to 207–215°, unchanged by further recrystallization.

Anal. Calcd. for $C_{24}H_{32}O_2N_2$: C, 75.8; H, 8.5; N, 7.4. Found: (*meso*) C, 75.9; H, 8.7; N, 7.4; (*racemic*) C, 75.9; H, 8.6; N, 7.8.

3,4-Bis-(*p*-aminophenyl)-hexane.—A mixture of 0.22 g. of the *meso* propionyl derivative, 2 cc. of alcohol and 2 cc. of concentrated hydrochloric acid was refluxed ninety minutes, diluted with water and basified with 3 cc. of 28% ammonia; white crystals from heptane, m. p. 132–134°; yield, 0.135 g. (88%).

(9) Fuson, Kuykendall and Wilhelm, THIS JOURNAL, **53**, 4191 (1931).

(10) Adams, Geissman, Baker and Teeter, *ibid.*, **63**, 531 (1941).

(11) Derick, *ibid.*, **35**, 1283 (1913).

Similarly the *racemic* diamine was obtained from the corresponding diamide, m. p. 63–65°.

Anal. Calcd. for $C_{18}H_{24}N_2$: C, 80.6; H, 9.0; N, 10.5. Found: (*meso*) C, 80.7; H, 8.8; N, 10.7; (*racemic*) N, 10.5.

To determine the configuration a solution of 0.22 g. of diamine (m. p. 132–134°) in 4.5 cc. of water and 1 cc. of concentrated sulfuric acid was treated at 0° with 0.3 g. of sodium nitrite in 3 cc. of water. After fifteen minutes the excess nitrous acid was destroyed with sulfamic acid and the filtered solution added dropwise to a boiling solution of 15 cc. of water and 20 cc. of concentrated sulfuric acid. The cooled mixture, diluted with water, was extracted with ether, the phenol removed with dilute alkali, acidified and crystallized from benzene–chloroform. The product was further purified by sublimation at 170° (1 mm.); white crystals, m. p. 184–187°. A mixture with an authentic sample of *meso*-hexestrol gave no depression in melting point.

2-Ethyl-4-methoxybenzaldehyde.—From 60 g. of *m*-ethylanisole,[12] 56 g. of zinc cyanide, 106 g. of anhydrous aluminum chloride and dry hydrogen chloride in 180 cc. of benzene was obtained 39 g. (53%) of a water-white liquid according to the method of Adams and Montgomery,[4] b. p. 133–134° (12 mm.); $n^{28}D$ 1.5543, which was mainly the desired aldehyde.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.2; H, 7.3 Found: C, 72.2; H, 7.3.

2-Ethyl-4-hydroxybenzaldehyde.—*m*-Ethylphenol (61 g.) was treated with 66 g. of zinc cyanide, 120 g. of anhydrous aluminum chloride, 180 cc. of benzene and dry hydrogen chloride.[4] The reaction mixture was decomposed with a mixture of ice and 50 cc. of concentrated sulfuric acid and steam-distilled to remove the volatile isomeric 2-hydroxy-4-ethylbenzaldehyde. The residual oil was extracted with ether, the extract washed with sodium bicarbonate solution and distilled. The product (16 g., 21%) boiled at 140–145° (1 mm.) and solidified in the receiver; white crystals from ether–petroleum ether, m. p. 51–53°.

Anal. Calcd. for $C_9H_{10}O_2$: C, 72.0; H, 6.7. Found: C, 71.9; H, 6.8.

The azine formed yellow crystals from ethanol, m. p. 204.5–206°.

Anal. Calcd. for $C_{18}H_{20}O_2N_2$: C, 73.0; H, 6.8; N, 9.5. Found: C, 73.6, 73.6; H, 6.9, 6.9; N, 9.6.

2-Ethyl-4-methoxybenzaldazine.—(A) From 18.5 g. of the aldehyde, 3.7 g. of 85% hydrazine hydrate and 2 cc. of acetic acid in 40 cc. of boiling ethanol for fifteen minutes was obtained 10.8 g. (59%) of product; yellow crystals from alcohol, m. p. 117–118°.

