ARTIFICIAL ESTROGENS

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Received May 25, 1956

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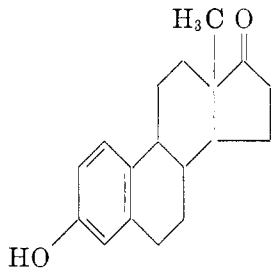
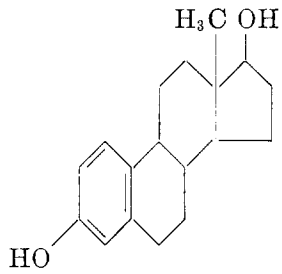
I. Introduction

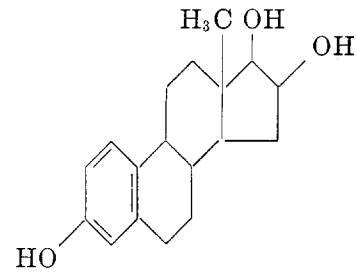
The lack of molecular specificity in the series of natural estrogens estrone (I), "α"-estradiol (II), estriol (III), equilenin (IV), and equilin (V) led Dodds and his colleagues, about 1930, to examine how the molecule of a natural estrogen might be changed without destroying estrogenic activity. This work culminated



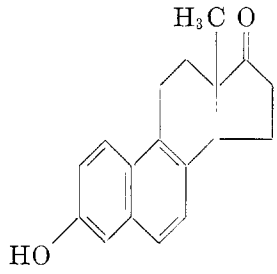
I
Estrone



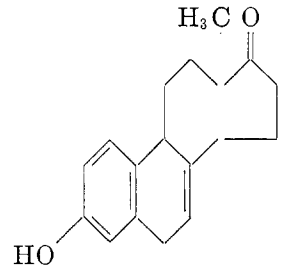
II
"α"-Estradiol



III
Estriol



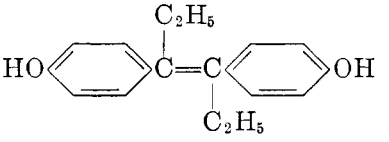
IV
Equilenin



V
Equilin

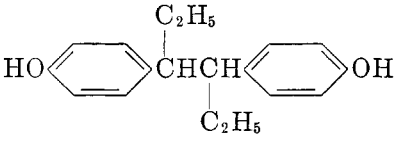
in 1938 in the discovery of the estrogenically potent synthetic compounds diethylstilbestrol (VI) (100), hexestrol (VII) (53), and dienestrol (VIII) (101). These compounds remain the most potent, useful estrogens of the stilbene type. These results of the workers at the Courtauld Institute had immediate importance in estrogen therapy, since previously only natural products had been available and their administration necessitated injection. The synthetic compounds were found to possess all the qualitative estrogenic properties of the

natural estrogens, were cheap to produce, and were active by mouth. They have attained considerable clinical importance (187).



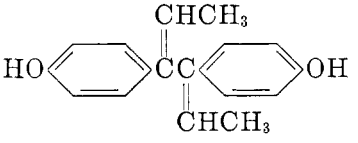
VI

Diethylstilbestrol



VII

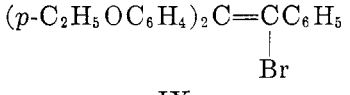
Hexestrol



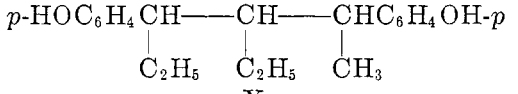
VIII

Dienestrol

Stemming from the classical work of Lacassagne (250) and Huggins (196)' the study of estrogens in their relation to cancer has become a field of some extent (42), and diethylstilbestrol has found a place in prostatic cancer therapy. The stimulus of the early successes has led to the preparation and biological testing of a vast number of compounds more or less closely related to the three stilbene-type estrogens. Although few have attained practical significance, this work has provided valuable data on chemical constitution and estrogenic activity. The syntheses of the triphenylethylenes by Robson and coworkers (363, 364, 365), of 1,1-bis(*p*-ethoxyphenyl)-2-bromo-2-phenylethylene (IX), which



IX

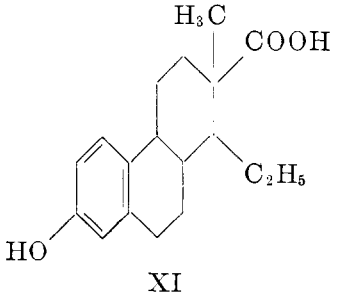


X

Benzestrol

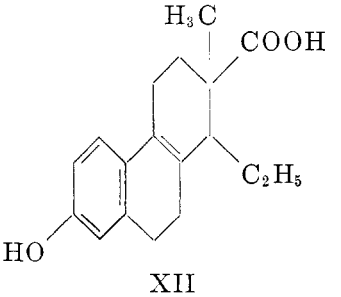
has clinical use, and of benzestrol (X) by Blanchard, Stuart, and Tallman (25) were notable discoveries.

In 1944 the elaboration of some earlier observations was initiated by Miescher and coworkers in Switzerland (285). This work led to the discovery of an entirely



XI

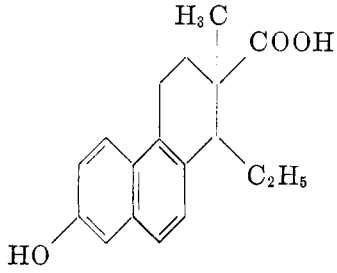
Doisynolic acid



XII

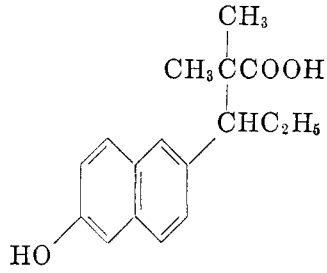
Monodehydrodoisynolic acid

new type of estrogen, closely related to the natural hormones. Doisynolic acid (XI), monodehydrodoisynolic acid (XII), and bisdehydrodoisynolic acid (XIII) are examples of these highly potent estrogens.



XIII

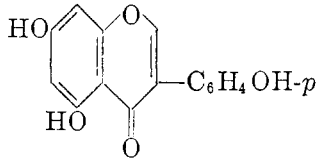
Bisdehydrodoisynolic acid



XIV

Horeau acid

Structural simplification in this series was achieved by the discovery of the allenolic acids in 1947 by Horeau and Jacques (186). Horeau acid (XIV) is an example of this class of estrogen. More recently, in 1951, Bradbury and White (31) discovered the estrogenic activity of isoflavones such as genistein (XV).



XV

Genistein

While work is yet at an early stage, it would seem that these compounds are heterocyclic ring-closed analogs of the stilbene type of estrogen. Nonnatural estrogens have previously been referred to as synthetic estrogens, but in view of the recent total syntheses of the natural products and in accordance with a suggestion due to Horeau (185), the preferable title "artificial estrogens" has been used.

A fundamental aim of estrogen chemistry, as in all such fields, is to correlate estrogenic activity and chemical constitution. However, at the outset it must be emphasized that this is no simple matter and that the estrogenic potency of a compound is dependent on other factors besides the superficial structure of the molecule. Thus, the division of dose, the route and mode of administration, the rate of absorption and destruction, the possibility of *in vivo* biochemical modification, and the sensitivity of the animal used are important factors in determining the observed potency of a substance. These factors make the estrogenic activities reported for various compounds difficult to compare and there is frequently considerable variation in the data for the same substance; in any case, no absolute significance can be attached to the biological results. In spite of these difficulties the extensive work in this field does make a case for some attempt at correlating estrogenic activity and chemical constitution, and some success has been achieved

in this direction. Such attempts are valuable, since they may point the way to the synthesis of simple compounds having the biological function of other steroid hormones as well as throw light on some aspects of the cancer problem.

Throughout this review the estrogenically more active *trans*-diethylstilbestrol is referred to simply as diethylstilbestrol; this name is now generally preferred to the shortened form, stilbestrol. The more potent *meso*-hexestrol is similarly referred to as hexestrol. Of the three dienestrols, the more active isomer is referred to as dienestrol or α-dienestrol (252).

The subject has been taken up from the termination of Solmssen's review (451) and covers *Chemical Abstracts* from 1946 to 1955, inclusive; earlier work has occasionally been referred to for purposes of continuity. All compounds related to diethylstilbestrol, hexestrol, or dienestrol have been included. Other reviews (62, 68, 84, 137, 208, 230, 255, 279, 328, 329, 330, 331, 332, 333, 334, 335) of chemical interest have appeared during the period.

The estrogenic acids and estrogenic heterocyclic compounds have been omitted, since they have as yet made a smaller contribution to the understanding of the molecular features associated with estrogenic activity. Various miscellaneous compounds have also been omitted. Because of the extensive published work it has not been possible to discuss the relationship of estrogens to cancer or the analytical chemistry of estrogens. The nomenclature used is that of *Chemical Abstracts*.

II. Syntheses of Diethylstilbestrol, Hexestrol, and Dienestrol

Much of the more recent synthetic work directed specifically to the three principal artificial estrogens has been based on earlier methods (445, 446, 447). However, some novel modifications and new syntheses have been introduced, and some aspects of reaction mechanisms have been investigated.

A. Syntheses of Diethylstilbestrol

1. Modifications of the Dodds synthesis

The original synthesis of Dodds, Golberg, Lawson, and Robinson (100) involved the following steps:

$$p\text{-}CH_3OC_6H_4CHO \xrightarrow{KCN}$$

Anisaldehyde

$$p\text{-}CH_3OC_6H_4CHOHCOC_6H_4OCH_3\text{-}p \xrightarrow[100^\circ C.,\ 24\ hr.]{Zn\ dust,\ CH_3COOH}$$

Anisoin

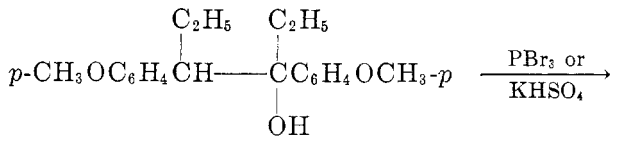
$$p\text{-}CH_3OC_6H_4CH_2COC_6H_4OCH_3\text{-}p \xrightarrow[C_2H_5I]{C_2H_5ONa}$$

Desoxyanisoin

$$p\text{-}CH_3OC_6H_4CH(C_2H_5)COC_6H_4OCH_3\text{-}p \xrightarrow{C_2H_5MgBr}$$

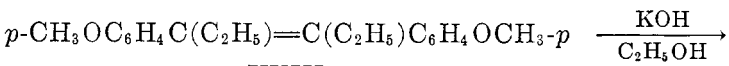
XVI

α-Ethyldesoxyanisoin



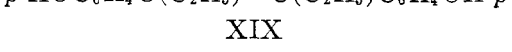
XVII

3,4-Bis(*p*-methoxyphenyl)-3-hexanol



XVIII

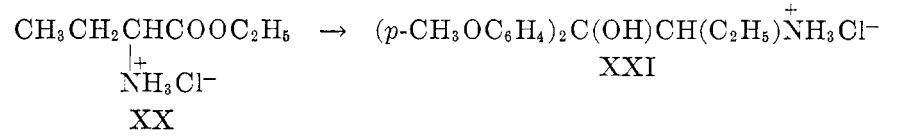
Diethylstilbestrol dimethyl ether



XIX

Diethylstilbestrol

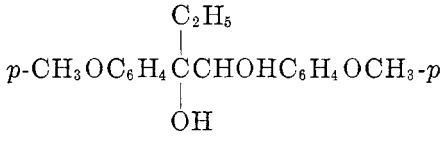
In this and related syntheses (369, 550) α-ethyldesoxyanisoin (XVI) is the key intermediate. Wilder Smith (418) obtained this intermediate in good yield by a novel route: the hydrochloride of ethyl α-aminobutyrate (XX) was reacted with *p*-methoxyphenylmagnesium bromide to give the hydrochloride of 2-amino-1,1-bis(*p*-methoxyphenyl)-1-butanol (XXI) in 64 per cent yield. Conversion of



XX XXI

XXI to the free base, in 92 per cent yield, followed by pinacolic deamination with nitrous acid (269, 270, 271, 506), gave α-ethyldesoxyanisoin in 90 per cent yield. Variation of the α-aminoester hydrochloride and the Grignard reagent should permit the synthesis of a variety of substituted stilbenes by this method.

Kuwada and Sasagawa (247) obtained α-ethyldesoxyanisoin by acid rearrangement of the pinacol 3,4-bis(*p*-methoxyphenyl)-3,4-butanediol (XXII), the latter being prepared by the interaction of anisoin and ethylmagnesium

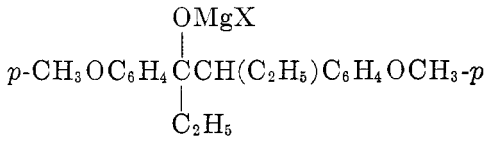


XXII

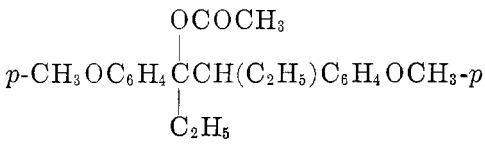
iodide. Sah (374), however, could not substantiate the yields claimed by Kuwada and Sasagawa and introduced slight modifications of the conditions in the overall synthesis of diethylstilbestrol. It was found better to carry out the dehydration step to XVIII by phosphorus pentoxide, and the final demethylation was done with aluminum bromide at 120°C.

Schwarzkopf (389) introduced the improvement of omitting the isolation of

the carbinol XVII; instead, the Grignard reaction product (XXIII) was converted directly to XVIII by heating with an excess of an inorganic or organic



XXIII



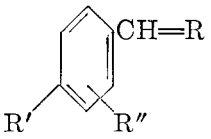
XXIV

acid chloride or anhydride. Esters such as the acetate of 3,4-bis(*p*-methoxyphenyl)-3-hexanol (XXIV) could be isolated and were considered to be the reaction intermediates. XXIV eliminates acetic acid on heating or even on standing to give the stilbene; acetyl chloride with XXIII gives a 72 per cent yield of diethylstilbestrol dimethyl ether. In a second synthesis, Schwarzkopf (390) obtained XXIII from 3-(*p*-methoxyphenyl)-3-propanone and the Grignard reagent from 2-bromo-3-(*p*-methoxyphenyl)propane; the product was dehydrated to diethylstilbestrol dimethyl ether by distillation at 170°C. at 0.4 mm. pressure after removal of the solvent. Takahashi (489) used a similar method and obtained diethylstilbestrol directly from α-ethyldesoxyanisoin by the action of ethylmagnesium iodide, followed by removal of the solvent and heating at 165–170°C.

Rabald and Kraus (345) improved the yields of diethylstilbestrol in the Dodds type of synthesis by triturating residues from the dehydration step with a little iodine; the asymmetric alkenes are thereby isomerized to the stilbene. In the course of other work Hofstetter and Wilder Smith (183) dehydrated a mixture of 3,4-bis(*p*-methoxyphenyl)-2-hexanol and the 1-hexanol with an acetyl chloride–acetic anhydride mixture and isomerized the product with iodine in toluene to obtain diethylstilbestrol dimethyl ether.

2. Syntheses from anethole

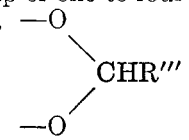
Kharasch (233) exemplified the extension of the Kharasch–Kleiman synthesis of diethylstilbestrol (237). Starting materials of the type shown in formula XXV



XXV

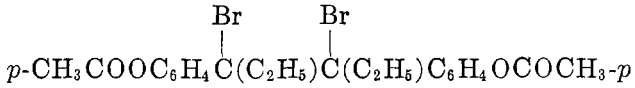
R = alkylidene group of two to six carbon atoms
R′ = alkoxy group of one to four carbon atoms

R″ = hydrogen or alkoxy group of one to four carbon atoms
R′ and R″ may be united, e.g.,



R‴ = alkyl group of one to four carbon atoms

may be used. Treatment with gaseous hydrogen bromide at −10° to −20°C. yielded the α-bromo compound, which with sodium amide in liquid ammonia gave the stilbene. Bowman (30) dehydrohalogenated benzyl chloride to stilbene, using a complex prepared by heating magnesium and iodine together. Turnbull (510, 511) treated 3,4-bis(*p*-acetoxyphenyl)-3,4-dibromohexane (XXVI), ob-

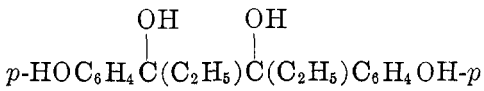


XXVI

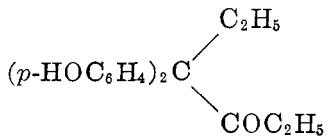
tained by brominating diethylstilbestrol or hexestrol, with zinc dust in alcohol and obtained a product melting at 141–142°C. This product was considered identical to one previously obtained by Dodds, Golberg, Lawson, and Robinson (102) and later shown by Walton and Brownlee (533) to be a eutectic made up of 60 per cent of ψ-diethylstilbestrol and 40 per cent of the trans isomer. Turnbull (510, 511) found that treatment of the eutectic with acetic anhydride in pyridine gave the diacetate of *cis*-diethylstilbestrol.

3. Syntheses involving pinacol–pinacolone and retropinacolone rearrangements

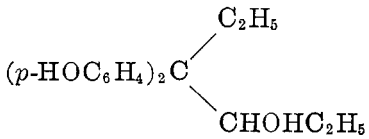
Adler, Gie, and v. Euler (3) improved previous syntheses of this type (448) by using unprotected *p*-hydroxypropiophenone as the starting material and reducing it with sodium amalgam in alkaline solution instead of the usual amalgamated aluminum. By this method they obtained the higher-melting form, m.p. 215–217°C., of the pinacol 3,4-bis(*p*-hydroxyphenyl)-3,4-hexanediol (XXVII) in 95 per cent yield. Rearrangement of XXVII in ether solution by



XXVII



XXVIII



XIX

gaseous hydrogen chloride gave the pinacolone 3,3-bis(*p*-hydroxyphenyl)-4-hexanone (XXVIII) quantitatively (501, 502). Reduction of XXVIII with sodium in amyl alcohol at 140°C. gave a 95 per cent yield of the pinacolone alcohol,

3,3-bis(*p*-hydroxyphenyl)-4-hexanol (XXIX), and finally retropinacolone rearrangement of this carbinol resulted in a 68 per cent overall yield of diethylstilbestrol. Contrary to these results, Shishido and Nozaki (398) found that pinacolic reduction of phenolic ketones or their esters does not proceed well; however, they used amalgamated aluminum. Using *p*-methoxypropiophenone, Shishido and Nozaki obtained a mixture of pinacols of the type shown in formula XXVII and by sulfuric acid rearrangement of the mixture obtained the pinacolone in 54 per cent overall yield. The pinacolone alcohol, obtained by reducing the pinacolone with sodium in xylene at 140°C., could not be satisfactorily rearranged with sulfuric acid, but iodine in chloroform (547) gave diethylstilbestrol dimethyl ether in 14 per cent overall yield. Demethylation to diethylstilbestrol was accomplished by treating the dimethyl ether with an ethereal solution of methylmagnesium iodide, evaporating the solvent, and heating the residue at 170°C. (248, 467).

