[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE WASHINGTON SQUARE COLLEGE OF NEW YORK UNIVERSITY]

Synthetic Estrogens. Phenyl and Benzyl Hexestrols and Dienestrols[1,2]

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Studies in the introduction of alkyl radicals into the benzene rings of synthetic estrogens, with subsequent enhancement of therapeutic properties in at least two cases,[3] have now been extended to include phenyl and benzyl substituted hexestrols and dienestrols.

3,4-bis-(*m*-Phenyl-*p*-hydroxyphenyl)-2,4-hexadiene and 3,4-(*m*-benzyl-*p*-hydroxyphenyl)-2,4-hexadiene were prepared from *o*-phenylphenol and *o*-benzylphenol, respectively, using the following method of synthesis.[4] The phenols were esterified with propionic anhydride. The resulting esters were subjected to a Fries rearrangement to yield the 3-phenyl-4-hydroxy- and the 3-benzyl-4-hydroxy-propiophenones which were then esterified. These ketones were reduced to the corresponding pinacols which in turn were dehydrated and saponified to the desired dienestrols. Catalytic hydrogenation yielded the corresponding hexestrols.

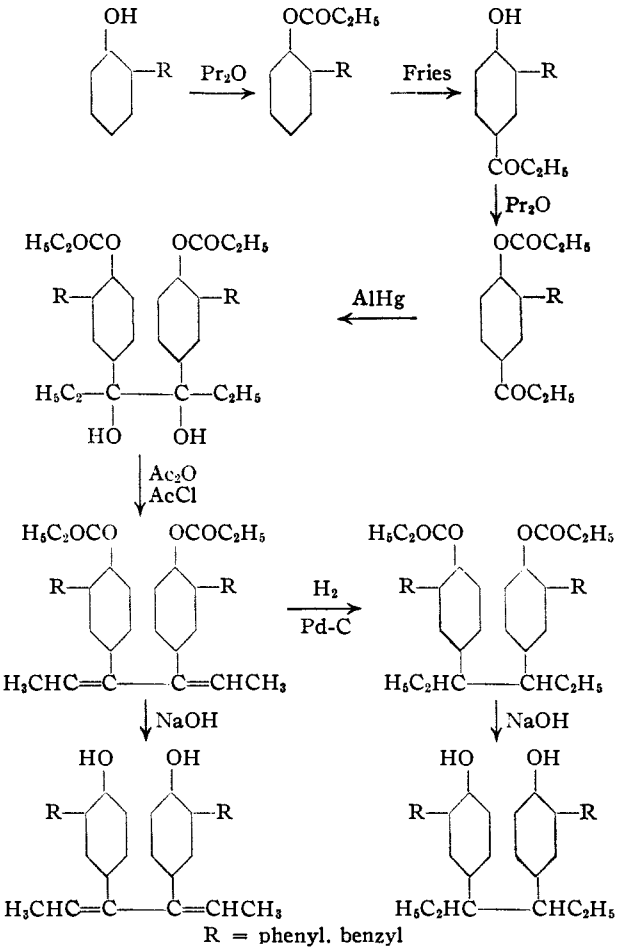
Experimental

o-Phenylphenylpropionate (I) and o-Benzylphenylpropionate (II).—*o*-Phenylphenola nd *o*-benzylphenol were esterified with propionic anhydride. The propionic acid formed and the unreacted anhydride were removed under reduced pressure and the residue used without further purification.

3-Phenyl-4-hydroxypropiophenone (III) and 3-Benzyl-4-hydroxypropiophenone (IV).—These compounds were obtained by a Fries rearrangement[5] of (I) and (II). One and one-half moles of anhydrous aluminum chloride was dissolved in 400 ml. of nitrobenzene. When the solution cooled to room temperature one mole of the ester (I, II) was added dropwise with constant stirring at such a rate that the temperature did not rise above 30°. The flask was protected with a calcium chloride tube, allowed to stand overnight, then heated to 50° for three hours. The solution was poured into about three times its volume of an ice–water mixture and allowed to stand for several hours until the aluminum chloride complex was hydrolyzed. The aqueous layer was separated and extracted with ether which was then combined with the nitrobenzene layer. The ether–nitrobenzene mixture was extracted with 10% sodium hydroxide. After washing with several portions of ether to remove traces of nitrobenzene, the alkaline extract was acidified with dilute hydrochloric acid. The precipitate was filtered, washed, dried and used in the next step without further purification.

