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

SYNTHETIC ESTROGENS. CYCLOHEXYL DIENESTROL AND HEXESTROL[1]

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Studies carried out in this laboratory have been concerned with the effects of ring substituents on synthetic estrogens of the dienestrol and hexestrol types. Thus far, aryl and aralkyl (1), tetra-alkyl (2), and di-alkyl (3) groups have been used.

In continuation of these studies, the cyclohexyl substituted dienestrol and hexestrol have been prepared along with some of their organic esters. The starting material was *o*-cyclohexylphenol; the general plan of synthesis is shown in the flow sheet.

EXPERIMENTAL

o-Cyclohexylphenylpropionate (I) (yield quantitative; b.p. 177° at 15 mm.), *3-cyclohexyl-4-hydroxypropiophenone (II)* (yield 75%; m.p. 150–152°), and *3-cyclohexyl-4-acetoxypropiophenone (III)* (yield 95%; b.p. 190–192° at 3 mm.) were prepared essentially by the same methods as the analogous compounds previously reported (1).

3,4-Bis-(m-cyclohexyl-p-acetoxyphenyl)-3,4-hexanediol (IV). A modification (3) of the classical pinacol reduction was utilized, involving ethyl acetate rather than ether as the solvent. Fifty grams of aluminum foil was cut into strips, crumpled loosely, etched with alkali, washed, amalgamated with 0.5% mercuric chloride, washed rapidly with water, ethanol and ethyl acetate, then covered with 500 ml. of ethyl acetate which had previously been saturated with water. One-third of a mole of (III) was added in one batch. The mixture was stirred for two hours during which time the temperature rose to 65° and dropped back to 35°. The aluminum hydroxide formed and the unreacted aluminum were filtered off and washed with ethyl acetate, which was then combined with the filtrate. About half of the ethyl acetate was removed by distillation, and the rest was allowed to evaporate from a wide, flat crystallizing dish over a period of several days. The result was a hard white solid mass covered by a viscous gum. The gum was removed by washing with petroleum ether. The solid, on recrystallization from dilute ethanol melted at 183–185°. The yield was 39%.

3,4-Bis-(m-cyclohexyl-p-acetoxyphenyl)-2,4-hexadiene (V). Seventeen grams of (IV) was refluxed for twenty minutes with 50 ml. of acetic anhydride and 30 ml. of acetyl chloride. The solution was cooled, poured into a large volume of ice-water, shaken vigorously, and allowed to stand for several hours with occasional shaking. The semisolid 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. The yield after recrystallization was 80%. The product gave a positive unsaturation test with bromine, and melted at 175–177°. An additional amount of hexadiene was obtained from the petroleum ether solution of the pinacol gum by removing the solvent and treating the gum by the above procedure.

3,4-Bis-(m-cyclohexyl-p-hydroxyphenyl)-2,4-hexadiene (VI). Two grams of (V) was saponified by heating to 50° for two hours with Claisen solution and allowing to stand overnight at room temperature. On diluting with water, the sodium salt precipitated. Carbon

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

dioxide was passed into this suspension until it was acid. The precipitate was filtered, washed, and recrystallized from dilute ethanol. The yield after recrystallization was 85%; m.p. 177–178°. Analysis indicated that this product was a monohydrate. On drying in a vacuum desiccator at 80° and 40 mm. for 8 hours, a correct analysis for the anhydrous substance was obtained.

3,4-Bis-(m-cyclohexyl-p-acetoxyphenyl)hexane (VII). Four grams of (V) was dissolved in 100 ml. of dioxane. One-tenth gram of palladium on carbon was added, and the mixture was shaken with hydrogen at 3 atmospheres and room temperature for one hour. The catalyst was filtered off, and the filtrate concentrated to about half its original volume. On slow evaporation of the remaining solvent, crystals were deposited. After washing with methanol, these crystals melted at 138–146°. A constant and sharp m.p. of 146–147.5° was obtained after three recrystallizations from dilute acetic acid. The final yield was 50%. A mixture of acetone and ethyl acetate (the hexadiene was insoluble in acetone alone) was tried as the hydrogenation solvent, but was not as satisfactory as dioxane. The m.p. of this product before recrystallization was 120–144°.

TABLE OF COMPOUNDS

	FORMULA	M.P., °C.	CALC'D		FOUND	
			C	H	C	H
3-Cyclohexyl-4-hydroxypropionphenone	$C_{15}H_{20}O_2$	151–152	77.54	8.68	77.55	8.64
3-Cyclohexyl-4-acetoxypropiophenone	$C_{17}H_{22}O_3$	[a]	74.42	8.08	74.40	8.19
3,4-Bis-(*m*-cyclohexyl-*p*-acetoxyphenyl -3,4-hexanediol	$C_{34}H_{46}O_6$	183–185	74.14	8.42	74.14	8.51
3,4-Bis-(*m*-cyclohexyl-*p*-hydroxyphenyl)-2,4-hexadiene						
Free phenol monohydrate	$C_{30}H_{40}O_3$	177–178	80.31	8.99	80.48	9.09
Free phenol	$C_{30}H_{38}O_2$	177–178	83.67	8.89	83.55	8.83
Diacetate	$C_{34}H_{42}O_4$	175–177	79.34	8.22	79.48	8.43
Dipropionate	$C_{36}H_{46}O_4$	150–150.5	79.66	8.54	79.50	8.72
Dibenzoate	$C_{44}H_{46}O_4$	189–190.5	82.72	7.26	82.55	7.48
3,4-Bis-(*m*-cyclohexyl-*p*-hydroxyphenyl)-hexane						
Free phenol monohydrate	$C_{30}H_{44}O_3$	195–197	79.58	9.87	79.61	10.04
Free phenol	$C_{30}H_{42}O_2$	195–197	82.89	9.70	83.13	10.04
Diacetate	$C_{34}H_{46}O_4$	146–147.5	78.72	8.94	78.77	8.88
Dipropionate	$C_{36}H_{50}O_4$	138–139	79.08	9.22	79.02	9.25
Dibenzoate	$C_{44}H_{50}O_4$	195–197	82.20	7.84	82.17	7.63