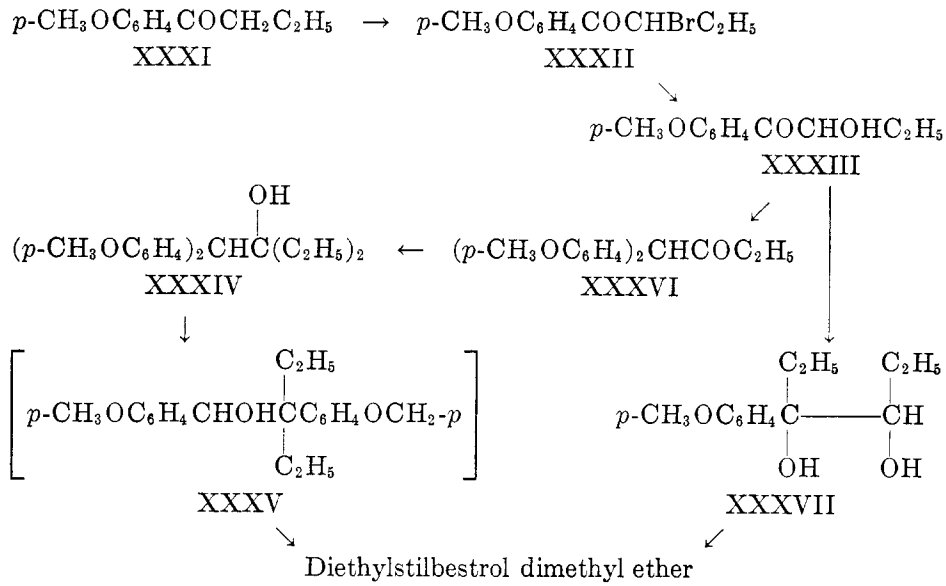
In this type of synthesis 3,3-bis(*p*-hydroxyphenyl)-4-hexanone (XXVIII) may be considered the key intermediate. Various routes for its preparation were investigated by Shishido, Nozaki, and Kurihara (406). First, in a synthesis of the diacetate of XXVIII on the basis of their earlier work (404) they reacted phenol and bipropionyl in acetic acid–sulfuric acid and obtained a 19 per cent yield of 3,3-bis(*p*-acetoxyphenyl)-4-hexanone. A second method involved the ethylation of 1,1-bis(*p*-methoxyphenyl)acetonitrile (XXX) by ethyl iodide and sodium amide, followed by conversion of the 1,1-bis(*p*-methoxyphenyl)-butyronitrile obtained to 3,3-bis(*p*-methoxyphenyl)-4-hexanone by reaction

$$(p\text{-}CH_3OC_6H_4)_2\ CHCN$$

XXX

with ethylmagnesium bromide. Reduction and retropinacolone rearrangement then gave diethylstilbestrol dimethyl ether in 20 per cent yield on the basis of the butyronitrile. The action of five moles of the Grignard reagent on the butyronitrile at 130–170°C. also effected demethylation to give 3,3-bis(*p*-hydroxyphenyl)-4-hexanone, which could be converted to diethylstilbestrol. In a third method a Grignard reagent replaced sodium amide as the condensing agent; thus XXX was treated with ethylmagnesium iodide and ethyl iodide to give a 24 per cent yield of 3,3-bis(*p*-methoxyphenyl)-4-hexanone. This type of reaction had been used previously in other connections (135, 157, 538).

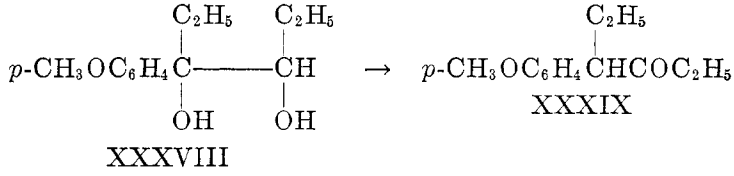
In a synthesis developed by Peteri (340) 1,1-bis(*p*-methoxyphenyl)-2-ethyl-2-butanol (XXXIV) was converted by phosphorus trichloride in toluene into diethylstilbestrol dimethyl ether, the reaction presumably proceeding via the intermediate XXXV. Tanabe, Onishi, and Takamura (500) converted *p*-methoxybutyrophenone (XXXI) into the α-bromo compound (XXXII) by treatment with bromine in acetic acid below 20°C. Hydrolysis with sodium carbonate solution after treatment of XXXII with potassium acetate gave the carbinol (XXXIII), which on reaction with anisole in the presence of sulfuric acid gave 1,1-bis(*p*-methoxyphenyl)-2-butanone (XXXVI). The latter with ethylmag-



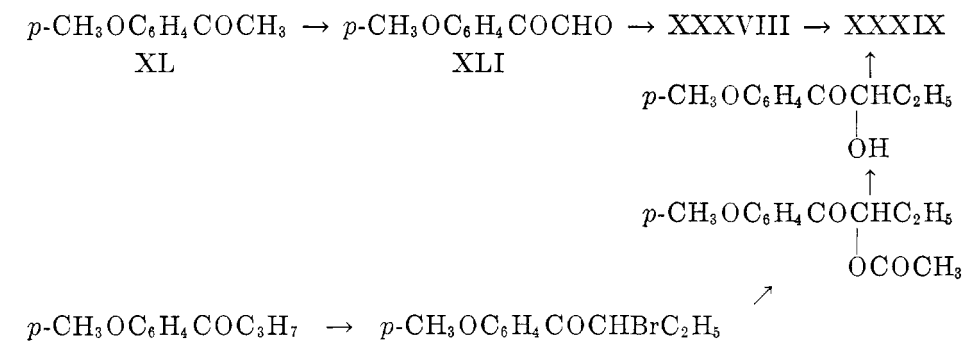
nesium bromide yielded XXXIV. Alternatively, XXXIII was converted to 3-(*p*-methoxyphenyl)-3,4-hexanediol (XXXVII) by ethylmagnesium bromide. Reaction of XXXVII with anisole in sulfuric acid at 30°C. gave diethylstilbestrol dimethyl ether. Yoshida and Akagi (559) obtained XXXIII by the same method but converted it into XXXVI by reaction with *p*-methoxyphenylmagnesium bromide, followed by dehydration of the 1,1-bis(*p*-methoxyphenyl)-1,2-butanediol obtained. Diethylstilbestrol dimethyl ether was then obtained via XXXIV as indicated.

4. Introduction of the anisyl group by a Grignard reaction

Three syntheses of this type have been developed (126, 249, 547). The intermediate was 3-(*p*-methoxyphenyl)-4-hexanone (XXXIX), obtained by acid rearrangement of 3-(*p*-methoxyphenyl)-3,4-hexanediol (XXXVIII).



Treatment of XXXIX with *p*-methoxyphenylmagnesium bromide followed by dehydration and demethylation yielded diethylstilbestrol. Shishido and Nozaki (400) developed two new routes to the intermediate ketone (XXXIX). In one method *p*-methoxyacetophenone (XL) was converted in improved yield (7, 227) into *p*-methoxyphenylglyoxal (XLI) by selenium dioxide oxidation; subsequent reaction with ethylmagnesium iodide gave XXXIX via the diol (XXXVIII).



The second series of reactions used were essentially the same as those previously described for converting a ketone into its α-hydroxy derivative (500, 559). The diol (XXXVIII) obtained in both these methods was the new β-form (m.p. 99–100°C.); the diastereoisomeric α-form (m.p. 83–84°C.) had been obtained in the previous syntheses of this type.

5. Other methods

Rubin and Wishinsky (370) obtained a 4-amino-4′-hydroxy-α,α'-diethylstilbene, m.p. 155–156°C. Weiss (541) carefully purified the crude material obtained by these workers and obtained an isomer, m.p. 180–183°C., which by the diazo reaction yielded diethylstilbestrol. It was concluded that the isomer melting at 155–156°C. was the cis form and the higher-melting isomer the trans form.

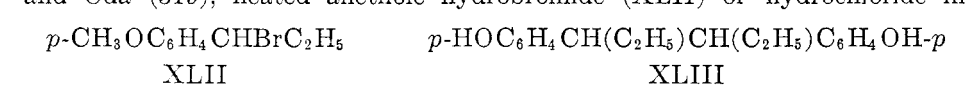
According to a Hungarian patent (350) *p*-methoxypropiophenone hydrazone when shaken in petroleum ether with mercuric oxide gave a solution of (*p*-methoxyphenyl)ethyldiazomethane. Treatment of this solution with gaseous sulfur dioxide gave an inseparable mixture of 1,2-bis(*p*-methoxyphenyl-1,2-diethylethylene sulfone and *p*-methoxypropiophenone azine. The mixture was melted to decompose the sulfone; fractional crystallization of the solid residue yielded diethylstilbestrol dimethyl ether.

B. SYNTHESES OF HEXESTROL

1. Wurtz-type syntheses

A Wurtz-type coupling of two molecules of a *p*-(α-halopropyl)anisole has been the method used in some previous hexestrol syntheses devised by Peak and Short (337), Docken and Spielman (96), and Bernstein and Wallis (17). These methods used alkali or alkaline earth metals in anhydrous organic media as the coupling agents. Kharasch and Kleiman (236) used the same starting materials but effected coupling by the cobaltous chloride–Grignard reagent method.

Shishido and Nozaki (399, 402), employing an earlier reaction due to Ogata and Oda (319), heated anethole hydrobromide (XLII) or hydrochloride in



ligroin with water and iron powder and obtained hexestrol dimethyl ether in 10–15 per cent yields. The method avoids the anhydrous media or low temperatures used in previous methods and has the advantage that the presence of water stabilizes the halide starting materials (344). Hexestrol dimethyl ether was demethylated to hexestrol (XLIII) by the Grignard method. Later Shishido and Nozaki (403) improved and generalized their synthesis by using reduced iron as the coupling agent. By this method anethole hydrobromide in toluene solution gave a 20 per cent yield of hexestrol dimethyl ether; the hydrochloride gave only a 14–15 per cent yield. Buu-Hoï and Hoán (48) also used reduced iron in a similar procedure and recorded an overall yield from anethole of 40 per cent of a mixture of hexestrol dimethyl ethers. The mixture contained about equal amounts of the meso and racemic ethers. It was further found that the ratio of the meso to the racemic form depended on the metal used for coupling. With reduced iron powder, Raney alloy, or Raney nickel high yields of the meso form were obtained, but with Devarda's alloy, zinc dust, the zinc–copper couple, or magnesium, much of the racemic form was obtained; with reduced copper a high yield of the racemic form, as sole product, was produced.

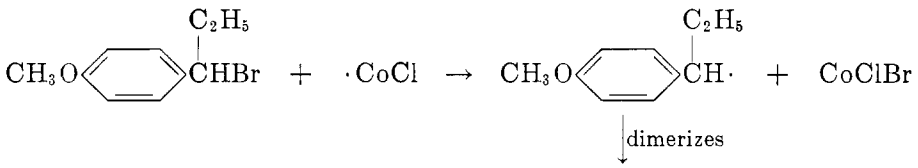
Girard and Sandulesco (142) converted anethole hydrobromide to hexestrol dimethyl ether, using powdered sodium or sodium strips (143) in benzene below 48°C. Schoeller, Inhoffen, Steinruck, and Hoss (385) obtained racemic hexestrol by the action of sodium on anethole hydrobromide, followed by demethylation. Guzman (152) claimed that he was able to improve the Docken–Spielman synthesis by passing gaseous hydrogen bromide into anethole for 4 hr. instead of 20 min. and by isolating and purifying the anethole hydrobromide. According to a Japanese patent (10) anethole hydrobromide can be converted into hexestrol dimethyl ether by using the magnesium–magnesium iodide complex; demethylation with hydrogen iodide in acetic acid at 140–150°C. was almost quantitative. Fu and Sah (411) improved the yield of hexestrol dimethyl ether in the Bernstein and Wallis synthesis from 8 to 20 per cent by condensing 3-bromo-3-(*p*-ethoxyphenyl)propane with copper bronze; aluminum iodide was found to be an excellent dealkylating agent. Torf and Khromov-Borisov (508) condensed α-chloropropylbenzene to a mixture of *meso*-3,4-diphenylhexane and racemic 3,4-diphenylhexane by magnesium and a little iodine in ether solution. Nitration of the meso form to 3,4-bis(*p*-nitrophenyl)hexane in 66 per cent yield, reduction to the diamine in 82.4 per cent yield, and conversion, via the diazo reaction, to the dihydroxy compound in 73.4 per cent yield gave hexestrol. Luis (268) obtained a 50–60 per cent yield of *p*-(α-chloropropyl)anisole by reacting anisole and propionaldehyde in acetic acid–hydrochloric acid. Treatment of the chloro compound with magnesium in ether was claimed to give an almost quantitative yield of hexestrol.

The Kharasch–Kleiman Grignard synthesis (236) was reinvestigated by Wilds and McCormack (554), using phenylmagnesium bromide and anethole hydrobromide in the presence of cobaltous chloride. Kharasch and Kleiman had claimed a 42 per cent yield of hexestrol dimethyl ether; Wilds and McCormack found that ethylmagnesium bromide gave 29–31 per cent yields of the ether

and that all other Grignard reagents, including phenylmagnesium bromide, gave yields of only 23–25 per cent. With anethole hydrochloride much lower yields were obtained, and anethole hydroiodide proved useless. This work revealed that temperatures up to 30°C. had little effect on yields of the ether and that, contrary to the reports of Kharasch and Fields (235) and of Kharasch and Sayles (238), the higher temperatures gave the better yields. Ether was found to be essential as solvent, for in benzene alkylations occurred. The method of Docken and Spielman (96), which used magnesium as coupling agent, was improved by Wilds and McCormack by the addition of cobaltous chloride, indicating that the synthesis proceeds via a Grignard reagent. From the reaction using ethylmagnesium bromide and anethole hydrobromide Wilds and McCormack were able to isolate a 25–30 per cent yield of racemic hexestrol dimethyl ether in addition to the meso form. The mechanism proposed by Kharasch and Kleiman for the reaction was as shown below:

$$C_6H_5MgBr + CoCl_2 \rightarrow C_6H_5CoCl + MgBrCl$$

$$2C_6H_5CoCl \rightarrow C_6H_5C_6H_5 + 2 \cdot CoCl$$



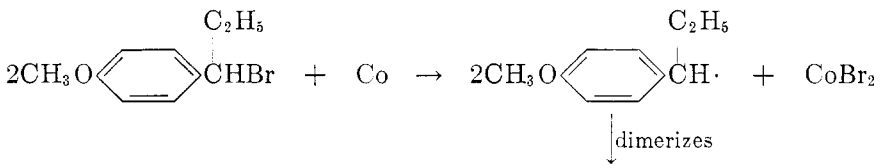
dimerizes

Hexestrol dimethyl ether

On the basis of their results Wilds and McCormack postulated a Wurtz-type coupling, the free radicals being produced by the action of metallic cobalt on the anethole hydrobromide.

$$2C_2H_5MgBr + CoCl_2 \rightarrow (C_2H_5)_2Co + MgBr_2 + MgCl_2$$

$$(C_2H_5)_2Co \rightarrow C_2H_4 + C_2H_6 + Co$$



dimerizes

Hexestrol dimethyl ether

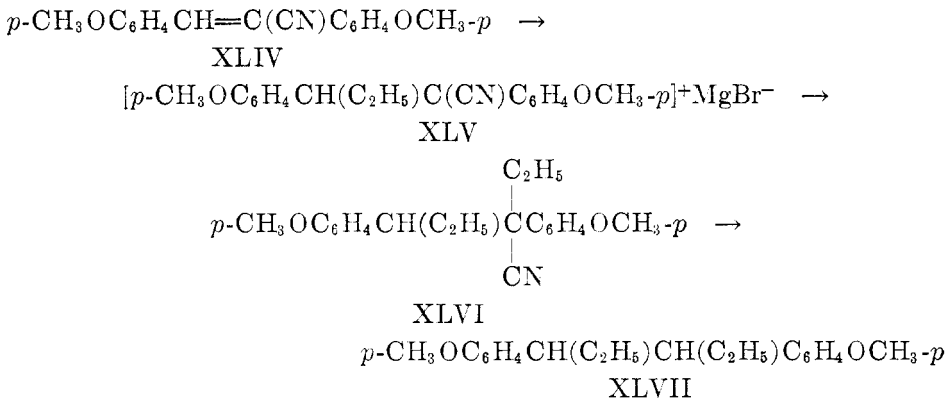
Support for the mechanism was obtained by showing that finely divided cobalt could convert anethole hydrobromide to hexestrol dimethyl ether in 8.5 per cent yield.

From a study of the demethylation of hexestrol dimethyl ether, Kharag (232) concluded that the best method was to reflux the ether for 4 hr. with fifteen parts of hydriodic acid (density 1.65–1.70); he claimed an 86 per cent yield of hexestrol. Hughes and Thompson (198) demethylated hexestrol dimethyl ether by the novel method of heating for 4 hr. at 200°C. with thiophenol in alcoholic

potassium hydroxide or merely in water. Group migration occurred with the formation of hexestrol quantitatively and of thioanisole. The method was also applied to diethylstilbestrol dimethyl ether (199). An interesting observation due to Wilds and McCormack (553) was that pyridine hydrochloride at 210°C. converted hexestrol monomethyl ether monobenzoate into the monobenzoate.

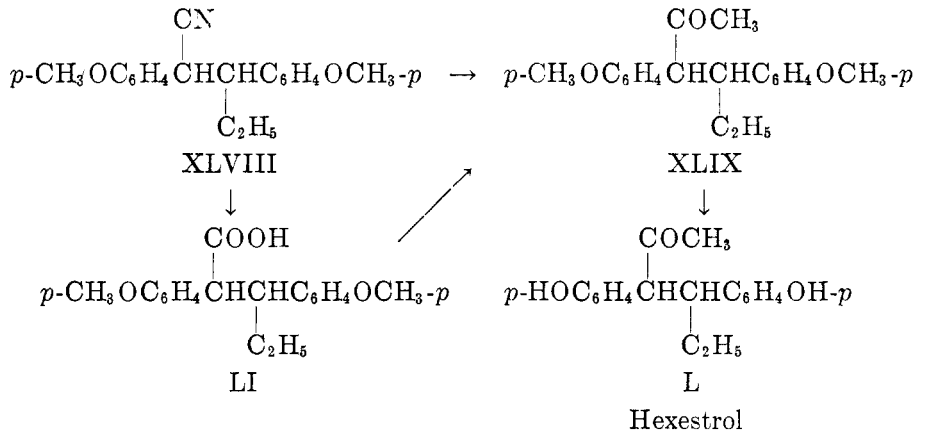
2. Syntheses utilizing the addition of Grignard reagents to α,β-unsaturated systems

Developing this newer method, based on the previous work of Kohler (243), Wawzonek (538) added ethylmagnesium bromide across α-(*p*-methoxyphenyl)-*p*-methoxycinnamonitrile (XLIV).



Direct treatment of the Grignard reaction product (XLV) with ethyl iodide yielded an oil from which crystalline α-ethyl-α,β-bis(*p*-methoxyphenyl)valeronitrile (XLVI), m.p. 73–74°C., was obtained. The mother liquors yielded a glassy isomer. Treatment of the oily nitrile mixture with sodium in isoamyl alcohol gave a mixture of hexestrol dimethyl ethers (XLVII) in 80 per cent yield, from which the meso ether was obtained in 33 per cent yield.

In related work Burckhalter and Sam (41) obtained XLIV in 95 per cent yield by condensing *p*-methoxybenzyl cyanide and anisaldehyde; this was a slight improvement over previous results (202, 311). Subsequent reaction of XLIV with an excess of ethylmagnesium bromide gave the diastereoisomeric forms of α,β-bis(*p*-methoxyphenyl)valeronitrile (XLVIII): one form, melting at 131°C., was obtained in 42 per cent yield; the other, an oil, in 49 per cent yield. The solid nitrile, treated with a 3 molar excess of methylmagnesium iodide in ether–benzene, gave an 87 per cent yield of 3,4-bis(*p*-methoxyphenyl)-2-hexanone (XLIX), m.p. 143°C., and a small amount of the diastereoisomer, m.p. 104°C. Rorig (366) had failed to achieve this conversion, owing to the use of an insufficient quantity of the Grignard reagent. In an alternative route to XLIX Burckhalter and Sam hydrolyzed the solid nitrile (XLVIII) to an acid (LI), m.p. 181–183°C. An isomeric lower-melting acid claimed by Hunter and Korman (202) was not found. The acid, as its acid chloride, reacted with ethoxymagnesiomalonic ester (532) to give, finally, the ketone XLIX. Conversion of

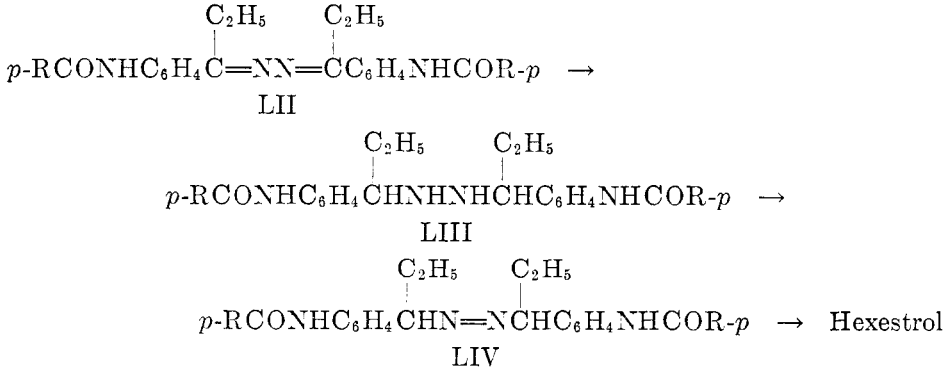


XLIX to hexestrol was carried out by demethylation with aluminum bromide in benzene (the only satisfactory reagent), followed by Huang-Minlon reduction; an 81 per cent yield of hexestrol was obtained. Direct Huang-Minlon reduction of XLIX with long heating gave hexestrol in 48–52 per cent yield. Reaction of L with acetic anhydride gave a diacetate melting at 143–144°C. and the residues from the preparation of L gave an isomeric diacetate, m. p. 103–104°C.; each on hydrolysis regenerated the original ketone.