Anal. Calcd. for $C_{20}H_{24}O_2N_2$: C, 74.1; H, 7.5; N, 8.7. Found: C, 73.9; H, 7.9; N, 8.3.

(B) To a solution of 2.0 g. of 2-ethyl-4-hydroxybenzaldehyde and 1.75 cc. of methyl sulfate in 2.3 cc. of methanol was added 1.3 g. of potassium hydroxide in 4 cc. of water and the mixture heated on the steam-bath for ten minutes. The separated methoxyaldehyde was extracted with ether and washed with 10% sodium hydroxide, then water. After removal of the ether, the residue was refluxed with 0.4 g. of 85% hydrazine hydrate and 0.5 cc. of acetic acid in 3 cc. of ethanol to give 1.3 g. (59%) of yellow crystals, m. p. 117–118°. A mixed melting point with the product obtained by procedure A gave no depression

2-Ethyl-4-methoxybenzaldazine Dihydride.—A mixture of 6.6 g. of 2-ethyl-4-methoxybenzaldazine, 0.5 g. of palladium chloride, 15 cc. of acetic acid and 75 cc. of methanol was shaken with hydrogen at one atmosphere until the azine dissolved, which required slightly more than two molecular equivalents of hydrogen. Solvent was removed *in vacuo* (bath 40°), the residue aerated for ninety minutes in ethanol containing 3 cc. of 10% sodium hydroxide and 1 cc. of 10% copper sulfate, then diluted with water; yield, 5.0 g. (76%), m. p. 45–63°, suitable for the next step. For analysis a sample was recrystallized from methanol, cream colored leaflets, m. p. 70–73°.

Anal. Calcd. for $C_{20}H_{26}O_2N_2$: C, 73.7; H, 8.0; N, 8.6. Found: C, 74.0; H, 8.6; N, 8.6.

1,2-Bis-(2-ethyl-4-methoxyphenyl)-ethane.—A solution of 4 g. of the above compound in 25 cc. of xylene was refluxed one hour, solvent removed *in vacuo* and the residue distilled, b. p. 180–200° (1 mm.). The distillate (1.8 g.), dissolved in methanol, deposited 0.32 g. (8%) of white crystals, m. p. 60–62°.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.5; H, 8.8. Found: C, 80.1; H, 8.6.

1,2-Bis-(2-ethyl-4-hydroxyphenyl)-ethane (V).—A mixture of 0.18 g. of the corresponding ether, 3 cc. of 48% hydrobromic acid and 3 cc. of acetic acid was refluxed four hours, diluted with water and extracted with ether. The extract was washed with dilute sodium bicarbonate, then the diphenol removed with 10% sodium hydroxide. The product was purified by evaporative distillation at 150° (1 mm.) and recrystallization from benzene, white needles, m. p. 131–133°.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.9; H, 8.2. Found: C, 79.9; H, 8.6.

1-Anisyl-2-nitro-1-butene (X).—A mixture of 280 g. of anisaldehyde, 200 cc. of 1-nitropropane and 20 cc. of ethanolamine was allowed to stand at room temperature for forty-eight hours. Water, excess 1-nitropropane, and anisaldehyde were removed *in vacuo*, finally at 2 mm. The product then distilled at 143–144° (2 mm.) and solidified on standing; yield, 188 g. (44%). The combined forerun were treated with 10 cc. of ethanolamine and after three days an additional 89 g. of nitroölefin was obtained (total 64%). Recrystallization from methanol gave blunt yellow needles, m. p. 55–57°.

Anal. Calcd. for $C_{11}H_{13}O_3N$: C, 63.7; H, 6.3; N, 6.8. Found: C, 63.6; H, 6.4; N, 7.0.

1-Anisyl-2-butanone (XII).—A mixture of 207 g. of 1-anisyl-2-nitro-1-butene, 400 g. of iron filings, 5 g. of ferric chloride, 50 cc. of concentrated hydrochloric acid, 200 cc. of ethanol and 400 cc. of water was refluxed and stirred for sixteen hours, 135 cc. more of acid being added in three portions during the first ninety minutes. After the addition of 500 cc. of ethyl acetate, the mixture was filtered through Celite and the separated organic layer

(12) Obtained in 87% yield, b. p. 75–76° (12 mm.), by methylation of *m*-ethylphenol (Eastman) using the method of Perkin (*J. Chem. Soc.*, **89**, 1649 (1906)); *cf.* Klages, *Ber.*, **36**, 3592 (1903).

distilled, b. p. 105–120° (1 mm.). Redistillation gave 115 g. (65%) of product; colorless liquid, b. p. 142–147° (13 mm.).[13] The semicarbazone formed white crystals from ethanol, m. p. 153–154°.