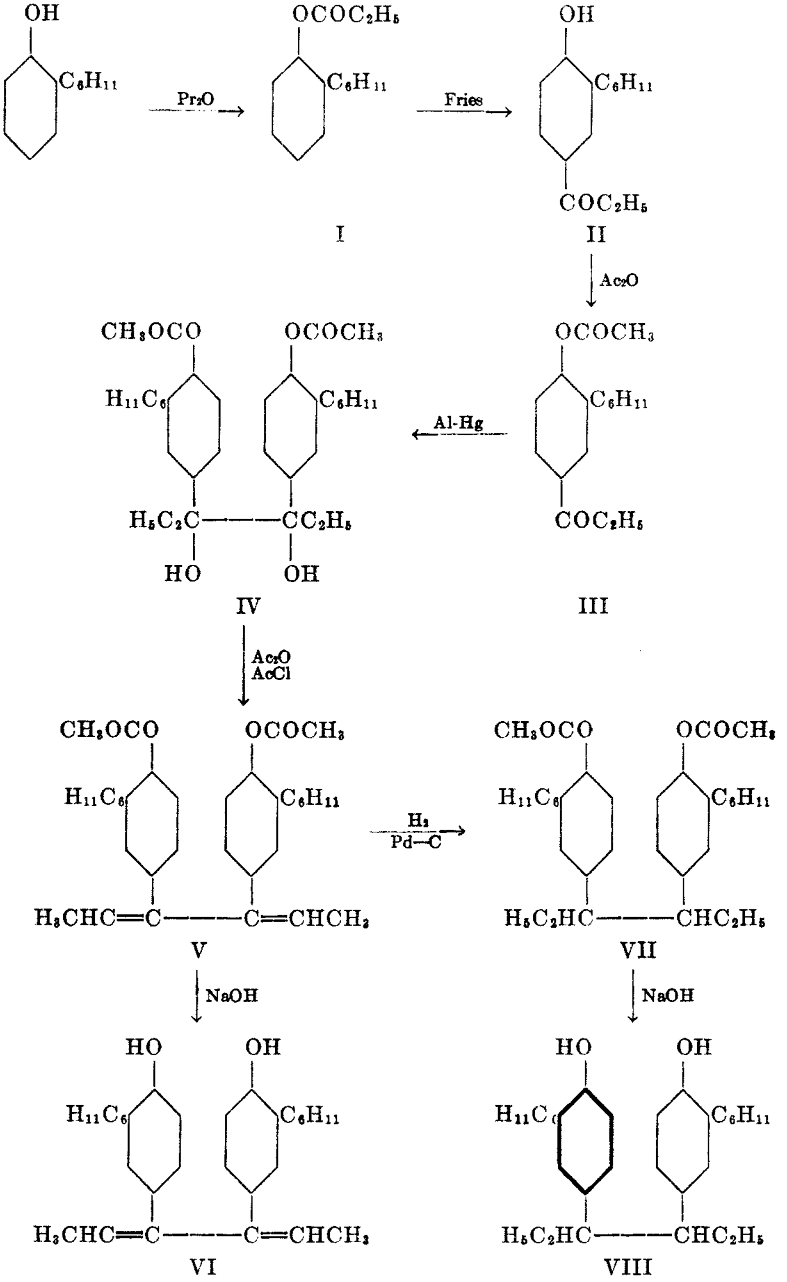
[a] Boiling point 190–192° at 3 mm.

3,4-Bis-(m-cyclohexyl-p-hydroxyphenyl)hexane (VIII). Two grams of (VII) was saponified with Claisen solution as under (VI), and recrystallized from dilute acetic acid. The yield after recrystallization was 85%; m.p. 195–197°. Analysis indicated that the product was a monohydrate. On drying in a vacuum desiccator at 80° and 25 mm. for 8 hours, a correct analysis for the anhydrous substance was obtained.

Esters. The dipropionates of (VI) and (VIII) were prepared by refluxing with propionic anhydride and recrystallizing from dilute acetic acid. The dibenzoates of (VI) and (VIII) were prepared by the Schotten-Baumann method, and recrystallized from an absolute ethanol-ethyl acetate mixture.

Pharmacology. Assays were performed according to standard procedure by subcutaneous injection into ovariectomized rats of oil solutions of the compounds. At the 50 gamma dose level, 3,4-bis-(*m*-cyclohexyl-*p*-hydroxyphenyl)hexane elicited estrogenic response in 10% of the animals tested.

Flow Sheet



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SUMMARY

In continuation of the work done in this laboratory in the field of synthetic estrogens, cyclohexyl substituted dienestrol and hexestrol have been prepared. The introduction of the cyclohexyl groups resulted in considerable diminution of estrogenic activity.

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