3. Syntheses involving azine intermediates

This type of synthesis was first used to obtain hexestrol by Campbell, Dodds, and Lawson (54); it is notorious for poor yields. Sah (375) used an essentially similar synthesis. Anisaldazine was treated with ethylmagnesium iodide and the product pyrolyzed at 300°C. in dibenzyl ether; demethylation with hydriodic acid gave hexestrol.

In a method (258) based on the original one of Bretschneider, Bretschneider, and Ajtai (35) an acylated *p*-aminopropiophenone was converted by hydrazine hydrate to the ketazine LII. Catalytic reduction of LII followed by air oxidation gave LIV via the intermediate LIII. Fusion of LIV gave a mixture of the meso and racemic forms of the diacyl derivative of 3,4-bis(*p*-aminophenyl)-



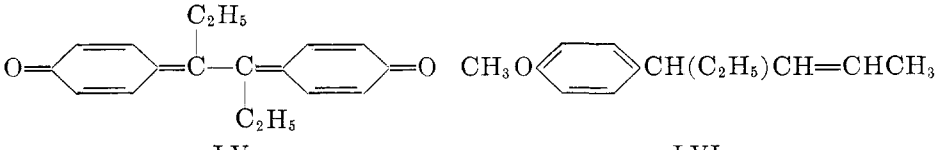
hexane. Hydrolysis of the separated diacyl derivatives followed by the diazo reaction, gave, with the meso diamine, hexestrol. Foldi and Fodor (132) and Fodor (130) applied the same method to *p*-methoxypropiophenone, and a patent (72) described the use of *p*-hydroxy-, *p*-alkoxy-, or *p*-acyloxypropiophenones as starting materials.

Fodor and Wein (131) investigated various applications of this synthesis as routes to 3,4-bis(*p*-aminophenyl)hexanes which may be converted to hexestrols as described. From *p*-acetamidopropiophenone a mixture of the meso and racemic diamino compounds was obtained; starting from *p*-aminopropiophenone only, the meso diamino compound was produced. The meso diamino compound was the final product also when the synthesis was applied to *p*-bromopropiophenone, followed by treatment of the dibromo compound obtained with cuprous iodide and aqueous ammonia at 205°C. in a sealed tube. A last route used propiophenone itself, which yielded meso and racemic 3,4-diphenylhexanes; separation of these, followed by nitration and catalytic reduction, gave the meso and racemic diamines. Application of the diazo reaction provided meso and racemic hexestrol.

4. Other methods

Huang-Minlon (191) reacted *p*-nitropropylbenzene with hydrazine hydrate and potassium hydroxide in triethylene glycol and obtained a mixture of *p*-aminopropylbenzene and both forms of 3,4-bis(*p*-aminophenyl)hexane; the latter were converted to the hexestrols by the diazo reaction. In the absence of potassium hydroxide reduction but no coupling occurred. The compound 3,4-bis(*p*-methoxyphenyl)-3-hexanol, previously described in connection with the Dodds and related syntheses, was converted directly to hexestrol dimethyl ether by Sah (374) by subjecting it to Clemmensen reduction. Alternatively, Clemmensen reduction of 3,4-bis(*p*-methoxyphenyl)-3,4-hexanediol gave hexestrol dimethyl ether. Turnbull (510, 511) obtained 3,4-bis(*p*-methoxyphenyl)-3,4-dibromohexane by the addition of bromine to diethylstilbestrol dimethyl ether or by the irradiated bromination of hexestrol dimethyl ether in the presence of dibenzoyl peroxide. Treatment of the dibromo compound with potassium iodide in acetone or zinc dust in acetic acid gave hexestrol dimethyl ether, thus providing a method for the transformation of diethylstilbestrol into hexestrol.

Adler (1, 178) obtained α,α'-diethylstilbenequinone (LV) by the oxidation of diethylstilbestrol with lead dioxide, ferric chloride, silver oxide, or lead tetra-



LV LVI

acetate. The compound was obtained pure, whereas previous preparations were brown-red resins (122). Hydrogenation of LV led largely to the *trans*-diethylstilbestrol. Both *cis*- and *trans*-stilbestrols may be oxidized to the quinone, and

since hydrogenation gives the *trans*-stilbestrol the reactions provide a chemical method for cis-to-trans interconversion. Diethylstilbestrol was converted to 3,4-bis(*p*-hydroxyphenyl)-2,4-hexadiene in 73 per cent yield by rearrangement of the quinone with sodium hydroxide solution; acids also bring about this rearrangement. Subsequent hydrogenation of the diene with palladium–charcoal gave a 50 per cent yield of hexestrol, together with some racemate. Hydriodic acid and red phosphorus may also be used as the reducing agent. The diene referred to melted at 184–185°C. and was called isodienestrol, since it was different from the isomeric dienestrol of Dodds (101, 102), which melted at 227–228°C.

It may be noted that direct hydrogenation of diethylstilbestrol gives an almost quantitative yield of racemic hexestrol (391).

The pinacolone alcohol 3,3-bis(*p*-hydroxyphenyl)-4-hexanol, previously mentioned in connection with the synthesis of diethylstilbestrol, on retropinacolone rearrangement with hydrogen iodide was simultaneously reduced to give a 20 per cent yield of hexestrol (3, 175).

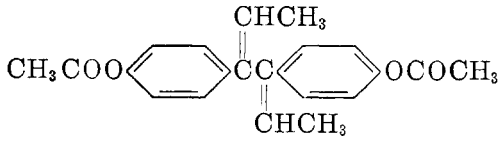
Reesor, Smith, and Wright (346) metalated stilbene with sodium and reacted the disodium derivative with an alkyl halide, thus obtaining a mixture of meso and racemic α,α'-dialkyldiphenylethanes.

Tanabe and Onishi (497) obtained hexestrol dimethyl ether by the condensation of LVI with anisole by the action of sulfuric acid at 10°C.

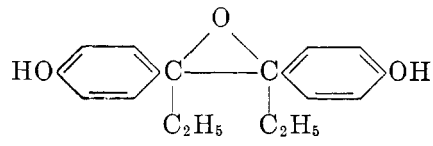
C. SYNTHESES OF DIENESTROL

1. Syntheses via 3,4-bis(p-hydroxyphenyl)-3,4-hexanediol

Dienestrol, the third principal stilbene-type estrogen, was first obtained by Dodds, Golberg, Lawson, and Robinson (101, 102) by acetyl chloride dehydration of 3,4-bis(*p*-hydroxyphenyl)-3,4-hexanediol (XXXVII). Although other methods have been used to synthesize dienestrol (447), this method has received most attention. The 3,4-bis(*p*-hydroxyphenyl)-3,4-hexanediol obtained by Dodds et al. was a mixture of diastereoisomers, and the mixture was separated into its meso and racemic forms by Adler and Lundin (6). These workers acetylated the mixture with acetic anhydride; on cooling the higher-melting meso diacetate (m.p. 208–210°C.) separated in 58.5 per cent yield. The racemic diacetate, m.p. 83–84°C., was obtained as the monoalcoholate by addition of water to the filtrate, extraction with ether, and recrystallization from ethanol. The diacetates were hydrolyzed to the corresponding pinacols, m.p. 217–219°C. and m.p. 212–214°C., and dehydrated by means of acetic anhydride–acetyl chloride. The meso compound gave the diacetate of 3,4-(*p*-hydroxyphenyl)-2,4-hexadiene or dienestrol diacetate (LVII) in 71 per cent yield; the racemic form also gave dienestrol diacetate but in 47 per cent yield. Both pinacols also gave the same rearrangement product, the pinacolone XXXVIII. A compound melting at 94–95°C. had been previously obtained by Hobday and Short (172) and had been thought to be a diastereoisomeric form of 3,4-bis(*p*-hydroxyphenyl)-3,4-hexanediol. Adler and Lundin considered that this compound might be 3,4-epoxy-3,4-bis(*p*-hydroxyphenyl)hexane (LVIII).



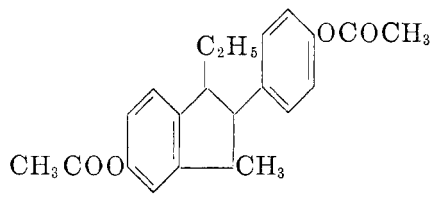
LVII



LVIII

The original Dodds synthesis gave only 25–30 per cent yields of dienestrol; the method of Adler and Lundin using isomer separation gave 64 per cent total yields of the estrogen. This superior method of synthesis of dienestrol is the basis of several patent claims (2, 176, 177). Other modifications, such as the use of sodium, potassium, or calcium amalgams to convert *p*-hydroxypropiophenone to the pinacol and the use of benzoyl chloride or *p*-toluenesulfonyl chloride as acylating agent, have been introduced (170, 171, 409).

Three dienestrols are now known. α-Dienestrol or dienestrol, m.p. 227–228°C., was obtained by Dodds, Golberg, Lawson, and Robinson (101, 102). β-Dienestrol or isodienestrol, m.p. 184–185°C., was prepared by Hobday and Short (172) and was also obtained, as previously mentioned, a year later by v. Euler and Adler (122). A third isomer, γ-dienestrol, m.p. 121–122°C., was obtained by Breivogel in 1948 (252). The isolation of the three dienestrols led Lane and Spialter (252) to investigate the nature and amounts of dienestrols and other products obtained in the dehydration of the meso and racemic pinacols. These authors also introduced the α-, β-, γ-dienestrol nomenclature. Dehydration of 3,4-bis(*p*-acetoxyphenyl)-3,4-hexanediol with acetic anhydride–acetyl chloride, followed by chromatography of the product on silicic acid, gave four fractions. One fraction contained the diacetates of the three dienestrols, together with that of indenestrol A (LIX). This latter compound had been ob-



LIX

tained previously by the cyclization of dienestrol by Adler and Hagglund (4) and by Hausmann and Wilder Smith (158, 159). The dienestrols could not be separated, but the α- and γ-isomers were estimated by reaction of the mixture with bromine in acetic acid in the presence of sodium acetate. The α- and γ-diacetates react rapidly with the reagent, while the β-diacetate and that of indenestrol A do not; titration gave the combined $\alpha + \gamma$ content. A second fraction was 3,3-bis(*p*-acetoxyphenyl)-4-hexanone, the intermediate for the synthesis of diethylstilbestrol. A third fraction contained polymerized dienes, and some unreacted pinacol was also obtained as a separate fraction.

In later work Lane and Spialter (253) examined the dehydration and pinacolic rearrangement competition when the isomeric 3,4-bis(*p*-acetoxyphenyl)-3,4-

hexanediols were treated with acidic reagents and so clarified the conditions for obtaining diethylstilbestrol or dienestrol from this same starting material. The reagents acetyl chloride–acetic anhydride and hydrogen chloride–acetic anhydride gave dienestrols; the meso pinacol was more easily dehydrated than the racemic one. Apparently acetyl chloride is essential to the formation of dienestrol; the second reagent contains acetyl chloride produced by the interaction of hydrogen chloride and acetic anhydride (525). The function of acetic anhydride is apparently solely as a solvent; in pure acetyl chloride the dehydration was almost quantitative. When formic acid, sulfuric acid in acetic anhydride, or hydrogen chloride in acetic acid was used, the pinacolone was exclusively produced. The possible mechanisms for these changes were discussed by the authors. A preliminary acetylation step was suggested for the conversion of the pinacol to the diene.

2. Other methods

Turnbull (510, 511, 512) obtained 3,4-bis(*p*-acetoxyphenyl)-3,4-dibromohexane by the bromination of diethylstilbestrol and hexestrol diacetates under the conditions previously described. Treatment of this compound with potassium iodide in ethyl alcohol or with pyridine under nitrogen yielded dienestrol.

III. Some Physicochemical Considerations

A. ISOMERISM

Theoretically two diethylstilbestrols must exist, a cis isomer and a trans isomer. The highly active diethylstilbestrol, m.p. 171°C., is considered from a variety of evidence (449) to be the trans isomer. A substance previously mentioned, melting at 141°C., was obtained by Dodds, Golberg, Lawson, and Robinson (100) and was later purified by Walton and Brownlee (533), who obtained from it both the trans isomer and a compound melting at 151°C.; the latter was called ψ-stilbestrol and was provisionally considered to be the cis isomer.

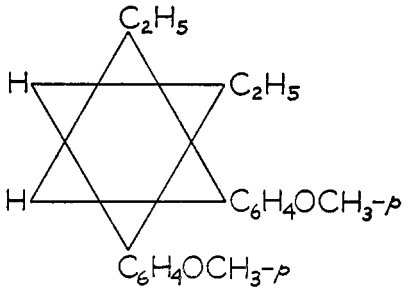
More recently, Wessely, Bauer, Chwala, Plaichinger, and Schönbeck (544) also failed to rearrange the trans isomer to the cis form. Treatment of *trans*-diethylstilbestrol with propionic anhydride in pyridine at 25°C. gave a 100 per cent yield of the known trans dipropionate, m.p. 105–106°C. The known cis dipropionate, m.p. 79°C., was obtained by ultraviolet irradiation of the trans dipropionate or in 30 per cent yield from *trans*-diethylstilbestrol and propionic anhydride at 50–100°C. Iodine in benzene did not isomerize the cis dipropionate. Hydrolysis of the cis dipropionate with methanolic sodium hydroxide gave only the *trans*-diethylstilbestrol. Hydrolysis with alcoholic ammonia at room temperature yielded some cis dihydroxy compound, but this could not be isolated in the pure state. Methylation of the cis dipropionate with methyl sulfate and 20 per cent sodium hydroxide solution gave the cis dimethyl ether. These workers also obtained the *cis*- and *trans*-2,3-bis(*p*-methoxyphenyl)-2-butenes, melting at 50°C. and 131°C., respectively. Similar and supporting results were obtained by Derkosch and Friedrich (89), who also failed to obtain pure *cis*-diethylstil-

bestrol by the hydrolysis of its dipropionate. By a spectroscopic method these workers found that hydrolysis of the cis dipropionate with alcoholic ammonia at 20°C. gave a stable solution of the cis dihydroxy compound, but a pure specimen of the latter could not be isolated. Use of alcoholic sulfuric acid at 20°C. as the hydrolyzing agent gave the *cis*-diethylstilbestrol, but this rapidly isomerized in solution to the trans isomer. Hydrolysis of the trans dipropionate with either reagent regenerated the trans dihydroxy compound.

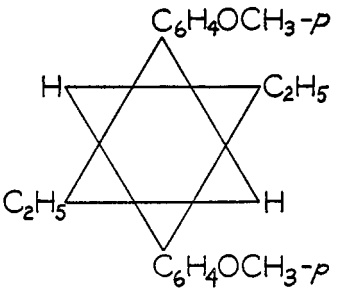
These results clearly indicate that *cis*-diethylstilbestrol has not yet been obtained as a pure compound; indeed, it may be too labile for isolation. It is expected to have a melting point of about 110°C. In view of these facts Wessely and coworkers considered the substance melting at 151°C., ψ-stilbestrol, to be a geometric isomer of 3,4-bis(*p*-hydroxyphenyl)-2-hexene which they had obtained previously (345) with a melting point of 153°C.; the other isomer has a melting point of 143°C. The identity of the 3,4-bis(*p*-hydroxyphenyl)-2-hexene, m.p. 153°C., with ψ-stilbestrol had been previously suggested by Jones (217). Contrary to the earlier report of Walton and Brownlee, Malpress (276) found that heating the trans or ψ compound with 2.5 *N* aqueous hydrochloric acid produced an equilibrium mixture of the trans and ψ compounds in the ratio 9:1. This result is of importance in the chemical estimation or bioassay of the products of hydrolysis of the conjugated forms of diethylstilbestrol from biological fluids; hexestrol is quite stable under these hydrolyzing conditions. Buckles (39) made the interesting observation that ultraviolet irradiation of *cis*- or *trans*-stilbene in dilute alcoholic solution for 20 days yielded phenanthrene. Simamaru and Suzuki (414) found that *cis*- or *trans*-α,α'-dimethylstilbene with a little sulfuric acid at 210°C. gave an equilibrium mixture containing 55 per cent of the trans and 45 per cent of the cis isomer. Iodine at 210°C. gave *meso*-2,3-diphenylbutane; bromine produced some isomerization and also gave some 1,4-dibromo-2,3-diphenyl-2-butene.

The hexestrols exist as the meso isomer, m.p. 185°C., the racemic isomer, m.p. 129°C., and the antipodes, m.p. 80°C., of the latter (452). The meso isomer is the potent estrogen; the racemic form is frequently referred to as isohexestrol. The evidence for the assignment of configuration was obtained earlier (452). Using hexestrol dimethyl ether as model, Suetaka (476) considered the possibility of rotational isomerism about the central carbon–carbon bond in *meso*-hexestrol. Assuming the possibility of gauche (LX) and trans (LXI) forms, Suetaka calculated their dipole moments as 2.06 D and 1.75 D, respectively. The observed moment in carbon tetrachloride solution was 1.77 D, showing that the trans form is almost the sole species present. This result is expected on steric grounds, but the observed dipole moment of 1.57 D in benzene is difficult to interpret. The confirmation of the trans form for *meso*-hexestrol in solution is important, in that under physiological conditions *meso*-hexestrol will exert its biological action in a structural form corresponding to that of the natural estrogens. Suetaka also found a dipole moment in benzene solution of 1.24 D for *trans*-α,α'-bis(methylthio)stilbene (LXII). Assuming no anomalies, this value was shown to be compatible with a structure in which the aromatic rings

are rotated 75° from the plane of the ethylenic unit and the methyl groups rotated 34° from this plane in the opposite directions and about the sulfur–carbon bonds. These steric effects of the aliphatic portion seem of considerable importance in estrogen chemistry and are discussed later.



LX



LXI

$C_6H_5C(SCH_3)=C(SCH_3)C_6H_5$

LXII

α-Dienestrol or dienestrol, m.p. 227–228°C., the potent estrogen, was considered to have the trans-trans structure (57). As will be discussed later, this configuration for dienestrol has been substantiated. On the basis of estrogenic activities the γ-isomer, m.p. 121–122°C., is probably the cis-trans form, while the β-isomer, m.p. 184–185°C., also called isodienestrol, is probably the cis-cis form.

B. SPECTROSCOPIC STUDIES

Early work by Ley and Rincke (261) and by Arends (11) showed that the ultraviolet absorption spectrum of *trans*-stilbene has its maximum shifted to progressively shorter wavelengths by the introduction of one, and then two, methyl substituents on the alkene unit. This maximum is attributed to the triple chromophore consequent from the electron interaction in the two aromatic rings with the ethylenic system. It is of interest that the saturated carbon system in bibenzyl also is chromolatory (32). Oki (320) gave the ultraviolet absorption data in table 1 for various 4,4′-dimethoxy-α,α′-dialkylstilbenes.

There is a shift of the maximum further to shorter wavelengths with increasing size of the alkyl group, and the steric effect of an α-alkyl group on the ortho hydrogen of the α′-phenyl group was proposed by Jones (218) and Lewis and Calvin (260) as an explanation of the spectroscopic effect.

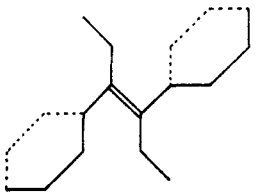
Jeffrey, Koch, and Nyburg (214) and Koch (239) concluded from a study of molecular models, x-ray crystallographic data, and ultraviolet absorption data that in α,α′-dialkylstilbenes, and hence diethylstilbestrol, the desire to attain coplanarity and the full resonance energy of the *trans*-stilbene stystem is prevented by the steric effect of the alkyl groups. These molecules will therefore have their aromatic rings rotated, and it was presumed symmetrically, so that a staggered configuration (LXIII) is acquired. This structural characteristic is

TABLE 1

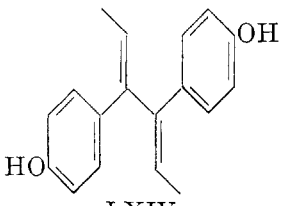
Ultraviolet absorption data for some 4,4'-dimethoxy-α,α'-dialkylstilbenes in 95 per cent ethanol

p-$CH_3OC_6H_4C(R)$=$C(R)C_6H_4OCH_3$-p

R in compound	λ_{max}	$\epsilon_{max} \times 10^{-4}$	R in Compound	λ_{max}	$\epsilon_{max} \times 10^{-4}$
	mμ			mμ	
H	230	1.27	CH_3	247	2.85
	305	3.47	C_2H_5	236	2.20
	326	3.37	C_3H_7	235	1.81



LXIII



LXIV

present in bibenzyl (358). The ethyl groups in diethylstilbestrol were considered oriented away from the phenyl groups for steric reasons. This conclusion refuted the idea that diethylstilbestrol simulated the natural estrogens but only on the point of the orientation of the ethyl groups. The fact that diethylstilbestrol is the trans isomer and, from the work of Jeffrey, Koch, and Nyburg, has definite thickness, make the similarity to the natural estrogens closer than was originally appreciated. The staggered configuration also applies to hexestrol, but here it is an intrinsic rather than an enforced characteristic. Similar conclusions were drawn about dienestrol (214); in this compound the data indicated a rotation of 50° for the phenyl groups from the plane of the hexadiene system, the latter having the trans-trans form (LXIV). This configuration would be expected in view of the relation to diethylstilbestrol and its estrogenic potency. It is expected that the cis phenyl group in triphenylethylene will have a steric effect, particularly on its adjacent phenyl group. Braude (32) found that isodienestrol showed styrene chromophore adsorption corresponding to the summation of two 4-hydroxy-β-methylstyrene systems. This was considered to indicate that the two halves of the isodienestrol molecule were rotated about the central carbon–carbon bond into planes approximately at right angles. This configuration would be expected for the cis-cis structure and, as pointed out previously, this is also in agreement with the biological results. While Jeffrey, Koch, and Nyburg considered rotation of the aromatic rings in these compounds into parallel planes, Oki (320) considered the direction of rotation to be ambiguous. However, consideration of the biological results for dienestrol and isodienestrol indicates that rotations which tend to bring the nuclei into planes at right angles will lead to decreased estrogenic activity; active estrogens are expected to have the staggered configuration. Havinga and Nivard (160) also concluded from spectroscopic data that diethylstilbestrol has a nonplanar structure and suggested that in *cis*-cinnamic acid nonplanarity of the carboxyl

group and the aromatic ring is important for the activity of the compound as a plant hormone.