Anal. Calcd. for $C_{12}H_{17}O_2N_3$: C, 61.3; H, 7.4; N, 17.9. Found: C, 61.5; H, 7.5; N, 17.9.

1-Anisyl-2-butanone Dihydroazine.—The ketone (10 g.) was converted to the oily azine, its methanol solution treated with Raney nickel, then reduced with palladium chloride and hydrogen in the same manner as 2-ethyl-4-methoxybenzaldazine, white crystals from methanol, m. p. 89–90°; yield, 4.1 g. (41%).

Anal. Calcd. for $C_{22}H_{30}O_2N_2$: C, 74.6; H, 8.5; N, 7.9. Found: C, 74.2; H, 8.2; N, 8.0.

Attempts to remove nitrogen from the dihydroazine by pyrolysis resulted mainly in half-molecular weight compounds and some azine.

Ethyl α-Cyano-β-(*p*-methoxybenzyl)-α-pentenoate (XIII).—A mixture of 38.7 g. of 1-anisyl-2-butanone, 3.5 g. of ammonium acetate, 27 cc. of ethyl cyanoacetate, 10 cc. of acetic acid and 50 cc. of benzene was refluxed under a constant water separator[5] for five hours, washed with water and distilled; yellow oil, b. p. 167–168° (1 mm.), $n^{32}D$ 1.5321; yield, 43.6 g. (72%).

Anal. Calcd. for $C_{16}H_{19}NO_3$: N, 5.1. Found: N, 5.3.

Ethyl α-Cyano-β-(*p*-methoxybenzyl)-valerate (XIV).—A solution of 43.5 g. of the above compound in 100 cc. of methanol was shaken with hydrogen at 2–3 atmospheres in the presence of 0.3 g. of Adams catalyst; one molecular equivalent of hydrogen was absorbed rapidly; yellow oil, b. p. 158–159° (1 mm.), $n^{32}D$ 1.5050; yield, 39.6 g. (91%).

Anal. Calcd. for $C_{16}H_{21}NO_3$: N, 5.1. Found: N, 5.2.

Ethyl α-Cyano-α-ethyl-β-(*p*-methoxybenzyl)-valerate (XV).—To a suspension of sodium ethylate from 4 g. of sodium and 25 cc. of absolute ethanol in 25 cc. of benzene was added 40 g. of ethyl α-cyano-β-(*p*-methoxybenzyl)-valerate in 25 cc. of benzene and 35 cc. of ethyl bromide. After being refluxed ten hours, the mixture was diluted with water, acidified with acetic acid, the separated organic layer washed with water and distilled; yellow oil, b. p. 176–178° (2 mm.) $n^{30}D$ 1.5022; yield, 40.5 g. (92%).

Anal. Calcd. for $C_{18}H_{25}O_3N$: C, 71.3; H, 8.3; N, 4.6. Found: C, 71.1; H, 8.2; N, 4.9.

α-Ethyl-β-(*p*-methoxybenzyl)-valeronitrile (XVI).—A mixture of 15 g. of the above cyano ester and 3.3 g. of potassium hydroxide in 60 cc. of diethylene glycol was heated at 135–140° for fifteen minutes, cooled, diluted with water, acidified and extracted with benzene. Solvent was removed and the residue heated at 200° with a trace of copper oxide until decarboxylation was complete, then distilled; light yellow oil, b. p. 135–136° (1 mm.), $n^{29}D$ 1.5082; yield, 10.6 g. (94%).

Anal. Calcd. for $C_{15}H_{21}ON$: C, 77.9; H, 9.2; N, 6.1. Found: C, 78.0; H, 9.0; N, 5.8.