3-Phenyl-4-propionoxypropiophenone (V) and 3-Benzyl-4-propionoxypropiophenone (VI).—(III) and (IV) were esterified with propionic anhydride. After removing the propionic acid and anhydride and a forerun probably consisting of the ortho rearranged isomer, the esters distilled at 190–192° (3 mm.) and 208–209° (3 mm.), respectively, and crystallized on standing.

FLOW SHEET



R = phenyl, benzyl

3,4-bis-(*m*-Phenyl-*p*-propionoxyphenyl)-3,4-hexanediol (VII) and 3,4-bis-(*m*-Benzyl-*p*-propionoxyphenyl)-3,4-hexanediol (VIII).—Two moles of aluminum foil were cut into strips, crumpled loosely, amalgamated with mercuric chloride, washed rapidly with water, ethanol and ether, then covered with 500 ml. of ether in a 2-liter 3-necked flask. The flask was fitted with a sealed stirrer, a dropping funnel and a reflux condenser. One third of a mole of the ketone (V, VI) was added in one batch. Water was added dropwise through the dropping funnel at such a rate that a gentle reflux of ether was maintained. The reaction took about eight hours until the aluminum was exhausted. The mass was filtered and the residue extracted with ether which was then combined with the filtrate. The ether was removed and the viscous residue used in the next step. Neither of the reaction products could be crystallized.

3,4-bis-(*m*-Phenyl-*p*-propionoxyphenyl)-2,4-hexadiene (IX) and 3,4-bis-(*m*-Benzyl-*p*-propionoxyphenyl)-2,4-hexadiene (X).—Fifty grams of the hexanediol (VII, VIII)

(1) This material has been abstracted from the Ph.D. Thesis to be presented by R. M. Silverstein to the faculty of the Graduate School of New York University.

(2) Presented before the Medicinal Chemistry Division at the Atlantic City meeting of the American Chemical Society, April, 1947.

(3) C. A. Siconalfi and C. T. Van Meter, Chicago Meeting, September, 1946, and J. B. Niederl and co-workers, New York Meeting, September, 1947, of the American Chemical Society.

(4) E. C. Dodds and co-workers, *Proc. Roy. Soc. (London)*, **B127**, 140 (1939).

(5) H. Wojahn, *Arch. Pharm.*, **271**, 417 (1933).