Oki and Urushibara (327) concluded from spectroscopic data that thickness of the molecule of diethylstilbestrol is important for its estrogenic activity and that this compound had optimum thickness. These authors pointed out that thickness and width were complementary and that the width may also be important for biological activity. However, thickness is the factor responsible for orienting the phenolic groups, and from the existence of estrogenic activity in many large molecules, width appears to be a very secondary factor. In support of the hypothesis of molecular thickness, these authors showed 4,4′-dimethoxy-α,α'-bis(methylthio)stilbene, which is active at 10 micrograms in mice, to have a molecular thickness similar to that of the corresponding α,α'-dipropylstilbene. It appears that ethyl groups are not fundamental to activity and that other sterically similar groups can replace them. Pursuing these ideas Oki (321) correlated estrogenic activity and spectroscopic properties or molecular thickness in a series of 4,4′-dimethylthio-α,α'-dialkylstilbenes (table 2) and found optimum activity at optimum thickness corresponding to the diethyl compound.

Oki (320) replaced the alkyl groups by halogen atoms and prepared a series of 4,4′-dimethoxy-α,α'-dihalogenostilbenes; spectroscopically steric effects were found to be operative. The bromine atom, which has a van der Waals radius similar to that of the methyl group, was found to have a smaller steric effect on rotation of the ring. The dichloro compound (table 3) was found to have an estrogenic activity similar to that of the dibromo compound; whereas the latter molecule has a thickness of the same order as diethylstilbestrol, the chloro compound has not. This was interpreted as being due to the existence of another optimum molecular thickness to which the dichloro compound approximated. However this seems unlikely, and probably properties of these compounds other than molecular thickness are important. The reality of hindered rotation, and so molecular thickness, in these molecules was shown by Oki (321a). Resolution provided the first example of an optically active stilbene containing no asymmetric carbon atom.

The concept of optimum molecular thickness is probably of considerable im-

TABLE 2

Ultraviolet absorption data (in 95 per cent ethanol) and estrogenic activities for some 4,4′-bis(methylthio)-α,α'-dialkylstilbenes

p-$CH_3SC_6H_4CR{=}CRC_6H_4SCH_3$-$p$

R in Compound	λ_{max}	$\epsilon_{max} \times 10^{-4}$	Estrogenic Activity in Mice, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose‡
	mμ		*micrograms*
CH_3	271	3.1	300 (50%)
C_2H_5	266.5	2.7	40
C_3H_7	265	2.5	200 (incomplete)

‡ Compound administered in two portions.

TABLE 3

Ultraviolet absorption data (in 95 per cent ethanol) and estrogenic activities for some 4,4'-dimethoxy-α,α'-dihalogenostilbenes

p-$CH_3OC_6H_4CX{=}CX'C_6H_4OCH_3$-$p$

Compound		λ_{max}	$\epsilon_{max} \times 10^{-4}$	Estrogenic Activity in Mice, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose‡
X	X'			
		mμ		*micrograms*
Cl	Cl	282	2.87	200
Br	Br	263	2.53	300
I	I	235	2.24	800 (inactive)
Cl	I	227	1.22	100
		267	1.27	
Br	I	234	1.72	> 600
		261	1.58	

‡ Compound administered in two portions.

portance in determining estrogenic activity and goes a long way towards explaining the low activity of compounds such as 4,4'-dihydroxystilbene and the varying activities of the alkylstilbestrols (450). Nevertheless it is clear from the above discussion that the nature of the steric factor and its effect on the molecule as a whole must also be considered.

C. ADSORPTION PROPERTIES

Rideal and Schulman (355) and Rideal (354) measured the adsorption capacity, on a gliadin monolayer, of various stilbene estrogens. The order of increasing adsorption capacity of these α,α'-dialkylstilbestrols was found to correspond essentially with the order of increasing estrogenic activities of the compounds. The peak of both properties was shown to occur with diethylstilbestrol. Variation of the aliphatic portion of diethylstilbestrol affects the estrogenic activity (450), and this variation was found by Rideal and Schulman to have a definite effect on the adsorption capacity of the substance. Adsorption at a chemoreceptor is probably an important requirement for an estrogen, and the results of Rideal and Schulman indicate that the aliphatic portion may make an important contribution to such van der Waals adsorption. This is probably an important second function of the aliphatic portion and would account for the need for a steric factor having suitable adsorption capacity.

D. SOLUBILITY

Cheymol and Carayon-Gentil (57, 67) determined the solubilities of diethylstilbestrol, hexestrol, and dienestrol in various solvents (table 4).

Unfortunately, few data in this direction are available, although solubilities are probably of considerable significance to estrogenic potency. Water solubility confers high translocatability, and in general water-soluble estrogens have a more rapid action. Effort has been expended to produce water-soluble estrogens, since these may be administered intravenously.

An interesting observation due to Wilder Smith and Williams (420) was the

TABLE 4

Some solubility data for diethylstilbestrol, hexestrol, and dienestrol

Solvent	Solubility		
	Diethylstilbestrol 15–18°C.	Hexestrol 15–18°C.	Dienestrol 15–18°C.
	g./100 cc.	*g./100 cc.*	*g./100 cc.*
Water	0.028	0.007	0.0035
Ethyl alcohol (99%)	18.5	18.3	11.25
Methyl alcohol	7.5	24.55	13.6
Benzene	0.22	0.17	0.069
Chloroform	0.80	0.19	0.14
Ether	32.0	29.1	8.06
Ethyl acetate	23.51	33.0	18.55
Acetone	18.4	10.22	11.64
Dioxane	10.71	8.28	

instability of diethylstilbestrol and dienestrol in aqueous solution, particularly in acid or alkaline solution. Polymerization was suggested as a mechanism, since in neutral solution the loss of activity was greatly enhanced by traces of hydrogen peroxide but inhibited by hydroquinone. The instability of these substances in solution was also found, by chemical estimation, by Warren and Goulden (536). These results are of consequence in assaying these estrogens in solutions. Hexestrol and natural estrogens were found to be stable.

E. SOME STRUCTURAL CONSIDERATIONS IN RELATION TO ESTROGENIC ACTIVITY

Giacomello and Bianchi (139) found, by x-ray crystallography, that the molecules of diethylstilbestrol and of estrone were 8.55 A. long and 3.88 A. wide. Carlisle and Crowfoot (58) similarly found the trans configuration for solid *meso*-hexestrol, which thus simulates the natural hormones. In view of these results Ungnade and Morriss (517) examined the melting-point behavior of various estrogens. Diethylstilbestrol or hexestrol was found to form mixed crystals with "α"-estradiol; hence the compounds are isomorphic. Mixed-crystal formation with diethylstilbestrol and hexestrol was found and is evidence for the trans configuration of the former compound, since *cis*-stilbene does not form mixed crystals with the corresponding dihydro compound (304).

Schueler (388) used the results of Giacomello and Bianchi and concluded that a substance may be estrogenic if it consists of a rather large, rigid, inert molecule with two active hydrogen-bonding groups at an optimum separation of 8.55 A. The latter point was stressed, but the other suggestions were not elaborated. Estrone, which does not have two hydrogen-bonding groups, was considered to function as the enol or to be reduced *in vivo*. There is evidence in support of this latter idea (348, 349, 468). Devis (90), however, found 6-ketotestosterone acetate to have moderate estrogenic activity and attributed this to enolization of the carbonyl group. Macovski and Georgescu (272) suggested an optimum separation of oxygen atoms of 9.6 A. The suggestion of an optimum separation of hydrogen-bonding groups is of course quite incomplete without consideration of other factors. In any case, 8.55 A. is a molecular length, as shown for estrone

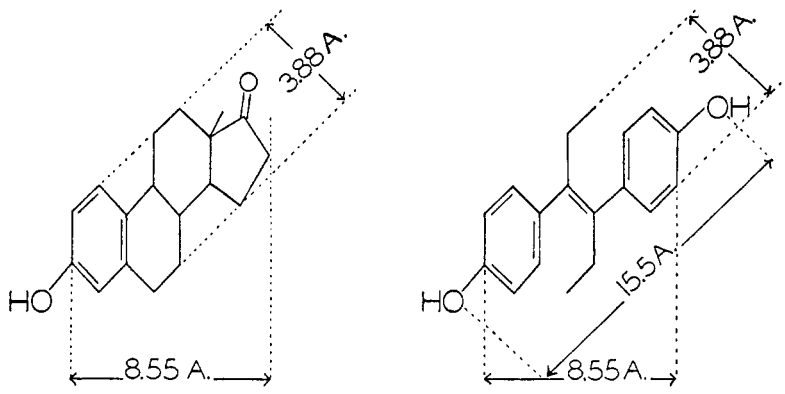
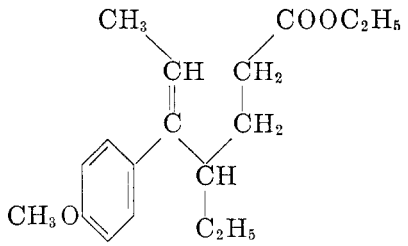


FIG. 1

and diethylstilbestrol (figure 1), and is not the distance of separation of hydrogen-bonding groups. For diethylstilbestrol this latter separation is about 15.5 A. Keasling and Schueler (228) modified the earlier suggestion and found, for 4,4′-substituted azomethines, an optimum separation of groups at 14.5 A. Schueler suggested that weaker hydrogen bonding groups and a separation of 9–10 A. was associated with androgenic activity. Velasquez, Valenzuela, and Aguilar (530) found the hydroxyl groups of diethylstilbestrol essential to its bacteriostatic activity. In agreement with the concept of hydrogen bonding the value of groups to an estrogenic molecule appears to be in the order alcoholic hydroxyl group < phenolic hydroxyl group < carboxyl group. As mentioned previously, Oki and his collaborators (323) considered that besides optimum separation of hydrogen-bonding groups appropriate orientation of the groups is necessary. This is attained by the molecule having thickness, although the staggered structure is probably of other stereochemical importance as well. Although the general shape of the aliphatic portion of the potent artificial estrogens does not resemble that in natural estrogens, it points to the presence of a possibly valuable stereochemical feature not possessed by natural estrogens.

Clark (73) found LXV to be estrogenically active and considered that the lack of van der Waals adsorption of the molecule at the chemoreceptor was made good by the potential carboxyl group, which might function as an anchoring group at a center on the chemoreceptor. Grundland (149, 150) suggested that,



LXV

in the body, estrogens and lipides form van der Waals adhesion complexes, the latter thereby temporarily acquiring polar groups and being more readily dispersed in the aqueous phase of the blood. This suggestion does not account for the influence of the number and spacing of hydroxyl groups on the estrogenic activity shown by a molecule. McShan and Meyer (280) found that diethylstilbestrol, hexestrol, and dienestrol inhibited the succinic oxidase system and that this was a function of the number of hydroxyl groups present. Vargas and Escubos (527) considered that estrogenic activity in a substance was related to its cellular permeability and that this was optimum in the more homopolar or trans forms of molecules.

IV. Estrogenic Activities of Diethylstilbestrol, Hexestrol, and Dienestrol

Owing to the operation of various factors, data for the estrogenic activities of substances have no absolute significance, as previously pointed out. Data from various sources for the three principal stilbene estrogens are collected in table 5. The data give some indication of the potencies of these compounds and are also useful as a guide.

Bishop, Kennedy, and Wynn-Williams (20) and Bishop, Richards, Neal-Smith, and Perry (21) attempted the assessment of estrogens in the human. The estrogen was administered orally and daily for 14 days to amenorrheic women, and the criterion of uterine bleeding upon the withdrawal of the estrogen was used. Dienestrol was found to have 25 per cent of the activity of diethylstilbestrol, while hexestrol had only 6 per cent of its activity. Doisynolic acid had 20 per cent of the activity of diethylstilbestrol, but ethinylestradiol was 20–25 times as potent. These authors found diethylstilbestrol to be more toxic at therapeutic dosage than the other estrogens and in higher dosage more likely to cause nausea. It appears that toxicity is related to estrogenic potency, since ethinylestradiol

TABLE 5

Estrogenic activities of diethylstilbestrol, the hexestrols, and the dienestrols

Compound	Melting Point	Estrogenic Activity in Rats (100% Response Unless Indicated Otherwise); Minimal Effective Dose		Reference
		Subcutaneously	Orally	
	°C.	*micrograms*	*micrograms*	
Diethylstilbestrol	171	0.4		(102)
			5	(102)
Hexestrol (meso form)	186	0.2		(53)
			3	(102)
Hexestrol (racemic form)	129	1000		(54)
Hexestrol (+ antipode)	80	100		(549)
Hexestrol (− antipode)	80	1000 (40%)		(549)
α-Dienestrol	227–228	0.5		(102)
			3	(102)
β-Dienestrol	184–185	0.003 (α-isomer = 1)		(252)
γ-Dienestrol	121–122	0.03 (α-isomer = 1)		(252)

at higher dosage was toxic. Using rhesus monkeys and the criterion of uterine bleeding, Eckstein, Krohn, Zuckerman, and Healy (111) found the order of activity to be diethylstilbestrol > hexestrol > dienestrol; the estrogen was given as a single dose intramuscularly. The confusing and contradictory biological results (55, 112, 229) for the stilbene estrogens prompted Harmer and Broom (156) to attempt the correlation of the results on animals and the clinical results of Bishop and coworkers. In the rat hexestrol given orally in oil had 10 per cent of the activity of diethylstilbestrol, while dienestrol had 67 per cent of this activity. In aqueous solution and subcutaneously these orders were reversed; hexestrol had 67 per cent and dienestrol < 33 per cent of the activity of diethylstilbestrol. Ryden (371), using the criterion of proliferation in women, found that the activities were diethylstilbestrol > dienestrol > hexestrol. Ryden (372) also found, in women, that dienestrol was 5–6 times more active intramuscularly than orally, and that diethylstilbestrol was 1.5–2 times more active than dienestrol orally and 3–5 times more active than hexestrol. These results make interesting comparison with those in table 5 and clearly show the difficulties of comparing the estrogenic potencies of compounds. Munro and Kosin (298) found, on the basis of the response of the chick oviduct, that hexestrol was more active than diethylstilbestrol. Similarly, Dorfman and Dorfman (108) found 7-methylbisdehydrodoisynolic acid quite close in activity to diethylstilbestrol. In women and using gonadotropin excretion as the method of assay, Tokuyama, Leach, Sheinfeld, and Maddock (507) found diethylstilbestrol to be 5 times more active than "α"-estradiol. The oral efficiency of an estrogen is considered to be related to the ability of the liver to inactivate it. Nielsen, Pedersen-Bjergaard, and Tønnesen (314) found that diethylstilbestrol and dienestrol were not inactivated by the liver in the rat when given orally. Hexestrol, estrone, and "α"-estradiol did suffer inactivation; parenterally none of these estrogens was inactivated. Dienestrol has been reported to be 3 times more active subcutaneously than orally (256).

V. Esters and Ethers of Diethylstilbestrol, Hexestrol, and Dienestrol

A. Esters

Estrogens take several days to act and a readily absorbed compound is more readily eliminated. Such compounds will have short duration of activity and may even be inactive. Diethylstilbestrol and hexestrol, both orally and subcutaneously and in large or small dosage, are short acting (504). These difficulties have been overcome by injection in divided dosage or some other suitable mode of administration (98) or by the use of esters. The latter apparently require hydrolysis *in vivo* before exerting their estrogenic function and have protracted action (220). The hydrolysis of diethylstilbestrol dipropionate is most effective in the liver and the kidney (91). Emmens (113) considered the function of hydroxyl groups in diethylstilbestrol to be for elimination of the estrogen via esterification. This is hardly likely to be the primary purpose of the hydroxyl function. Zima, Ritsert, and Kreitmair (561) found that the duration of estrus in the rat provoked by a series of esters of diethylstilbestrol paralleled their ease of hydrolysis in alcoholic potassium hydroxide. This supports the concept of *in vivo* hy-

drolysis of esters and the need for free hydrogen-bonding groups. The long-acting esters have obvious clinical value.

Esters have been prepared by the interaction of an organic acid chloride or anhydride or an inorganic acid chloride with the phenolic estrogen, in the presence or absence of an organic or inorganic base. Dienestrol esters were prepared (267) by reaction of the phenol with a Grignard reagent and subsequent treatment with an acylating agent. The minimal effective dose for an estrogen ester is higher than that of the parent estrogen; the effective dosage varies with the ester. Dienestrol difuroate has greater activity than the dibenzoate (75). Diethylstilbestrol and its dipropionate were fifteen times as effective as estrone in stimulating uterine growth (195). In rats diethylstilbestrol was found to be 8 times, and its dipropionate 2 times, as active as "α"-estradiol benzoate (195). Contrary to these results Veziris and Melzer (531) found "α"-estradiol benzoate more active than the dipropionates of hexestrol and diethylstilbestrol. Hexestrol dipropionate was more active than diethylstilbestrol itself (531). By the use of uterine bleeding upon withdrawal of the estrogen as a criterion and a single intramuscular dose in the rhesus monkey, "α"-estradiol and diethylstilbestrol dipropionates were found to be more active than the parent substances (111). Trimborn, Werle, and Semm (509) found the threshold dosage of dienestrol diacetate to be 0.25 microgram for mice intramuscularly, while for full estrus response 0.5 microgram was needed; twice these levels were required when the substances were administered orally.