(13) Wessely, Kerschbaum, Kleedorfer, Prillinger and Zojic, *Monatsh.*, **73**, 127 (1940), prepared this ketone, b. p. 150–160° (bath temperature) at 10 mm., by the less convenient condensation of ethyl propionate and *p*-methoxybenzyl cyanide and give the melting point of the semicarbazone as 156–157°.

α,β-Diethylsuccinic Anhydride.—The following method of preparation was found superior to the condensation of ethyl α-bromobutyrate with ethyl cyanoacetate followed by ethylation, hydrolysis and conversion to the anhydride.[14]

To a suspension of ethyl sodiocyanoacetate from 113 g. of the ester, 23 g. of sodium and 400 cc. of absolute alcohol (commercial) was added 85 g. of propionaldehyde cyanohydrin in portions maintaining the temperature at 20–23° with the aid of an ice-bath. After twenty-two hours at room temperature, the solution was treated with 150 cc. of ethyl bromide, refluxed seven hours, poured into ice-water and extracted with ether. The α-carbethoxy-α,β-diethylsuccinonitrile was a colorless oil, b. p. 135–136° (3 mm.), $n^{32}D$ 1.4367; yield, 109 g. (52%).

Anal. Calcd. for $C_{11}H_{16}O_2N_2$: C, 63.3; H, 7.7; N, 13.4. Found: C, 63.4; H, 7.7; N, 13.3.

A mixture of 100 g. of the dinitrile and 800 cc. of 18% hydrochloric acid was refluxed forty-eight hours, the solid acid removed by filtration and the filtrate evaporated to dryness *in vacuo*. The residue was extracted with acetone, filtered and solvent distilled. An ether solution of both fractions of the acid was dried with anhydrous sodium sulfate, solvent removed and the residue refluxed one hour with 125 cc. of acetyl chloride. The α,β-diethylsuccinic anhydride was a colorless oil, b. p. 100–102° (1 mm.); yield, 68.5 g. (91%).

Methyl α-Ethyl-β-anisoylvalerate.—To a mixture of 22 g. of anhydrous aluminum chloride and 25 cc. of benzene was added dropwise 10 g. of anisole in 10 cc. of benzene followed by 10 g. of α,β-diethylsuccinic anhydride in 15 cc. of benzene maintaining the temperature at 15–20° with the aid of an ice-bath. After twenty-four hours at room temperature protected from moisture, the mixture was poured on iced hydrochloric acid and the separated benzene layer extracted with 10% sodium hydroxide. Acidification yielded an oily acid which was esterified by refluxing its solution in 75 cc. of methanol, 75 cc. of benzene and 7.5 cc. of concentrated sulfuric acid for eighteen hours in a Soxhlet apparatus containing anhydrous magnesium sulfate in the thimble. The cooled solution was washed with water, dilute sodium bicarbonate and water, then distilled, colorless oil, b. p. 150–152° (1 mm.), $n^{29}D$ 1.5193; yield, 16.3 g. (91%).

Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.0; H, 8.0. Found: C, 69.0; H, 7.9.

When the crude keto acid was refluxed one hour with acetyl chloride a 73% yield (based on the α,β-diethylsuccinic anhydride) of the enol lactone was obtained, b. p. about 170° (1 mm.), which would not dissolve in alkali even after prolonged heating.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.2; H, 7.3. Found: C, 73.0; H, 7.0.

α,β-Diethyl-γ-anisylbutyrolactone.—A mixture of 25 g. of zinc amalgam, 15 cc. of water, 35 cc. of concentrated hydrochloric acid, 20 cc. of toluene and 8 g. of methyl α-ethyl-β-anisoylvalerate was refluxed sixty-two hours with the addition of 50 cc. of concentrated hydrochloric acid in six portions and 15 g. more of zinc amalgam after forty hours. The separated organic layer was washed

(14) Verkade and Hartmann, *Rec. trav. chim.*, **52**, 945 (1933).

with dilute alkali and water, then distilled, b. p. 143–146° (2 mm.), $n^{29}D$ 1.4963; yield, 5 g. (70%).

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 72.6; H, 8.1. Found: C, 72.9; H, 8.5.