TABLE OF COMPOUNDS

	Formula	M. p., °C.	Analyses, % Calcd. C	Calcd. H	Found C	Found H	Over-all yields, %
3-Phenyl-4-propionoxypropiophenone	$C_{18}H_{18}O_3$	46	76.57	6.43	76.86	6.19	70
3,4-bis-(*m*-Phenyl-*p*-hydroxyphenyl)-2,4-hexadiene							
Free phenol	$C_{30}H_{26}O_2$	202–204d	86.14	6.23	86.40	6.36	9.5
Diacetate	$C_{34}H_{30}O_4$	170–171	81.25	6.02	81.35	6.10	9.5
Dipropionate	$C_{36}H_{34}O_4$	125–126	81.47	6.40	81.29	6.77	10
Dibenzoate	$C_{44}H_{34}O_4$	212–214	84.32	5.47	84.54	5.20	9.3
3,4-bis-(*m*-Phenyl-*p*-hydroxyphenyl)-hexane							
Free phenol	$C_{30}H_{30}O_2$	219–221d	85.27	7.16	85.52	7.32	7.0
Diacetate	$C_{34}H_{34}O_4$	188–190	80.60	6.76	80.40	6.72	7.0
Dipropionate	$C_{36}H_{38}O_4$	135–137	80.86	7.16	80.81	7.25	7.0
Dibenzoate	$C_{44}H_{38}O_4$	154–157	83.77	6.07	83.95	6.13	6.9
3-Benzyl-4-propionoxypropiophenone	$C_{19}H_{20}O_3$	88–89	77.00	6.80	77.25	6.96	70
3,4-bis-(*m*-Benzyl-*p*-hydroxyphenyl)-2,4-hexadiene							
Free phenol	$C_{32}H_{30}O_2$	150–152	86.06	6.77	85.94	6.82	5.3
Diacetate	$C_{36}H_{34}O_4$	122–124	81.48	6.46	81.43	6.40	5.3
Dipropionate	$C_{38}H_{38}O_4$	115–117	81.68	6.85	81.41	6.83	5.6
Dibenzoate	$C_{46}H_{38}O_4$	173	84.37	5.85	84.34	5.85	5.2
3,4-bis-(*m*-Benzyl-*p*-hydroxyphenyl)-hexane							
Free phenol	$C_{32}H_{34}O_2$	169–171	85.29	7.60	85.28	7.38	4.0
Diacetate	$C_{36}H_{38}O_4$	122–123	80.87	7.16	80.72	7.21	4.0
Dipropionate	$C_{38}H_{42}O_4$	119–121	81.13	7.52	80.73	6.96	4.0
Dibenzoate	$C_{46}H_{42}O_4$	148–149	83.86	6.42	83.95	6.40	3.9

was refluxed for twenty minutes with 150 ml. of acetic anhydride and 100 ml. of acetyl chloride. The solution was poured into a large volume of ice–water mixture in an Erlenmeyer flask, shaken vigorously and allowed to stand for several hours. The semi-solid mass which separated was shaken with several changes of water, then triturated with a small amount of cold methanol until solidification was effected. The flaky solid was filtered, washed with methanol and recrystallized from the same solvent.

3,4-bis-(*m*-Phenyl-*p*-hydroxyphenyl)-2,4-hexadiene (XI) and 3,4-bis(*m*-Benzyl-*p*-hydroxyphenyl)-2,4-hexadiene (XII).—Saponification of (IX, X) was effected by heating at 60° for two hours with Claisen solution and allowing to stand overnight at room temperature. The solution was diluted with water, filtered, the filtrate acidified, and the precipitate filtered, washed and recrystallized from dilute ethanol.

3,4-bis-(*m*-Phenyl-*p*-hydroxyphenyl)-hexane (XIII), and 3,4-bis-(*m*-Benzyl-*p*-hydroxyphenyl)-hexane (XIV).—These compounds were obtained by hydrogenation of (IX, X) in acetone with palladium on carbon at 3 atmospheres and room temperature for one hour. The solvent was removed but in neither case could the viscous residue be crystallized. Saponification was effected as under (XI, XII) and the compounds were recrystallized from dilute ethanol.

Esters.—The diacetates of (XI, XII) and (XIII, XIV) and the propionates of (XIII, XIV) were prepared by refluxing with acetic and propionic anhydrides, respectively, and recrystallizing from dilute ethanol. The dibenzoates were prepared from (XI, XII) and (XIII, XIV) by the Schotten–Baumann method and recrystallized from an absolute ethanol–ethyl acetate mixture.

Physiological.—Assays were performed according to standard procedure by subcutaneous injection into rats of oil solutions of the compounds. At the 50 gamma dose level 3,4-bis-(*m*-benzyl-*p*-hydroxy)-hexane showed no estrogenic activity. At the same dose level 3,4-bis-(*m*-phenyl-*p*-hydroxy)-hexane elicited estrogenic response in 10% of the animals tested.

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Summary

In continuation of the work done in this Laboratory in the field of synthetic estrogens the phenyl and benzyl hexestrols and dienestrols have been prepared. The introduction of the phenyl or benzyl group resulted in considerable diminution of estrogenic activity.

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