Esterification is a chemical method for prolonging estrus; physical methods also have some importance. Increased duration was obtained by using an oily suspension of the estrogen; the duration of its action was found to depend on the particle size (124). Compressed implanted pellets still further extend the duration (286). However, other experiments indicated that prolongation with crystal suspensions occurred only at higher dosage (282, 537). A second type of ester based on an inorganic acid, generally sulfuric or phosphoric acid, is of importance, since the solubility of these esters or of their salts permits intravenous use and they have rapid action. The disulfate of diethylstilbestrol has a high activity in the rat, the guinea pig, and the rabbit and is tolerated at 10 mg., 20 mg. and 60 mg., respectively (146). Cavallini (60) found, in the guinea pig, that the disodium salt of diethylstilbestrol disulfate had about the same activity as diethylstilbestrol dipropionate, although it acted more rapidly. Harmer and Broom (156) found that an aqueous solution of potassium hexestrol sulfate given orally to the rat had only 7 per cent of the activity of a solution of diethylstilbestrol in oil. Given subcutaneously the salt solution had only 1 per cent of the activity of an aqueous solution of diethylstilbestrol. The alkali metal salts of diethylstilbestrol bis(sulfoacetate) (180) were claimed to show the full activity of the parent estrogen, besides having water solubility and low toxicity. A product melting at 164°C., containing four molecules of diethylstilbestrol to one of camphor, and prepared by intimate mixing or co-crystallization of the components was claimed to have therapeutic value (278). The esters of diethylstilbestrol, hexestrol, and dienestrol which have been prepared more recently are collected in tables 6, 7, and 8. Most of these have been prepared previously, but improved methods of

TABLE 6

Esters of diethylstilbestrol

p-$ROC_6H_4C(C_2H_5)=C(C_2H_5)C_6H_4OR'$-$p$

Compound		Melting Point	References
R	R'		
		°C.	
CH_3CO—	CH_3CO—	123	(351, 561)
			(401)
CH_3CH_2CO—	H—	92–94	(422)
CH_3CH_2CO—	CH_3CH_2CO—	107	(561)
		106–107	(423)
		105–106	(71)
		71–72 (*isomeric form*)	(71)
		104–106	(351)
$CH_3(CH_2)_2CO$—	$CH_3(CH_2)_2CO$—	98–99	(424)
		91	(561)
$CH_3CH_2OCH_2CO$—	$CH_3CH_2OCH_2CO$—	136.5–137.5	(289)
$CH_3CH_2SCH_2CO$—	$CH_3CH_2SCH_2CO$	95–97	(290)
		99–101	(289)
CH_3CH_2OCO—	CH_3CH_2OCO—	118	(425)
$CH_3(CH_2)_3CO$—	$CH_3(CH_2)_3CO$—	76.5–77.5	(426)
CH_3CH_2CO—	$CH_3(CH_2)_4CO$—		(427)
$CH_3(CH_2)_4CO$—	$CH_3(CH_2)_4CO$—	76	(561)
		75–76	(428)
$CH_3(CH_2)_5CO$—	$CH_3(CH_2)_5CO$—	58	(561)
$CH_3(CH_2)_6CO$—	$CH_3(CH_2)_5CO$—	60	(561)
		59–60	(429)
$CH_3(CH_2)_7CO$—	$CH_3(CH_2)_7CO$—	50	(561)
$CH_3(CH_2)_8CO$—	$CH_3(CH_2)_8CO$—	68	(561)
$CH_3(CH_2)_{10}CO$—	$CH_3(CH_2)_{10}CO$—	80	(561)
$CH_3(CH_2)_{12}CO$—	$CH_3(CH_2)_{12}CO$—	82–84	(430)
		82	(561)
$CH_3(CH_2)_{16}CO$—	$CH_3(CH_2)_{16}CO$—	84–86	(437)
C_6H_5CO—	H—		(431)
C_6H_5CO—	C_6H_5CO—	215	(561)
$C_6H_5SO_2$—	$C_6H_5SO_2$—	139	(561)
 CO—	 CO—		(124)
$NaSO_3CH_2CO$—	$NaSO_3CH_2CO$—	228–230 (d.)	(180)
			(179, 181, 520)
$C_5H_5\overset{+}{N}H\overset{-}{S}O_3CH_2CO$—	$C_5H_5\overset{+}{N}H\overset{-}{S}O_3CH_2CO$—	223–225 (d.)	(520)
HSO_3—	HSO_3—		(146)
$NaSO_3$—	$NaSO_3$—		(60, 61, 410)
KSO_3—	KSO_3—		(410)
$\overset{-}{Cl}\overset{+}{N}H_3CH_2CO$—	$\overset{-}{Cl}\overset{+}{N}H_3CH_2CO$—	214 (d.)	(154)
CH_3CH_2CO—	$CH_3COOCH_2CH(CHOCOCH_3)_3CH$— (O)		(432)

preparation have been claimed. Few records of estrogenic activities have been made recently, but these have been given by Solmssen (453, 454).

B. ETHERS

Ethers of diethylstilbestrol, hexestrol, and dienestrol have, in general, a more protracted estrogenic action than esters. This is presumably due to the greater

TABLE 7

Esters of hexestrol

p-ROC$_6$H$_4$CH(C$_2$H$_5$)CH(C$_2$H$_5$)C$_6$H$_4$OR′-p

Compound		Melting Point	References
R	R′		
		°C.	
CH_3CO—	CH_3CO—	136–137	(287, 434) (69, 401)
CH_3CH_2CO—	CH_3CH_2CO—	123–124	(287)
		119–120	(69)
CH_3CH_2CO—	$CH_3(CH_2)_2CO$—		(287)
CH_3CH_2OCO—	CH_3CH_2OCO—	153–154	(436)
$CH_3(CH_2)_4CO$—	$CH_3(CH_2)_4CO$—	96–97	(287)
$CH_3(CH_2)_{16}CO$—	$CH_3(CH_2)_{16}CO$—	63	(69)
		177–178	(75)
C_6H_5CO—	C_6H_5CO—	235–237	(287) (69)
HSO_3—	HSO_3—		(444)
$NaSO_3$—	$NaSO_3$—		(60, 61, 410)
KSO_3—	KSO_3—		(410)
H_2PO_3—	H_2PO_3—		(13, 287)
Na_2PO_3—	Na_2PO_3—		(439)
C_6H_5CO—	$HOCH_2CH(CHOH)_3CH$— (O)	203–204	(433)
C_6H_5CO—	$CH_3COOCH_2CH(CHOCOCH_3)_3CH$— (O)	156	(433)

difficulty of fission of the ether link *in vivo*. It is a fact that ethers can be dealkylated *in vivo* (33, 470). Chedid and Horeau (66) found that methylation of the hydroxyl groups of "α"-estradiol and dimethylethylallenolic acid retarded their estrogenic activity by 6 hr. but did not diminish the intensity of their action. This is support for the need of free hydroxyl groups. Estrogens with free or esterified hydroxyl groups were found to be more effective against prostatic cancer than the corresponding ethers (479). Japp (213), using chicks and turkeys, found that diethylstilbestrol dimethyl ether was more potent than hexestrol dimethyl ether, diethylstilbestrol diethylstilbestrol dipropionate, diethylstilbestrol diethyl ether, or hexestrol. Hexestrol dimethyl ether was active in chicks but inactive in turkeys. These confusing results are obviously related to the metabolic processes of the test animals. Diethylstilbestrol is well known to have toxic effects, but it is not feasible to control them using the substance itself. Reid (347) prepared a series of diethylstilbestrol monoalkyl ethers and found that the monomethyl, mono-*n*-amyl, and mono-*n*-heptyl ethers were active in the rat at 3, 35, and 60 micrograms; thus they exhibit the general property of esters and ethers of decreased activity with increasing chain length of the acyl or alkyl group. It was claimed that these compounds are nontoxic and that the duration of their action can readily be controlled by the dosage. Hexestrol monoethers behave similarly (382). Cavallini, Goisis, and Massarani (64) found the bis(diethyl-

TABLE 8

Esters of dienestrol

p-$ROC_6H_4C(=CHCH_3)C(=CHCH_3)C_6H_4OR'$-$p$

Compound		Melting Point	References
R	R′		
		°C.	
CH_3CO—	CH_3CO—		(267)
CH_3CH_2CO—	CH_3CH_2CO—		(267, 287, 438, 440)
CH_3CH_2CO—	$CH_3(CH_2)_2CO$—		(438)
$CH_3(CH_2)_2CO$—	$CH_3(CH_2)_2CO$—		(441)
$(CH_3)_2CHCH_2CO$—	$(CH_3)_2CHCH_2CO$—		(267)
		181–182	(75)
C_6H_5CO—	C_6H_5CO—	217–218	(75)
$NaSO_3$—	$NaSO_3$—		(410)
KSO_3—	KSO_3—		(410)

TABLE 9

Ethers of diethylstilbestrol

p-$ROC_6H_4C(C_2H_5)=C(C_2H_5)C_6H_4OR'$-$p$

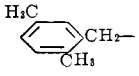
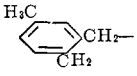
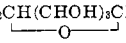
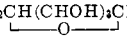
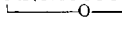
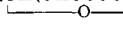
Compound		Melting Point	References
R	R′		
		°C.	
CH_3—	H—	110	(347)
			(138, 300, 386)
CH_3—	CH_3—	121.5–123	(322)
		123	(347)
			(138, 300, 386)
$NaOOCCH_2$—	$NaOOCCH_2$—		(103)
$CH_2=CHCH_2$—	$CH_2=CHCH_2$—	93–93.5	(224, 225)
$CH\equiv CCH_2$—	$CH\equiv CCH_2$—	106–107	(123)
$CH_3(CH_2)_4$—	H—	>77	(347)
$CH_3(CH_2)_4$—	$CH_3(CH_2)_4$—	64.8	(347)
$(C_2H_5)_2NCH_2CH_2$—	H—		(64, 288)
$(C_2H_5)_2NCH_2CH_2$—	$(C_2H_5)_2NCH_2CH_2$—		(64, 288)
$CH_3(CH_2)_6$—	H—	86.5	(347)
$CH_3(CH_2)_6$—	$CH_3(CH_2)_6$—	49.5	(347)
$HOCH_2CH(CHOH)_3CH$— (—O—)	H—	177–187	(432)
$HOCH_2CH(CHOH)_3CH$— (—O—)	$HOCH_2CH(CH_2OH)_2CH$— (—O—)	ca. 245 (d.)	(442)
$CH_3COOCH_2CH(CHOCOCH_3)_3CH$— (—O—)	$CH_3COOCH_2CHCHOCOCH_2CH$— (—O—)	227–230	(442)
		117–119	(222, 223)

aminoethyl) ethers of diethylstilbestrol and hexestrol to be inactive. However, Milla and Grumelli (288) found some activity for the hexestrol ether. This suggests the greater susceptibility of diethylstilbestrol derivatives to *in vivo* degradation, as might be expected from the unsaturated nature of the compounds. The

TABLE 10

A. Ethers of hexestrol

p-$ROC_6H_4CH(C_2H_5)CH(C_2H_5)C_6H_4OR'$-$p$

Compound		Melting Point	References
R	R′		
		°C.	
CH_3—	H—	119–121	(553)
		118.5	(382)
			(70)
CH_3—	CH_3—	144	(382)
CH_3CH_2—	CH_3CH_2—	133	(48)
			(233)
$CH_3(CH_2)_2$—	$CH_3(CH_2)_2$—	110	(48)
$(CH_3)_2CH$—	$(CH_3)_2CH$—	115	(48)
CH_2=$CHCH_2$	CH_2=$CHCH_2$—	81.5	(224, 226)
$CH_3(CH_2)_3$—	H—	105.5	(382)
$CH_3(CH_2)_3$—	$CH_3(CH_2)_3$—	107.5	(382)
$(CH_3)_2CHCH_2$—	$(CH_3)_2CHCH_2$—	109	(48)
$CH_3(CH_2)_4$—	H—	100.5	(382)
$CH_3(CH_2)_4$—	$CH_3(CH_2)_4$—	88.5	(382)
$(C_2H_5)_2NCH_2CH_2$—	H—		(288)
$(C_2H_5)_2NCH_2CH_2$—	$(C_2H_5)_2NCH_2CH_2$—		(64, 288)
$(CH_3)_2CH(CH_2)_2$—	$(CH_3)_2CH(CH_2)_2$—	83	(48)
$CH_3(CH_2)_5$—	$CH_3(CH_2)_5$—	73	(48)
$CH_3(CH_2)_7$—	$CH_3(CH_2)_7$—	66	(48)
$CH_3(CH_2)_9$—	$CH_3(CH_2)_9$—	57	(48)
$CH_3(CH_2)_{11}$—	$CH_3(CH_2)_{11}$—	79	(48)
$CH_3(CH_2)_{13}$—	$CH_3(CH_2)_{13}$—	65	(48)
$CH_3(CH_2)_{15}$—	$CH_3(CH_2)_{15}$—	72	(48)
$CH_3(CH_2)_{17}$—	$CH_3(CH_2)_{17}$—	92	(48)
		123–124	(222, 223)
$C_6H_5CH_2$—	$C_6H_5CH_2$—	219	(48)
p-$ClC_6H_4CH_2$—	p-$ClC_6H_4CH_2$—	194	(48)
		198	(48)
$C_6H_5(CH_2)_2$—	$C_6H_5(CH_2)_2$—	119	(48)
$C_6H_5(CH_2)_3$—	$C_6H_5(CH_2)_3$—	157	(48)
C_6H_5CH=CH—	C_6H_5CH=CH—	180	(48)
1—$C_{10}H_7CH_2$—	1—$C_{10}H_7CH_2$—	233	(48)
$HOCH_2CH(CHOH)_3CH$— 	$HOCH_2CH(CHOH)_3CH$— 	266–267	(443)
$CH_3COOCH_2CH(CHOCOCH_3)_3CH$— 	$CH_3COOCH_2CH(CHOCOCH_3)_3CH$— 	186–188	(443)

B. Ether of dienestrol

p-$ROC_6H_4C(=CHCH_3)C(=CHCH_3)C_6H_4OR'$-$p$

Compound		Melting Point	References
R	R′		
		°C. 155–155.5	(223)

bis(carboxymethyl) ether of diethylstilbestrol is inactive (103). A therapeutically valuable preparation was claimed (27, 29) to have been obtained by dissolving 0.5 per cent of diethylstilbestrol dimethyl ether and 0.75 per cent of diethylstilbestrol in oil. The preparation was found to have high potency at therapeutic dosage, rapid as well as prolonged action, and no toxicity intramuscularly.

The ethers have, in general, been obtained by interaction of the phenol and an alkyl sulfate or halide. Schönberg and Mustafa (386) claimed the preparation of diethylstilbestrol di-*n*-propyl ether by reacting the phenol and diazomethane in ether and *n*-propyl alcohol. Gerber and Curtin (138) obtained only the dimethyl ether from the reaction. This result was substantiated by Wegand and Grisebach (540), although in repetition of the work Mustafa (300) claimed that he obtained micro quantities of the di-*n*-propyl ether. Few biological activities for ether derivatives have been quoted recently, though they have been given previously by Solmssen (454). Ethers which have been recently prepared or reprepared are listed in tables 9 and 10. The new diallyl ethers of diethylstilbestrol and hexestrol (224) have about $\frac{1}{250}$ the activity of diethylstilbestrol.

VI. Variation of the Fundamental Structure of Diethylstilbestrol, Hexestrol, and Dienestrol

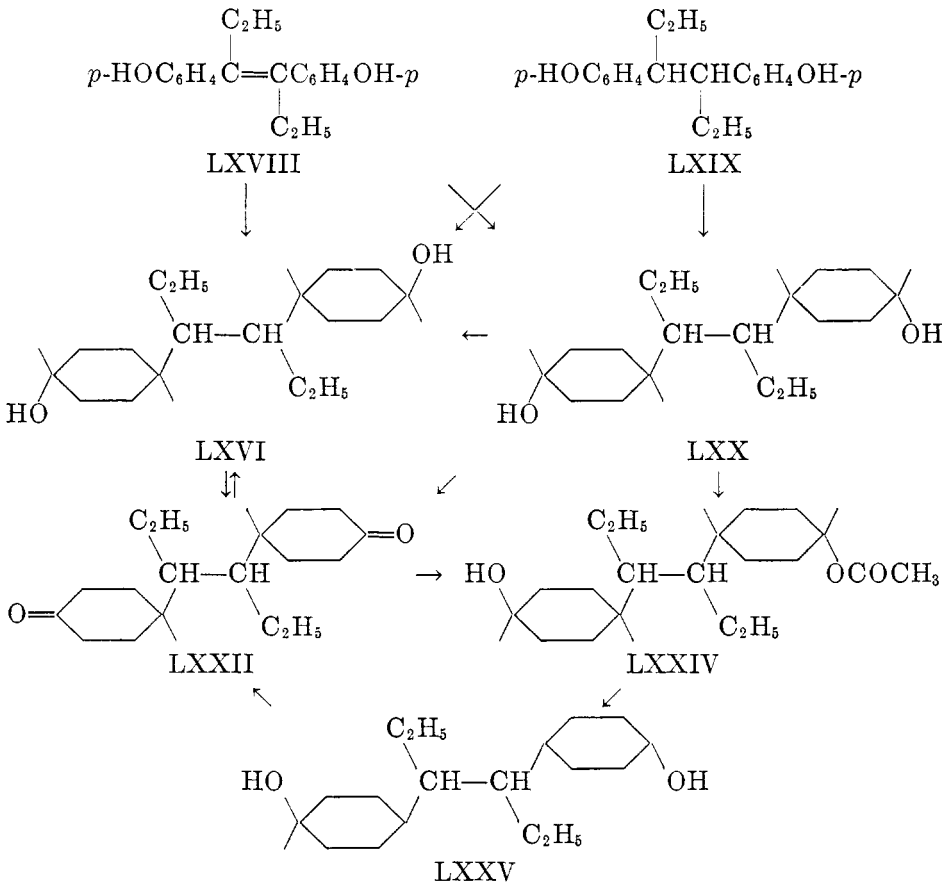
A. HYDROGENATED DERIVATIVES

1. Hydrogenation of exocyclic double bonds

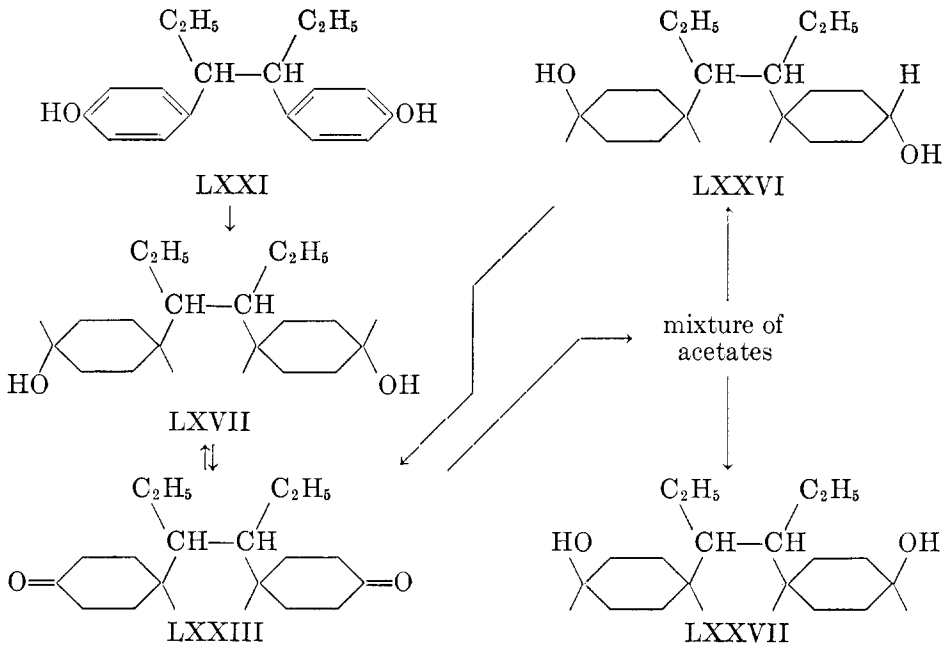
The hexestrols are dihydrodiethylstilbestrols or tetrahydrodienestrols; hence hydrogenation methods (293) have naturally been used to obtain hexestrol. *trans*-Diethylstilbestrol and its derivatives are hydrogenated in general to a mixture of racemic and *meso*-hexestrols, the former in preponderance; cis derivatives yield largely the meso dihydro compound with some racemic compound (455). Wessely and coworkers (231) obtained hexestrol dimethyl ether quantitatively from ψ-stilbestrol dimethyl ether. The mechanisms of these conversions are not fully understood. Campbell, Dodds, and Lawson (53) reported that the hydrogenation of dienestrol in acetone with a palladium catalyst gave a quantitative yield of hexestrol. Williams and Ronzio (556), however, found that in acetone and with 10 per cent palladium on charcoal and at atmospheric pressure a 72–77 per cent yield of *meso*-hexestrol and a 27 per cent yield of racemic hexestrol were obtained from dienestrol. Crystallization from benzene proved an excellent method of separating the isomers; the racemate remained in solution.