The alkali soluble fraction gave only a trace of acid on acidification.

1,4-Dianisyl-2,3-diethyl-1-butanone (XVII).—To the Grignard reagent from 15.6 g. of activated magnesium,[15] 78 cc. of *p*-bromoanisole and 260 cc. of dry ether was added 34.5 g. of α-ethyl-β-(*p*-methoxybenzyl)-valeronitrile in 260 cc. of benzene. After being refluxed fifteen hours the solution was poured on ice and 360 cc. of concentrated hydrochloric acid. Benzene and ether were removed *in vacuo* from the three layer system and the residual oil refluxed with the aqueous solution for one hour, then extracted with benzene. The product distilled at 210–215° (2 mm.) with some decomposition. A solution of the distillate in chloroform was washed with water, then redistilled; yellow oil, b. p. 208–211° (1 mm.); $n^{29}D$ 1.5620; yield, 20 g. (57%).

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.6; H, 8.3. Found: C, 77.8; H, 8.1.

In another run using 2.6 g. of magnesium, 13 cc. of *p*-bromoanisole and 5 g. of the nitrile, the yield was 5.5 g. (76%).

Ethyl α-Cyano-α,β-bis-(*p*-methoxybenzyl)-valerate (XIX).—To a suspension of sodium ethylate from 1.85 g. of sodium and 10 cc. of absolute ethanol in 25 cc. of benzene was added 20 g. of ethyl α-cyano-β-(*p*-methoxybenzyl)-valerate (XIV) in 10 cc. of benzene and 13.3 g. of *p*-methoxybenzyl chloride[16] in 25 cc. of benzene. After being refluxed for twenty hours, the mixture was washed with dilute acetic acid, then distilled; viscous yellow oil, b. p. 225–230° (1 mm.), $n^{32}D$ 1.5445; yield, 22 g. (77%).

Anal. Calcd. for $C_{24}H_{29}O_4N$: N, 3.5. Found: N, 3.5.

α,β-Bis-(*p*-methoxybenzyl)-valeronitrile (XX).—From 38.3 g. of the above compound and 7 g. of potassium hydroxide in the manner described for α-ethyl-β-(*p*-methoxybenzyl)-valeronitrile was obtained 26.9 g. (85%) of the product, b. p. 214–216° (1 mm.), which partially solidified in the receiver.

Anal. Calcd. for $C_{21}H_{25}O_2N$: N, 4.3. Found: N, 4.1.

Several recrystallizations from ethanol gave one of the pure racemates, m. p. 136–137°.

3,4-Bis-(*p*-methoxybenzyl)-2-hexanone (XXI).—To the Grignard reagent from 5.6 g. of magnesium and 15 cc. of methyl iodide in 50 cc. of dry ether was added 23.5 g. of α,β-bis-(*p*-methoxybenzyl)-valeronitrile in 75 cc. of benzene, then refluxed eighteen hours. The solution was poured on ice and 100 cc. of concentrated hydrochloric acid, ether and benzene evaporated from the mixture and the residue heated on the steam-bath for one hour. The separated oil was extracted with benzene and distilled, b. p. 213–216° (1 mm.), $n^{32}D$ 1.5462; yield 21.9 g. (89%).

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.6; H, 8.3. Found: C, 77.2; H, 8.4.

After several weeks the mixture of isomers partially crystallized. Several recrystallizations from methanol gave white crystals, m. p. 86–88°.

(15) Slotta and Heller, *Ber.*, **63**, 3031 (1930).

(16) Vavon, Bolle and Calin, *Bull. soc. chim.*, [5] **6**, 1025 (1939).

3,4-Bis-(*p*-methoxybenzyl)-hexane (XVIII).—(A) A mixture of 35 g. of zinc amalgam, 15 cc. of water, 35 cc. of concentrated hydrochloric acid, 10 cc. of acetic acid, 6 g. of 2,3-diethyl-1,4-dianisyl-1-butanone and 20 cc. of toluene was refluxed for one hundred hours with the addition of 168 cc. of concentrated hydrochloric acid in ten portions. After forty-eight hours an additional 17 g. of zinc amalgam was added. The cooled mixture was extracted with benzene, washed with dilute acid and distilled, yellow oil, b. p. 190–195° (1 mm.), $n^{29}D$ 1.5462; yield, 4.1 g. (72%). The analysis indicated that some ketone was still present, but a pure isomer could be isolated as described below.