2. Hydrogenation of aromatic rings

Hoehn and Ungnade (174) hydrogenated diethylstilbestrol at 210°C. and under 265 atm. pressure with Raney nickel and obtained two isomeric octahydro compounds, melting at 92–94°C. and 144–145°C., together with a perhydrogenated derivative melting at 188–188.5°C. By a similar technique Ungnade and Ludutsky (515) obtained six perhydro compounds, two of which—LXVI, m.p. 189–190°C. (174, 274), and LXVII, m.p. 167°C. (254)—were known previously. The compound LXVI was assigned the racemic bridge structure, since hydro-



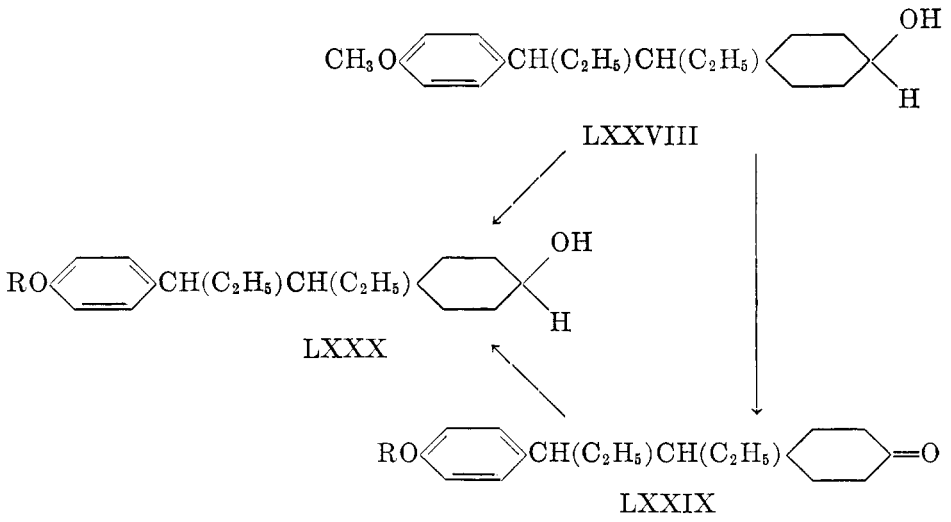
genation of diethylstilbestrol (LXVIII) with nickel was known to give racemic hexestrol. Reduction of racemic hexestrol (LXIX) with nickel also gave LXVI together with a new isomer (LXX), melting at 129–130°C. Analogously LXVII, obtained from *meso*-hexestrol LXXI (245), was assigned the meso bridge structure. The ketones LXXII and LXXIII, obtained by oxidation, will have the racemic and meso configurations, respectively. Reduction of LXXII with sodium in ethyl alcohol gave LXVI as the main product, indicating that the hydroxyl groups in the latter have the trans configuration (417). Inversion of LXX by sodium at 175°C. gave LXVI, but no LXVI was obtained by reduction of LXXII in acetic acid. Since inversion of *cis*-alkylcyclohexanols by sodium gives trans forms or cis-trans mixtures, the latter form predominating (529), and since only neutral or basic reduction of LXXII would favor the production of LXVI (417), the trans hydroxyl configuration of LXVI is confirmed and LXX will have at least one cis hydroxyl group. Ease of adsorption on sodium sulfate together with evidence from benzoylation indicated that the second hydroxyl group in LXX was trans. Catalytic reduction of LXXII using platinum in acetic acid gave a monoacetate (LXXIV), which with methylmagnesium iodide gave a



new perhydro isomer (LXXV). Evidence similar to the above indicated it to have cis-cis configuration for the hydroxyl group. Ungnade and Ludutsky repeated the hydrogenation of *meso*-hexestrol and obtained the isomer LXVII, m.p. 167°C., together with a new isomer (LXXVI), m.p. 124–125°C. On oxidation both these alcohols gave LXXIII. By the methods discussed LXVII was assigned the trans-trans configuration of the hydroxyl groups, LXXVI was assigned the cis-trans configuration, and the further isomer (LXXVII) was considered to have the cis-cis configuration.

Ungnade and Ludutsky (516) by partial hydrogenation of diethylstilbestrol at 210°C. and 265 atm. obtained from the mixture of products an octahydro compound melting at 147–148°C. Hydrogenation of this compound gave LXVI, indicating a trans hydroxyl and a racemic bridge in the octahydro compound. A second octahydro compound, m.p. 142–143°C., was also obtained and shown to be identical to that previously described by Hoehn and Ungnade (174) as melting at 144–145°C.; it was thought to be a meso compound. The octahydro compound described by Hoehn and Ungnade (174) as melting at 92–94°C. was found to be a complex of the compound melting at 142–143°C. and racemic hexestrol.

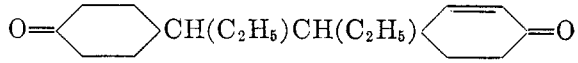
Wilds and McCormack (553), after failing to satisfactorily hydrogenate one ring of hexestrol or its monobenzoate, succeeded with hexestrol monomethyl ether and a chromium oxide catalyst (299); the phenolic ring was reduced to give LXXVIII. Oxidation of the crude hydrogenation product gave a 52 per cent yield of LXXIX (R = CH_3). Demethylation of LXXVIII gave a mixture from which two isomers of LXXX (R = H), melting at 183–184°C. and 134–135°C., were obtained, the latter preponderating. The perhydro compound (LXVII)



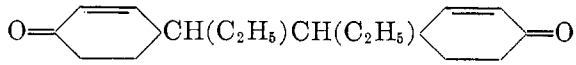
previously mentioned was obtained by Wilds and McCormack by hydrogenating both isomers (LXXX: R = H). Hydrogenation of LXXIX (R = CH_3) under neutral conditions followed by demethylation gave largely LXXX (R = H), m.p. 134–135°C.; under acid conditions LXXX (R = H), m.p. 183–184°C., was the main product. This suggested a cis hydroxyl group configuration for the higher-melting isomer and a trans configuration for the lower-melting one. However, by hydrogenation of hexestrol in methanol with Raney nickel at 210°C. and 5300 lb. pressure, Ungnade and Tucker (518) isolated an octahydro compound which proved identical with LXXX (R = H) melting at 134–135°C. Further hydrogenation of this gave LXVII which, however, in view of the results of Wilds and McCormack, was not evidence for the trans configuration of the octahydro compound. The compound was shown not to be identical to the octahydro compound, m.p. 142–143°C., previously obtained by Ungnade and Ludutsky and thought to be a meso isomer (516). The position was resolved by a reinvestigation of the racemic octahydro compounds by Ungnade and Tucker (519). Hydrogenation of racemic hexestrol monomethyl ether in dioxane at 250°C. and 440 atm. pressure over copper chromite gave three products melting at 146–147°C., 141–142°C., and 47–50°C. The first two substances were regarded as racemic octahydro compounds, the one melting at 141–142°C. being identical to that melting at 142–143°C. and previously considered to have the meso configuration. The substance melting at 47–50°C. was presumed to be a mixture of these two octahydro compounds. The actual configuration of the hydroxyl groups was not established. The biological activities of these perhydrogenation products has not been extensively investigated but appears to be very dependent on configuration. A perhydro compound examined by Brownlee and Green (37) was found to be almost inactive, but the compound LXXX (R = H), m.p. 183–184°C., was active at 500 micrograms and its isomer was active at 10 micrograms in rats when given subcutaneously.

Ungnade and Tucker (519a), following the work of Schoeller, Inhoffen, Stein-

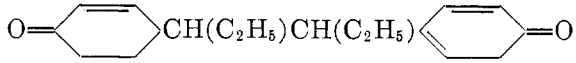
ruck, and Hoss (385), obtained a series of diketones (LXXXI, LXXXII, and LXXXIII) of both racemic and meso types.



LXXXI



LXXXII



LXXXIII

The ketones LXXII and LXXIII, previously mentioned, were brominated using *N*-bromosuccinimide; dehydrobromination with collidine gave the unsaturated ketones in good yield. Isolation of LXXXIII showed that even *N*-bromosuccinimide (383) can attack a tertiary carbon atom. The ketones had no detectable androgenic activity.

Oxidation of *meso*- and racemic hexestrols with lead tetraacetate gave the corresponding forms of 3,4-bis(3,3-diacetoxy-4-oxo-1,5-cyclohexadien-1-yl)hexane (548); hydrogenation and subsequent hydrolysis gave the 3,4-bis(3,4-dihydroxyphenyl)hexanes.

B. VARIATION OF AROMATIC SUBSTITUTION

Variation of the substitution of the aromatic rings of the three stilbene estrogens, with regard to the effect on estrogenic activity, has been intensively studied (tables 11, 12, and 13).

The para hydroxyl groups are essential to high activity. α,α'-Diethylstilbene required about 50 mg. for 50 per cent response (214); the hexestrol analog, 3,4-diphenylhexane (214), is rather more active and required less than 1 mg. for 50 per cent response. 3,4-Diphenylhexadiene required 10 mg. for 100 per cent response and 5 mg. for 60 per cent response (103). These compounds are presumably hydroxylated *in vivo* and this is probably responsible for the lower activity of the unsaturated compounds, these being more susceptible to degradation in the body. The introduction of even one para hydroxyl group considerably enhances activity (37). Removal of hydroxyl groups to meta or ortho positions (48) considerably decreases the activity of the parent substances.

Jenkins and Wilkinson (216) prepared 4′-amino-α,α'-diethyl-4-hydroxy-

$$p\text{-}HOC_6H_4C(C_2H_5) = C(C_2H_5)C_6H_4NH_2\text{-}p$$

LXXXIV

$$p\text{-}HOC_6H_4CH(C_2H_5)CH(C_2H_5)C_6H_4NH_2\text{-}p$$

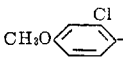
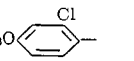
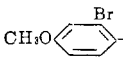
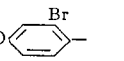
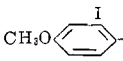
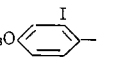
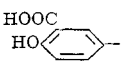
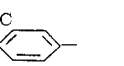
LXXXV

stilbene (LXXXIV) as a cis-trans mixture; in the final stage of the synthesis demethylation of the methyl ether of LXXXIV proved difficult. This compound

TABLE 11

Compounds related to diethylstilbestrol with variation of aromatic substitution

$RC(C_2H_5)=C(C_2H_5)R'$

Compound		Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
R	R'			
		°C.		
C_6H_5—	C_6H_5—	71 (trans form)	ca. 50 mg. (50%)	(214)
p-HOC_6H_4—	C_6H_5—		0.025	(37)
			0.017† (Diethylstilbestrol = 1)	(37)
p-$(C_2H_5)_2N(CH_2)_2OC_6H_4$—	C_6H_5—	240–245/5 mm. (b.p.)		(277)
Hydrochloride.....		195		(277)
p-HOC_6H_4—	*p*-$H_2NC_6H_4$—	134–137 (cis-trans mixture)	0.1 mg.*	(216)
			0.01 mg.* (50%)	(216)
		180–183 (trans form)		(541)
p-HOC_6H_4—	*m*-$H_2NC_6H_4$—	163–164	1 mg.*	(216)
p-$CH_3OC_6H_4$—	*p*-$[\overset{-}{Cl}\overset{+}{N}H_3C(=NH)]C_6H_4$—	202–203	1 mg.* (inactive)	(216)
m-HOC_6H_4—	*m*-HOC_6H_4—	188		(544)
o-HOC_6H_4—	*o*-HOC_6H_4—	159–160		(544)
C_6H_5—	*p*-$CH_3COC_6H_4$—	205–210/10 mm. (b.p.)	Inactive	(52)
p-HOC_6H_4—	*p*-$CH_3COC_6H_4$—	144.5–146.5	500–1000	(19)
		Impure	50	(19)
p-$CH_3OC_6H_4$—	*p*-$C_2H_5COC_6H_4$—	176–178/0.06 mm. (b.p.)	1 mg.*	(216)
p-$CH_3COOC_6H_4$—	*p*-$CH_3COOCH_2COC_6H_4$—	133.2–134	100	(19)
p-$CH_3OC_6H_4$—	*p*-$CH_3SC_6H_4$—	107–108	5*‡	(321)
p-$CH_3SC_6H_4$—	*p*-$CH_3SC_6H_4$—	132–132.5	40*‡	(321)
		105.5–106.5 (trans form)	100*‡	(322)
		88–89/0.07 mm. (b.p.) (cis form)	1 mg.*‡	(322)
		114.5–115 (trans form)	100*‡	(322)
		87–89/0.04 mm. (b.p.) (cis form)	1 mg.*‡	(322)
			200*‡ (trans form)	(322)
		108–110/0.02 mm. (b.p.) (cis form)	1 mg.*‡	(322)
p-HOC_6H_4—	*p*-$HOOCC_6H_4$—	143–146.5 (trans form)		(19)
		144–146 (trans form)	20	(303)
			40†	(303)
		143–146 (trans form)		(557)
p-$CH_3OC_6H_4$—	*p*-$HOOCC_6H_4$—	116–117	1 mg. (inactive)	(303)
p-HOC_6H_4—	*m*-$HOOCC_6H_4$—	180–183.5	1 mg. (inactive)	(303)
		270–275	100 (inactive)	(546)

* In mice.

† Orally.

‡ Administered in two portions.

TABLE 12

Hexestrol and dienestrol analogs with variation of aromatic substitution

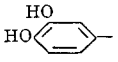
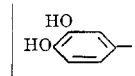
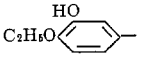
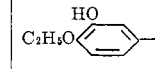
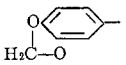
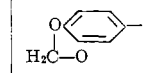
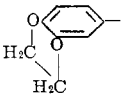
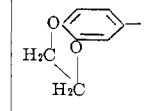
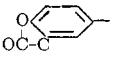
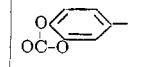
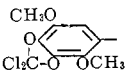
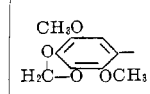
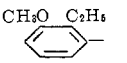
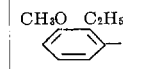
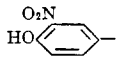
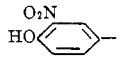
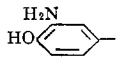
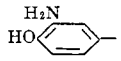
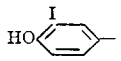
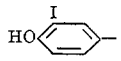
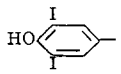
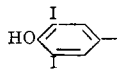
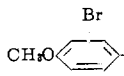
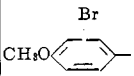
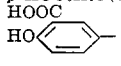
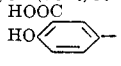
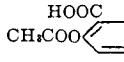
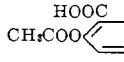
Compound		Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
R	R′			
A. Hexestrol analogs: RCH(C_2H_5)CH(C_2H_5)R′				
		°C.		
C_6H_5—	C_6H_5—	89 (meso form)	<1 mg. (50%)	(214)
		89–91		(538)
o-HOC_6H_4—	*o*-HOC_6H_4—	155 (meso form)		(48)
			0.1 mg.	(45)
p-HOC_6H_4—	C_6H_5—	143–144 (meso form)		(538)
		152–153/0.07 mm. (b.p.) (racemic form)		(538)
		233–236 (meso form)		(548)
		235 (d.) (meso form)		(376)
		230–235 (d.) (meso form)		(407)
				(142, 143)
		138 (racemic form)		(548)
Diacetate		167.5–168 (meso form)	Some activity at 500	(548)
		166–167 (meso form)		(407)
		133–134 (meso form)		(376)
		174–175 (meso form)		(403, 407)
				(233)
		175 (meso form)		(48)
		—		(233)
		186–187 (meso form)		(403, 407)
		157 (meso form)		(48)
		298–300/13 mm. (b.p.) (racemic form)		(48)
		163 (meso form)		(353)
		109 (racemic form)		(353)
p-HOC_6H_4—	*p*-$H_2NC_6H_4$—	186–188 (meso form)	20	(19)
p-$H_2NC_6H_4$—	*p*-$H_2NC_6H_4$—	132–134 (meso form)		(258)
		136–137 (meso form)		(131)
				(191)
		80 (racemic form)		(131)
p-$HOC_6H_4C(C_2H_5)(OH)CH(C_2H_5)C_6H_4NH_2$-*p*		181–182	1 mg.*	(216)
			0.1 mg.* (78%)	(216)
			0.01 mg.* (inactive)	(216)
p-BrC_6H_4—	*p*-BrC_6H_4—	168 (meso form)		(131)
p-$O_2NC_6H_4$—	*p*-$O_2NC_6H_4$—	170 (meso form)		(131)
		Oil (racemic form)		(131)

TABLE 12—*Concluded*

Compound		Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
R	R′			
		°C.		
		222 (meso form)	100 10 (inactive)	(169)
		258 (meso form)	5 1 (inactive)	(169)
		138–139 (meso form)	100 10 (66%) 5 (33%) 1 (inactive)	(169) (169) (169) (169)
		234 (d.)	100 (inactive)	(169)
		179–181		(510, 511, 512)
p-$CH_3SC_6H_4$—	*p*-$CH_3SC_6H_4$—	(153 meso form) 155–156 (meso form) 62–63 (racemic form)	Inactive 200*‡	(200) (49) (321)
p-HOC_6H_4— *p*-$CH_3COOC_6H_4$—	*p*-$CH_3COC_6H_4$— *p*-$CH_3COOCH_3COC_6H_4$—	159–160 (meso form) 152–153.5 (meso form) Impure meso form	100 500–1000 100	(19) (19) (19)
p-HOC_6H_4—	*p*-$HOOCC_6H_4$—	171.5–172.5 (meso form) Isomer mixture 166–168 (meso form) 126–128 (racemic form)	 50–70 (60%) 	(19) (303) (557) (19)
p-$HOC_6H_4C(C_2H_5)(OH)CH(C_2H_5)C_6H_4COOH$-*p*.....		144–146 (meso form)	100 (inactive)	(303)
		283–285 (meso form)	100 (inactive)	(546)
		>350 (meso form)	100 (inactive)	(546)
B. Dienestrol analogs: $RC(=CHCH_3)C(=CHCH_3)R'$				
C_6H_5—	C_6H_5—	101	>1 mg., <10 mg. (50%) 10 mg. 5 mg. (60%)	(214) (103) (103)
p-$CH_3SC_6H_4$—	*p*-$CH_3SC_6H_4$—	141		(201)

* In mice.
‡ Administered in two portions.

was found to produce 50 per cent response in mice at 0.01 mg. in contrast to 7.5 micrograms for 50 per cent response in the rat reported earlier by Rubin and Wishinsky (370). The results of the latter are more difficult to understand in view of the proof by Weiss (541) that their compound was in fact the cis isomer,

TABLE 13

Diethylstilbestrol, hexestrol, and dienestrol analogs with hydrocarbon group substitution of the aromatic rings

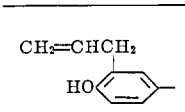
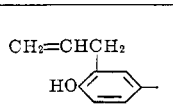
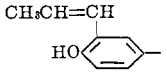
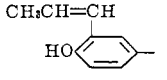
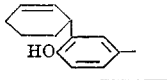
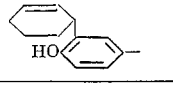
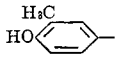
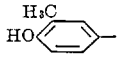
Compound		Melting Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
R	R′			
A. Diethylstilbestrol analogs: $RC(C_2H_5)=C(C_2H_5)R'$				
		°C.		
		103–104		(224, 225)
			6–7§	(224)
			10–20*§	(224)
		120–121		(224, 225)
			0.1–0.2*§	(224)
		154–156		(222, 223)
B. Hexestrol analogs: $RCH(C_2H_5)CH(C_2H_5)R'$				
		145		(26, 312, 313)
			1.5 (90%)	(313)
			1.0 (70%)	(313)
			0.6 (30%)	(313)
			15† (65%)	(313)
		165–166	0.005 mg.	(103)
			0.001 mg. (inactive)	(103)
Diacetate		132		(26, 312, 313)
			15 (95%)	(313)
			5 (75%)	(313)
			2.5 (10%)	(313)
			10† (70%)	(313)
			5† (30%)	(313)
			2.5† (inactive)	(313)
Dipropionate		115		(312, 313)
			15 (60%)	(313)
			10† (90%)	(313)
			5† (50%)	(313)
			2.5† (inactive)	(313)
				(26)
Di-*n*-butyrate		100–101		(312, 313)
			15† (60%)	(313)
				(26)
Dipalmitate		68–69		(313)
Bis(acid succinate)		198–200	15	(313)
			5† (30%)	(313)
Bis(ethyl carbonate)		138	50	(313)
			15† (70%)	(313)
Bis(methyl carbonate)		148–149		(313)
Dibenzoate		199–200	5† (85%)	(313)
Bis(*m*-sulfobenzoate, disodium salt		ca. 300 (d.)	6	(313)
			10† (50%)	(313)

TABLE 13—*Continued*

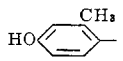
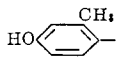
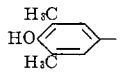
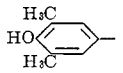
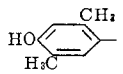
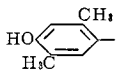
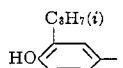
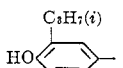
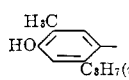
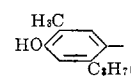
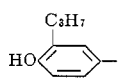
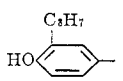
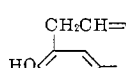
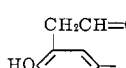
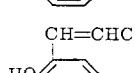
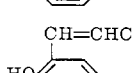
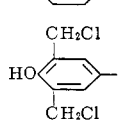
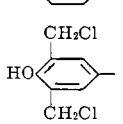
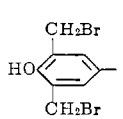
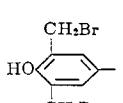
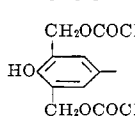
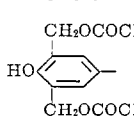
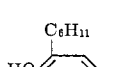
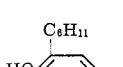
Compound		Melting Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms Unless Indicated Otherwise	References
R	R′			
		°C.		
		214-215 (meso form)	0.001 mg.	(103)
			0.0003 mg. (inactive)	(103)
		218-219 (meso form)		(403)
		191-192		(221)
		216	5	(310)
			2 (ca. 100%)	(310)
			1 (ca. 100%)	(310)
Diacetate		163		(310)
Dibenzoate		204		(310)
		177	50 (10%)	(310)
		171	50 (inactive)	(310)
		123.5-124.5		(224, 226)
			> 0.5*§	(224)
		107		(224, 226)
			<4*§	(224)
			1-2§	(224)
		153-154		(224, 226)
			<4*§	(224)
			<1§	(224)
		156-159		(221)
				(221)
		137.5-139		(221)
		195-197	50 (10%)	(309)

TABLE 13—*Continued*

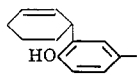
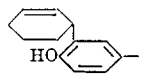
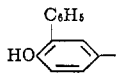
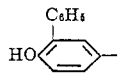
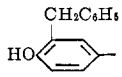
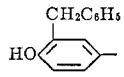
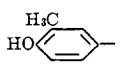
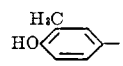
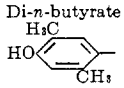
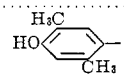
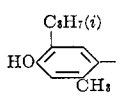
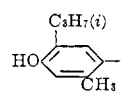
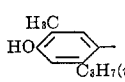
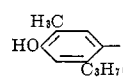
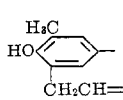
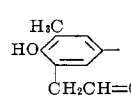
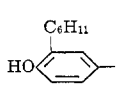
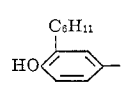
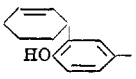
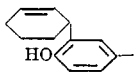
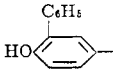
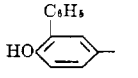
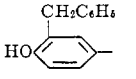
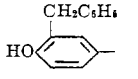
Compound		Melting Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
R	R′			
		°C.		
		169–171		(222, 223)
		219–221 (d.)	50 (10%)	(308)
		169–171	50 (inactive)	(308)
C. Dienestrol analogs: RC(=CHCH$_3$)C(=CHCH$_3$)R′				
		187–189		(313, 26)
			5	(313)
			2.5 (30%)	(313)
			15† (10%)	(313)
			5† (inactive)	(313)
		189–190	0.01 mg.	(103)
			0.005 mg. (75%)	(103)
Diacetate		166–168		(26, 312, 313)
			15 (80%)	(313)
			15† (65%)	(313)
Dipropionate		138–139		(26, 312, 313)
			15 (inactive)	(313)
			15† (85%)	(313)
			10† (30%)	(313)
			5† (inactive)	(313)
Di-*n*-butyrate		123–124	15† (15%)	(313)
		206		(310)
		169		(310)
		163		(310)
		Gum	100† (35%)	(542)
Diacetate		125–126	100† (25%)	(542)
Dipropionate		114–115	100† (20%)	(542)
		177–178		(309)

TABLE 13—*Concluded*

Compound		Melting Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
R	R′			
		°C.		
				(223)
		202-204 (d.)		(308)
				(308)

• In mice.
† Administered orally.
§ Diethylstilbestrol = 250.

as this would be expected to be inactive. Removal of the amino group to the meta position (216) further decreased the activity relative to LXXXIV. Biggerstaff and Wilds (19) obtained the hexestrol analog (LXXXV) and found it active at 20 micrograms in the rat. The methyl ether of LXXXV was relatively easy to demethylate. Although Jenkins and Wilkinson found no antiestrogenic properties for their amino compounds, Danneberg and Schmahl (85) reported *p*-aminostilbene and *p*-aminoazobenzene, as well as their *N*-acetyl and *N*-methyl derivatives, to be effective inhibitors of estrus. It appears that the amino group, in spite of its hydrogen-bonding capacity, cannot replace a hydroxyl group in an estrogen and, in fact, may result in an estrus inhibitor. This is probably due to the steric dissimilarity between the two groups.

Hughes and Thompson (200) reduced *p*-(methylthio)propiophenone with aluminum isopropoxide; dehydration of the indefinite product by potassium bisulfate at 180–190°C. gave an 85 per cent yield of thioanethole. This yield was obtained only when air was present during the distillation of the reduction product prior to dehydration. Conversion to thioanethole hydrobromide and reaction of this with phenylmagnesium bromide and cobaltous chloride gave finally a 12 per cent yield of dithiohexestrol dimethyl ether (LXXXVI).

$$p\text{-}CH_3C_6H_4CH(C_2H_5)CH(C_2H_5)C_6H_5SCH_3\text{-}p$$

LXXXVI

Buu-Hoï and Hoán (49) claimed a 25 per cent yield of LXXXVI by treatment of thioanethole hydrochloride with reduced iron and water at 95°C. The compound was found inactive (200), and there is evidence that replacement of phenol groups by thiophenol groups reduces or abolishes biological activity (49). While the thiophenol analog of hexestrol would be expected to show some estrogenic

activity, LXXXVI is presumably inactive because of the difficulty of *in vivo* demethylation. Thio ethers are well known to be very difficult to dealkylate (43, 199), and LXXXVI cannot be demethylated by pyridine hydrochloride or hydrogen iodide or bromide in acetic acid. Contrary to these results, Oki (321) found the racemic form of LXXXVI active in mice at 200 micrograms. LXXXVII, the thio analog of diethylstilbestrol dimethyl ether, was active at 40 micrograms and the monothio analog (LXXXVIII) was active at 5 micrograms.

$$p\text{-}CH_3SC_6H_4C(C_2H_5)=C(C_2H_5)C_6H_4SCH_3\text{-}p$$

LXXXVII

$$p\text{-}CH_3OC_6H_4C(C_2H_5)=C(C_2H_5)C_6H_4SCH_3\text{-}p$$

LXXXVIII

Replacement of one hydroxyl group of diethylstilbestrol by a carboxyl group, as in LXXXIX (303), gave a product active at 20 micrograms; the methyl ether was effectively inactive. The hexestrol analog (XC) was 60 per cent active at 50–70 micrograms (303). Extending the separation of hydrogen-bonding groups by

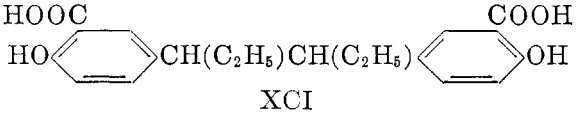
$$p\text{-}HOC_6H_4C(C_2H_5)=C(C_2H_5)C_6H_4COOH\text{-}p$$

LXXXIX

$$p\text{-}HOC_6H_4CH(C_2H_5)CH(C_2H_5)C_6H_4COOH\text{-}p$$

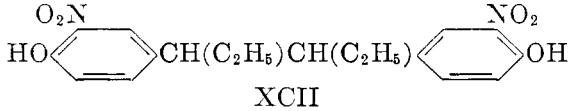
XC

the use of a carboxyl group is apparently permissible, but it leads to a decrease of activity. The electrostatic nature of the hydrogen bond suggests that some degree of elasticity in the separation of the hydrogen-bond-forming groups is permissible. 3,4-Bis(3-carboxy-4-hydroxyphenyl)hexane (XCI) (546), prepared by the Marasse reaction from hexestrol, was inactive at 100 micrograms. Probably intra-

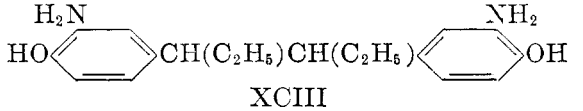


XCI

molecular hydrogen bonding is responsible for the diminished activity. Intramolecular hydrogen bonding would appear to account for the relative activities of 3,4-bis(4-hydroxy-3-nitrophenyl)hexane (XCII) and its amino analog (XCIII); the former was active at 100 micrograms and the latter at 5 micrograms (169).



XCII



XCIII

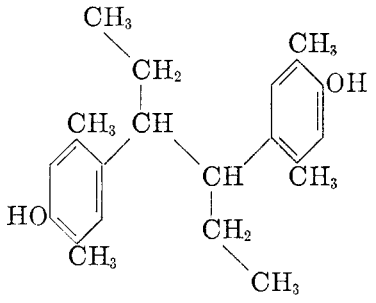
Biggerstaff and Wilds (19) prepared and tested a series of compounds related to diethylstilbestrol and hexestrol in which a hydroxyl group was replaced by an acetyl, acetoxy, or acetoxyacetyl group. 4′-Acetyl-α,α'-diethyl-4-hydroxystilbene (XCIV) was active at 500–1000 micrograms, and the impure compound was still more active, possibly owing to the presence of the carboxylic acid

$$p\text{-}HOC_6H_4C(C_2H_5)=C(C_2H_5)C_6H_4COCH_3\text{-}p$$

XCIV

analog; the hexestrol analog was some five times more active than XCIV. These orders of activity were reversed in the 4-acetoxy-4′-(acetoxyacetyl) compounds. Presumably, these compounds are biochemically modified *in vivo*. 4′-Acetyl-α,α'-diethylstilbene was inactive (52).

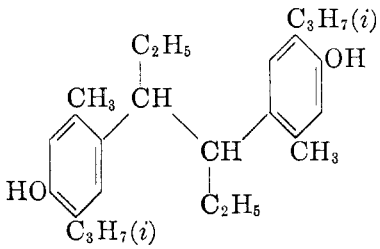
The introduction of alkyl or other hydrocarbon groups into the aromatic rings of the three principal stilbene estrogens has interesting effects on estrogenic activity (table 13). The introduction of 3-methyl groups into the hexestrol and dienestrol molecules does not drastically affect estrogenic potency (313). Following the general rule, the esters of 3,3′-dimethylhexestrol are more active subcutaneously than orally; even orally they are more active than estrone, similarly administered. In the analogous dienestrol derivatives the diacetate and parent phenol are more active subcutaneously, but the dipropionate is much more active when given orally. These compounds were reported as being relatively nontoxic; the median lethal dose of diethylstilbestrol in mice is 18 mg., but for 3,4-bis(3-methyl-4-acetoxyphenyl)-2,4-hexadiene and 3,4-bis(3-methyl-4-propionoxyphenyl)hexane the value was found to be 36 mg. The introduction of a second 2-methyl group into the rings, as in XCV, increased the activity; the dimethyl-substituted compound (XCV) is almost fully active at 1 microgram (310).



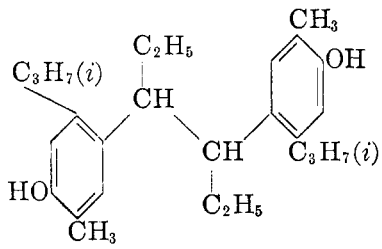
XCV

Presumably this tetramethyl compound has the configuration shown in formula XCV; the 2-methyl groups result in the "completion" of a new "ring system." Correcting earlier work (93, 94, 95, 204, 205, 206, 551, 552), Djerassi, Rosenkranz, Romo, Pataki, and Kaufmann (92) found that the introduction of a 1-methyl group into estrone decreased the activity of the latter by one-half. Apparently this type of methyl substitution does not abolish activity in the natural estrogens.

3,4-Bis(4-hydroxy-5-isopropyl-2-methylphenyl)hexane (XCVI) and 3,4-bis-(4-hydroxy-2-isopropyl-5-methylphenyl)hexane (XCVII) have little activity.



XCVI



XCVII

The 5-isopropyl group will have considerable steric effect on the hydroxyl group, impairing its biochemical function; the 2-isopropyl group possibly has an undesirable effect on molecular thickness.

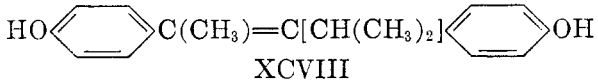
The 3,3′-diallyl-, 3,3′-dipropenyl-, and 3,3′-dipropylhexestrols and the 3,3′-diallyl- and 3,3′-dipropenyldiethylstilbestrols (224) have negligible activities. Cyclohexyl, phenyl, and presumably benzyl groups introduced into the 3,3′-positions of hexestrol or dienestrol (308) similarly decrease the activity of the parent compounds to negligible values. These results suggest a limit of three to four carbon atoms in extending the molecule by alkyl substitution in the 3,3′-positions.

C. VARIATION OF THE ALIPHATIC PORTION

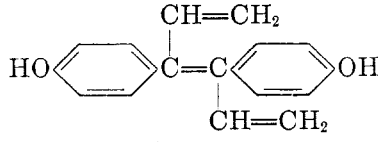
1. Variation of the α,α′-alkyl groups

The constitution of the aliphatic portion of diethylstilbestrol, hexestrol, and dienestrol is optimum for estrogenic activity in the stilbene-type estrogen (456).

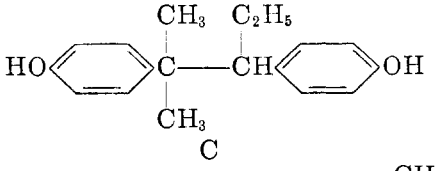
Removal of the ethyl groups from diethylstilbestrol (104) or from hexestrol (45) leads essentially to removal of activity. Replacement of ethyl groups by methyl or higher alkyl groups decreases the activity (45, 48); the higher the alkyl group, the greater the decrease. α′-Isopropyl-α-methylstilbestrol (XCVIII) (291) is exceptional, being almost as active as diethylstilbestrol.



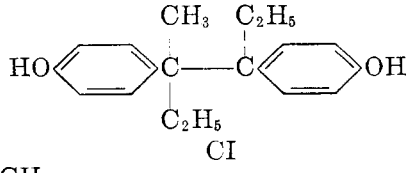
XCVIII



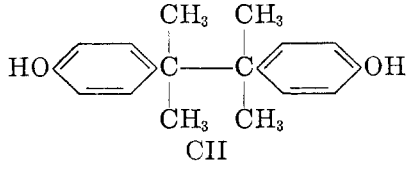
XCIX



C



CI



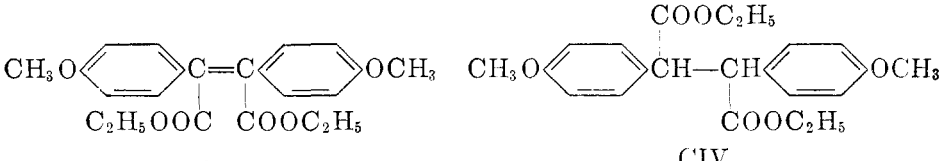
CII

More recently, Dodds, Huang, Lawson, and Robinson (103) found 3,4-bis(*p*-hydroxyphenyl)-1,3,5-hexatriene ("trienestrol") (XCIX) to be as active as diethylstilbestrol when given subcutaneously to the rat. Trienestrol had also been prepared earlier by Freiman (134). The methods of synthesis differed slightly, as Dodds, Huang, Lawson, and Robinson converted dienestrol to its 4,4′-bis(methoxycarbonyloxy) derivative and this into the 2,5-dibromo compound by the action of bromine in chloroform at 0°C., while Freiman obtained a 2,5-dibromo compound by bromination of diethylstilbestrol dipropionate with *N*-bromosuccinimide in carbon tetrachloride. Both methods obtained trienestrol by dehydrohalogenation of the bromo compounds in *N*-diethylaniline and subsequent hydrolysis. Replacing one ethyl group of hexestrol by two methyl groups gives a quite active compound (C); adding one methyl group to the aliphatic portion of hexestrol as in CI has little effect on activity (103). However, replacement of the ethyl groups by four methyl groups (191), as in CII, effectively abolishes activity.

The aliphatic portion of diethylstilbestrol appears to be optimum because it confers the appropriate solubility, adsorption capacity, and stereochemistry on the molecule. With the data available it is not possible to separate the adsorption and stereochemical factors. α'-Isopropyl-α-methylstilbestrol could owe its activity to an improved steric or adsorption factor caused by the isopropyl group. While 4,4′-dihydroxystilbene will have the unfavorable planar configuration, 4,4′-dihydroxybibenzyl has the favorable configuration, as previously mentioned. The meso dialkyl analogs of hexestrol similarly have appropriate stereochemistry. The functions of the alkyl groups in the hexestrol series appear to be to impart rigidity to the favorable configuration, preventing planarity, and to aid adsorption. The low activity of 4,4′-dihydroxystilbene is probably due to absence of molecular thickness and in 4,4′-dihydroxybibenzyl to lack of rigidity and adsorption capacity. The inactivity of CII is presumably due to an undesirable steric effect and indicates that estrogenic activity is sensitive to stereochemical change arising from the aliphatic portion.

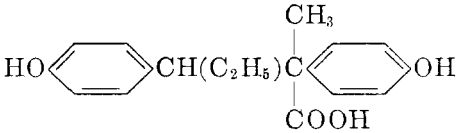
2. Other variations in the α,α' substituents

Hoch (173) condensed ethyl α-bromo-*p*-methoxyphenylacetate by means of sodium amide in ether and obtained diethyl bis(*p*-methoxyphenyl)maleate (CIII) together with a little diethyl α,β-bis(*p*-methoxyphenyl)succinate (CIV).



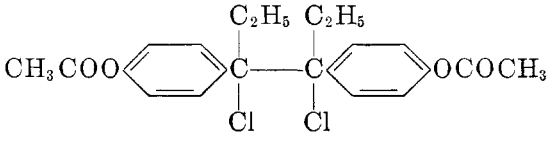
CIII

CIV

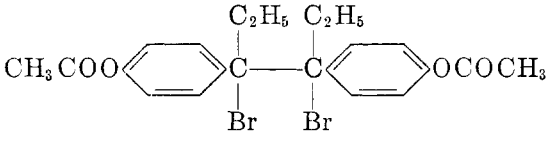


CV

With ethyl α-bromophenylacetate, 45 per cent of diethyl diphenylmaleate, 10 per cent of diethyl diphenylfumarate, and 4 per cent and 1 per cent of diethyl diphenylsuccinates, melting at 141° and 84°C., respectively, was obtained. The phenol anhydride and analogs from CIII were found to be inactive; this may be anticipated in view of the cis relationship of the aromatic rings. Attempts to isomerize CIII to the fumarate failed. By hydrolysis and demethylation CIV was converted to the phenol acid and, despite its being a racemate, was claimed to be estrogenically active. Huang and Tatt (189) confirmed that Hoch's compound was the racemate and they also obtained the meso form; both isomers were found to be effectively inactive, a result probably related to water solubility. The related compound CV is active at 20 micrograms (202), but the dimethyl ether is inactive at 500 micrograms. Presumably this compound also has high translocatability, which may result in elimination before extensive demethylation can occur. Replacement of one ethyl group of hexestrol dimethyl ether by an acetyl group (41, 539) results in activity at 0.01 mg.; the stereoisomer was inactive at 1 mg. The similar introduction of the cyano group leads to activity at 1 mg. (539). Oki (320) replaced the ethyl groups of diethylstilbestrol by halogen atoms and found the chlorine derivatives to have the optimum effect; α,α'-dichloro-4,4'-dimethoxystilbene was active subcutaneously in mice at 200 micrograms and the chloro-iodo compound had twice this activity. It appears that the considered specificity of ethyl groups is not in fact the case. However, Henne and Bruylants (164) found that replacement of the ethyl groups of hexestrol dimethyl ether by chlorine or bromine atoms led to inactivity, although CVI and CVII were active at 25 micrograms. The converse of these results might



CVI



CVII

have been expected, since CVI and CVII simulate the tetramethyl compound (CII), which is inactive.

Oki and coworkers, investigating the effect of molecular thickness on estrogenic activity, synthesized a series of compounds related to diethylstilbestrol and hexestrol in which the ethyl groups were replaced by methylthio, alkoxy, or methylamino groups. 1,2-Bis(*p*-methoxyphenyl)-1,2-bis(methylthio)ethylene (CVIII) was obtained by passing gaseous hydrogen chloride into anisoin and methanethiol in acetic acid (325). Hydroanisoin gave the hexestrol analog

p-$CH_3OC_6H_4C(SCH_3)=C(SCH_3)C_6H_4OCH_3$-$p$

CVIII

p-$HOC_6H_4CH(SCH_3)CH(SCH_3)C_6H_4OH$-$p$

CIX

p-$CH_3OC_6H_4CH(C_2H_5)CH(SCH_3)C_6H_4OCH_3$-$p$

CX

p-$HOC_6H_4CH(OCH_3)CH(OCH_3)C_6H_4OH$-$p$

CXI

p-$HOC_6H_4CH(OC_2H_5)CH(OC_2H_5)C_6H_4OH$-$p$

CXII

p-$CH_3OC_6H_4CH(NHCH_3)CH(NHCH_3)C_6H_4OCH_3$-$p$

CXIII

p-$HOC_6H_4CH(C_2H_5)CH(NHCH_3)C_6H_4OH$-$p$

CXIV

p-$HOC_6H_4CH(C_2H_5)CH(OCH_3)C_6H_4OH$-$p$

CXV

p-$CH_3OC_6H_4CHOHCHOHC_6H_4OCH_3$-$p$

CXVI

$[p\text{-}CH_3OC_6H_4CH(\overset{+}{N}CH_3)=CHC_6H_5]_2I_2^-$

CXVII

(CIX) (521). CVIII was active at 10 micrograms, but the hexestrol analog (CIX), in spite of having free hydroxyl groups, was active only at 40 micrograms. The oxygen analogs (CXI and CXII) were obtained by alkylation of hydroanisoin (CXVI) with an alkyl iodide and silver oxide, followed by demethylation. CXI was active at 0.5 microgram; CXII was active at 10 micrograms (487, 523). The nitrogen analog (CXIII), active at 1000 micrograms, was obtained by reduction of anisil monoxime monohydrazone with sodium amalgam in alcohol. Conversion of the diamino compound obtained to the di-*N*-benzylidene derivative, followed by treatment with methyl iodide at 100°C., gave the methiodide (CXVII). Hydrolysis and demethylation yielded CXIII (488). Although CXI showed high activity, this was only 5 per cent of that of hexestrol similarly tested. Steric and adsorption factors are probably responsible for the variation of activities in these compounds. The monoethyl compounds CX (522) and CXV (485) were less active than CIX and CXI, respectively, but CXIV (486), as the dimethyl ether, was more active than CXIII (488). Niederl and Dexter (307) also obtained CXIII and the free phenol and reported their hydrochlorides inactive at 100 micrograms.