Anal. Calcd. for $C_{22}H_{30}O_2$: C, 80.9; H, 9.3. Found: C, 80.4; H, 8.8.

When a solution of 3.3 g. of the product in methanol was seeded with the crystalline methyl ether (obtained by remethylation of 3,4-bis-(*p*-hydroxybenzyl)-hexane as described below), 0.7 g. of crystalline product separated, m. p. 60–68°. Recrystallization from methanol gave the pure isomer, m. p. 71–72°.

Anal. Found: C, 80.6; H, 9.3.

(B) To a suspension of sodium benzylate from 1 g. of sodium and 50 cc. of benzyl alcohol was added 5.5 g. of 3,4-bis-(*p*-methoxybenzyl)-2-hexanone and 5 cc. of 85% hydrazine hydrate, then the mixture refluxed for twenty hours using an air condenser. After removal of the benzyl alcohol by steam distillation, the residue was extracted with petroleum ether and distilled, yellow oil, b. p. 195–200° (1 mm.), $n^{32}D$ 1.5547; yield, 2.3 g. (44%).

Anal. Found: C, 81.2; H, 8.9.

When a methanol solution of 4.1 g. of a similar preparation was seeded with the crystalline isomer, 0.3 g., m. p. 70–72° was obtained. A mixture with the methyl ether obtained by procedure A gave no depression in melting point.

3,4-Bis-(*p*-hydroxybenzyl)-hexane (XXII).—A mixture of 4.0 g. of the isomeric 3,4-bis-(*p*-methoxybenzyl)-hexanes (obtained by procedure A), 20 cc. of hydriodic acid (d. 1.7) and 35 cc. of acetic acid was boiled in a modified Claisen flask until methyl iodide no longer distilled.

After dilution with water, the separated oil was extracted with ether, washed with water and dilute sodium bisulfite, then the phenolic material extracted with 10% sodium hydroxide solution. Acidification gave an oil which was extracted with ether, the extract dried with anhydrous sodium sulfate, solvent removed and the product crystallized from benzene–heptane; yield, 2.3 g., m. p. 125–140°. Several recrystallizations from ethylene dichloride gave one pure isomer (presumably the *meso* form), white crystals, m. p. 156–157°.

Anal. Calcd. $C_{20}H_{26}O_2$: C, 80.5; H, 8.8. Found: C, 80.5; H, 8.4.

Remethylation with methanolic potassium hydroxide and dimethyl sulfate gave a 93% yield of the methyl ether, m. p. 72–73°.

Anal. Calcd. for $C_{22}H_{30}O_2$: C, 80.9; H, 9.3. Found: C, 80.8; H, 9.3.

Summary

1. 1,6-Bis-(*p*-hydroxyphenyl)-hexane, 1,3-bis-(*p*-hydroxyphenyl)-hexane and 1,2-bis-(2-ethyl-

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.]

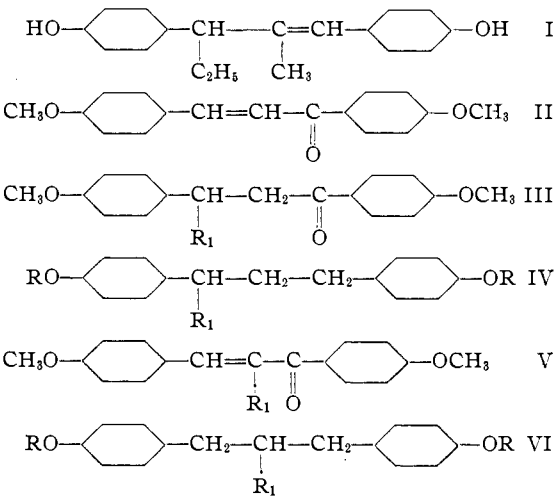
Synthetic Estrogenic Compounds. I. Monosubstituted Derivatives of 1,3-Di-(*p*-hydroxyphenyl)-propane

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.

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

(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).