3. Variation of the linking of the aromatic rings

Nomura (315, 316) found CXVIII to have some activity at 60 micrograms.

p-$CH_3OC_6H_4CH(C_2H_5)N(C_2H_5)C_6H_4OCH_3$-$p$

CXVIII

p-$HOC_6H_4SC_6H_4OH$-p

CXIX

p-$CH_3OC_6H_4CH(C_2H_5)SCH(C_2H_5)C_6H_4OCH_3$-$p$

CXX

p-$HOC_6H_4SSC_6H_4OH$-p

CXXI

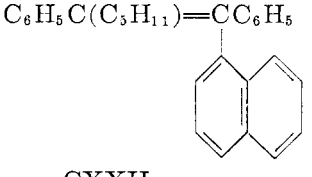
Chatten and Huston (65) found 4,4′-dihydroxydiphenyl sulfide (CXIX) active, but the corresponding disulfide (CXVII) was inactive; CXX, like CXIX, was also active at 100 mg. The authors considered these results to support the theory of Erlenmeyer (120, 121) that the sulfur atom is isosteric with the —CH=CH— group.

Schueler (388) found *trans*-4,4′-dihydroxyazobenzene active in the rat subcutaneously at 10–15 mg.; it was reported active at a much lower dosage intravaginally. The author used these results in support of his theory, previously mentioned. Druckrey, Danneberg, and Schmahl (110) and Urushibara and Takahashi (524) confirmed the activity of the compound; the latter found 80 per cent response in mice subcutaneously at 1 mg. The low activity is probably due to the deviation from optimum configuration. This conclusion applies to the series of azomethines prepared by Keasling and Schueler (228).

The data relating to the variation of the aliphatic portion of diethylstilbestrol and hexestrol are collected in table 14.

D. VARIATION OF THE ALIPHATIC PORTION AND OF AROMATIC SUBSTITUTION

Removal of the hydroxyl groups and simultaneous variation of the alkyl groups of the diethylstilbestrol molecule does not abolish estrogenic activity though it greatly reduces it. The activity falls off with increasing size of the alkyl groups (78), but even α-amyl-α'-(1-naphthyl)stilbene (CXXII) is active at 2.0 mg. and indeed is more active than α,α'-dipropyllstilbene (CXXIII). Bibenzyl is incompletely active at 100 mg. (78), and comparison with 4,4′-dihydroxybi-



$C_6H_5C(C_5H_{11})=CC_6H_5$

CXXII

$C_6H_5C(C_3H_7)=C(C_3H_7)C_6H_5$

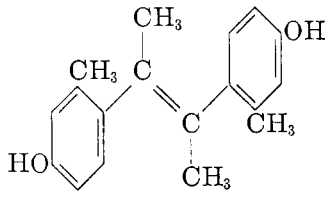
CXXIII

p-$C_2H_5C_6H_4C(C_2H_5)=CHC_6H_5$

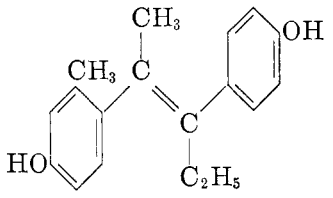
CXXIV

benzyl, previously mentioned, indicates that the former is hydroxylated *in vivo*. 4,α-Diethylstilbene (CXXIV) was found inactive (78); presumably the 4-ethyl

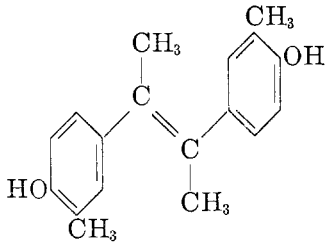
group will prevent hydroxylation biochemically. Hudson and Walton (194) prepared 4,4′-dihydroxy-α,α',2,2′-tetramethylstilbene by the Dodds synthesis from 2,2′-dimethylanisoin. The intermediate was obtained by the Friedel–Crafts reaction with 2-methyl-4-methoxyphenylacetyl chloride and *m*-methylan-



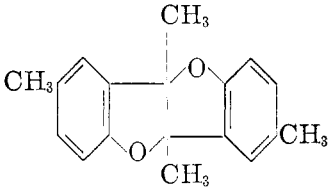
CXXV



CXXVI



CXXVII



CXXVIII

isole; the benzoin condensation with 4-methoxy-2-methylbenzaldehyde failed to give the intermediate. The compound presumably has the configuration shown in formula CXXV and is probably quite close to planar. CXXV, with respect to its methyl groups, has little resemblance to the carbon skeleton of the natural estrogens. The compound, perhaps surprisingly, is highly active, being 1.5 times as active as diethylstilbestrol when given subcutaneously to rats (37). The high activity of the saturated analog confirms the earlier report of Bretschneider, Bretschneider, and Ajtai (35). Orally CXXV has about six times the activity of diethylstilbestrol and is more active than the latter when given in the diet. It appears that the superior activity of CXXV lies in its more appropriate physical properties, such as solubility but, as indicated previously, the *o*-methyl groups may be useful in adsorption. The diacetate of CXXV is also highly active (404). α'-Ethyl-4,4′-dihydroxy-α,2-dimethyl-α'-ethyl stilbene (CXXVI) (194) is also more active than diethylstilbestrol both orally and subcutaneously. The hexestrol analogs of these compounds have been made (194, 534, 535). 4,4′-Dihydroxy-α,α',3′-tetramethylstilbene (CXXVII) with the methyl groups in the meta positions has decreased activity (404), being only half as active as diethylstilbestrol. It was prepared by the condensation of *o*-cresol and biacetyl in 70 per cent sulfuric acid. Attempts to extend the reaction to *m*- or *p*-cresol gave coumarano-coumarane type ethers; *p*-cresol yielded a 2,3,5,5′-tetramethylcoumarano-3′,2,2,3-coumaran, m.p. 196–197°C. (CXXVIII). The same product was obtained by attempted rearrangement of either form of the pinacol from 2-acetyl-4-methylphenol. Oki (322) prepared 2,2′-dichloro-4,4′-dimethoxy-α,α'-dimethylstilbene (CXXIX) and the 2,2′-dibromo and 2,2′-diiodo analogs. Al-

TABLE 14

Diethylstilbestrol, hexestrol, and dienestrol analogs with variation of the aliphatic portion

Compound	Melting Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
A. Diethylstilbestrol analogs			
	°C.		
p-$HOC_6H_4CH{=}C(CH_3)C_6H_4OH$-*p*	183–184 (trans form)		(18, 379)
Dimethyl ether	124		(188)
Diethyl ether	108–109		(188)
p-$CH_3OC_6H_4C(CH_3){=}C(CH_3)C_6H_4OCH_3$-*p*	50 (cis form)		(544)
	131 (trans form)		(544)
	140.5–142 (trans form)		(327)
p-$CH_3OC_6H_4C(C_3H_7){=}C(C_3H_7)C_6H_4OCH_3$-*p*	111–113 (trans form)	100*‡	(327)
p-$CH_3OC_6H_4C{=}CHC_6H_4OCH_3$-*p* $C{\equiv}CCH{=}CH_2$	84		(302)
p-$HOC_6H_4C(CH{=}CH_2){=}C(CH{=}CH_2)C_6H_4OH$-*p*	207–208	0.0004 mg.	(103)
		0.0003 mg. (80%)	(103)
		0.0002 mg. (40%)	(103)
	202–203		(134)
p-$HOC_6H_4C(C_2H_5){=}C[CH_2CH_2N(CH_3)_2]C_6H_4OH$-*p*			(469)
p-$HOC_6H_4C(C_2H_5){=}C[CH_2CH_2N(C_2H_5)_2]C_6H_4OH$-*p*			(469)
p-$HOC_6H_4C(C_2H_5){=}C[CH_2CH_2N(C_4H_9)_2]C_6H_4OH$-*p*			(469)
p-$HOC_6H_4C(C_2H_5){=}C\left(CH_2CH_2N\langle\rangle\right)C_6H_4OH$-*p*			(469)
p-$CH_3OC_6H_4C(SCH_3){=}C(SCH_3)C_6H_4OCH_3$-*p*	194–196	10*‡	(325, 522)
p-$HOC_6H_4C(C_2H_5){=}C(OCH_3)C_6H_4OH$-*p*	194–195	10*§	(489)
p-$CH_3OC_6H_4CH{=}C(CN)C_6H_4OCH_3$-*p*	105–107		(41)
			(539)
p-$HOC_6H_4C{=}CC_6H_4OH$-*p* $OC\ \ CO$ O	224	Inactive	(173)
Dimethyl ether	171	Inactive	(173)
Diacetate	163	Inactive	(173)
p-$CH_3OC_6H_4C{=}CC_6H_4OCH_3$-*p* $C_2H_5OOC\ \ COOC_2H_5$	80		(173)

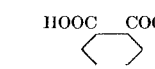
			
p-$HOC_6H_4C{=}CC_6H_4OH$-*p*	212–214	10 mg. (inactive)	(103)
p-$CH_3OC_6H_4CCl{=}CClC_6H_4OCH_3$-*p*	163–164	200*‡	(320)
p-$CH_3OC_6H_4CBr{=}CBrC_6H_4OCH_3$-*p*	198	300*‡	(320)
p-$CH_3OC_6H_4CI{=}CIC_6H_4OCH_3$-*p*	173 (d.)	800*‡ (inactive)	(320)
p-$CH_3OC_6H_4CCl{=}ClC_6H_4OCH_3$-*p*	176–177	100*‡	(320)
p-$CH_3OC_6H_4CBr{=}ClC_6H_4OCH_3$-*p*	207 (d.)	>600*‡	(320)
p-$HOC_6H_4N{=}NC_6H_4OH$-*p*		1 mg.*‡ (80%)	(490, 524)
		500*‡ (20%)	(490, 524)
		10–15 mg.	(388)
			(110)
p-$HOC_6H_4CH{=}NC_6H_4OH$-*p*	209	12.5 mg.‖	(228)
		25¶	(228)
	208 (polymorphic form)		(228)
	205 (polymorphic form)		(228)
p-$HOC_6H_4CH{=}NC_6H_4OCH_3$-*p*	211	25 mg. (inactive)	(228)
p-$CH_3OC_6H_4CH{=}NC_6H_4OH$-*p*	189	25 mg. (inactive)	(228)
p-$CH_3OC_6H_4CH{=}NC_6H_4OCH_3$-*p*	146	25 mg. (inactive)	(228)
$(p\text{-}HOC_6H_4)_2C{=}C(C_6H_4OH\text{-}p)_2$	—	1 mg. (inactive)	(103)
B. Hexestrol analogs			
p-$HOC_6H_4CH_2CH_2C_6H_4OH$-*p*		1 mg.* (inactive)	(45)
p-$HOC_6H_4CH(CH_3)CH(CH_3)C_6H_4OH$-*p*	233 (meso form)		(544)
	226–230 (meso form)		(1)
	139 (racemic form)		(544)
Dimethyl ether	136 (meso form)		(544)
	132.5–133 (meso form)		(399)
	88 (racemic form)		(544)
p-$HOC_6H_4CH(C_2H_5)CH(CH_3)C_6H_4OH$-*p*	186–187		(497, 498, 499)
p-$HOC_6H_4C(CH_3)_2CH(C_2H_5)C_6H_4OH$-*p*	186–187	0.001 mg. (ca. 80%)	(103)
p-$HOC_6H_4CH(C_4H_9)CH_2C_6H_4OH$-*p*	74–75		(302)
Dimethyl ether	174–175		(302)
p-$HOC_6H_4(CH_3)_2C(CH_3)_2C_6H_4OH$-*p*	210–212	10 mg.	(190)
p-$HOC_6H_4CH(C_2H_5)CH(C_3H_7)C_6H_4OH$-*p*	170–173		(497, 498, 499)
p-$HOC_6H_4C(CH_3)(C_2H_5)CH(C_2H_5)C_6H_4OH$-*p*	182–184	0.0005 mg.	(103)
		0.0003 mg. (ca. 50%)	(103)
p-$HOC_6H_4CH(C_3H_7)CH(C_3H_7)C_6H_4OH$-*p*	166–167 (meso form)		(403)
	168 (meso form)		(48)
			(233)
	Oil (racemic form)		(48)

TABLE 14—*Continued*

Compound	Melting Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
B. Hexestrol analogs—*Continued*			
	°C.		
Dimethyl ether	123 (meso form)		(48)
		1 mg.*	(45)
	Oil (racemic form)		(48)
p-$HOC_6H_4CH(C_2H_5)CH(C_4H_9)C_6H_4OH$-*p*	135–140		(497, 498, 499)
p-$HOC_6H_4CH(C_4H_9)CH(C_4H_9)C_6H_4OH$-*p*	167–168 (meso form)		(48)
		0.1 mg.*	(45)
	170–171 (meso form)		(403)
p-$HOC_6H_4CH(i\text{-}C_4H_9)CH(i\text{-}C_4H_9)C_6H_4OH$-*p*	206–207 (meso form)		(48)
		1 mg.*	(45)
	167–170 (meso form)		(403)
Dimethyl ether	127–128		(48)
		1 mg.* (inactive)	(45)
p-$HOC_6H_4CH(C_5H_{11})CH(C_5H_{11})C_6H_4OH$-*p*	145–146 (meso form)		(403)
p-$HOC_6H_4CH(i\text{-}C_5H_{11})CH(i\text{-}C_5H_{11})C_6H_4OH$-*p*	119–120 (meso form)		(48)
$(p\text{-}HOC_6H_4)_2CHCH(C_6H_4OH\text{-}p)_2$	299–300	100 (inactive)	(560)
Tetramethyl ether	187.5	100 (inactive)	(560)
Tetraethyl ether	159		(560)
Tetraacetate	283	100 (inactive)	(560)
p-$CH_3OC_6H_4CH(C_2H_5)CH(SCH_3)C_6H_4OCH_3$-*p*	152.5–154.5	100*‡	(324, 522)
p-$HOC_6H_4CH(SCH_3)CH(SCH_3)C_6H_4OH$-*p*	193.5–195	40*‡	(326, 521)
		20*‡(67%)	(326, 521)
p-$CH_3OC_6H_4CH(SCH_3)CH(OCH_3)C_6H_4OCH_3$-*p*	190–191	100*‡	(324, 522)
p-$HOC_6H_4CH(C_2H_5)CH(OCH_3)C_6H_4OH$-*p*	187–188	1*‡	(485)
Dimethyl ether	120–121	10*‡	(485)
p-$HOC_6H_4CH(OCH_3)CH(OCH_3)C_6H_4OH$-*p*	220–222 (meso form)	0.5*‡	(487, 523)
p-$HOC_6H_4CH(OC_2H_5)CH(OC_2H_5)C_6H_4OH$-*p*	212.5–214.5	10*‡	(487, 523)
p-$HOC_6H_4CH(C_2H_5)N(C_2H_5)C_6H_4OH$-*p*	100.5		(315, 316)
Dimethyl ether	64.5–65	60*‡ (incompletely active)	(315, 316)
p-$HOC_6H_4CH(C_2H_5)CH(NHCH_3)C_6H_4OH$-*p*	120	30*‡	(486)
Dimethyl ether	91.5–93	100*‡	(486)
		50*‡(60%)	(486)
p-$CH_3OC_6H_4CH(C_2H_5)CH(COOH)C_6H_4OCH_3$-*p*	181–183		(41)
	177.5–179		(202)
	163–164.5 (isomeric form)		(202)

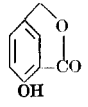
p-$HOC_6H_4C(CH_3)(COOH)CH(C_2H_5)C_6H_4OH$-*p*	225 (d.)	20	(202, 203)
Dimethyl ether	181–182.5	500 (inactive)	(202, 203)
p-$CH_3OC_6H_4CH(COOC_2H_5)CH(COOC_2H_5)C_6H_4OCH_3$-*p*	145 (meso form)		(173)
	143–144 (meso form)		(189)
p-$CH_3OC_6H_4CH(COOH)CH(COOH)C_6H_4OCH_3$-*p*	220 (impure racemic form)		(173, 189)
	214–215 (racemic form)		(189)
	272–273 (meso form)		(189)
p-$HOC_6H_4CH(COOH)CH(COOH)C_6H_4OH$-*p*	230 (impure racemic form)	Active	(173, 189)
	225–226 (d.) (racemic form)	5 mg.** (inactive)	(189)
	284 (d.) (meso form)	10 mg.** (inactive)	(189)
p-$HOC_6H_4CH(CH_2COOH)CH(CH_2COOH)C_6H_4OH$-*p*	318–320		(103)
		Inactive	(189)
p-$HOC_6H_4CH(CH_2CH_2OH)CH(CH_2CH_2OH)C_6H_4OH$-*p*	247–249 (meso form)	10 mg. (inactive)	(103)
	178 (racemic form)	10 mg. (inactive)	(103)
p-$CH_3COOC_6H_4CH(CH_2NO_2)CH(CH_2NO_2)C_6H_4OCOCH_3$-*p*	243–245		(34, 36)
	147–150 (isomeric form)		(34, 36)
p-$CH_3OC_6H_4CH(NHCH_3)CH(NHCH_3)C_6H_4OCH_3$-*p*	145		(307)
	134	1000*‡	(488)
Hydrochloride	273 (d.)	100 (inactive)	(307)
Hydroiodide	260 (d.)		(307)
p-$CH_3OC_6H_4CH(CH_3CONCH_3)CH(N(CH_3)COCH_3)C_6H_4OCH_3$-*p*	218		(307)
p-$CH_3OC_6H_4CH(ONNCH_3)CH(CH_3NNO)C_6H_4OCH_3$-*p*	238 (d.)		(307)
p-$HOC_6H_4CH(NHCH_3)CH(NHCH_3)C_6H_4OH$-*p*	183 (d.)		(307)
	175		(488)
Hydrochloride	269 (d.)	100 (inactive)	(307)
Hydrobromide	272 (d.)		(307)
Hydroiodide	278 (d.)		(307)
p-$HOC_6H_4CH(CH_3CONCH_3)CH(N(CH_3)COCH_3)C_6H_4OH$-*p*	331 (d.)		(307)
Diacetate	257		(307)
p-$CH_3OC_6H_4CH{=}N{-}N{=}CHC_6H_4OCH_3$-*p*	180		(307)

TABLE 14—*Continued*

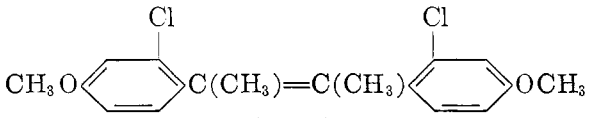
Compound	Melting Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
B. Hexestrol analogs—*Continued*			
	°C.		
Methiodide	230 (d.)		(307)
$CH_2ClCONH$ $NHCOCH_2Cl$ | | *p*-$CH_3OC_6H_4CH$—$CHC_6H_4OCH_3$-*p*	286 (d.)		(307)
$C_6H_5SO_2NH$ $NHSO_2C_6H_5$ | | *p*-$CH_3OC_6H_4CH$—$CHC_6H_4OCH_3$-*p*	280 (d.)		(307)
p-$HOC_6H_4CH(NH_2)CH(NH_2)C_6H_4OH$-*p*	205 (d.)		(307)
Hydrochloride	306 (d.)		(307)
Hydrobromide	323 (d.)		(307)
Hydroiodide	301 (d.)		(307)
p-$CH_3COOC_6H_4CH(NHCOCH_3)CH(NHCOCH_3)C_6H_4OCOCH_3$-*p*	350 (d.)		(307)
p-$CH_3OC_6H_4CH(NHCH_3)CH(NH_2)C_6H_4OCH_3$-*p*	94		(307)
CH_3CONCH_3 $NHCOCH_3$ | | *p*-$CH_3OC_6H_4CH$—$CHC_6H_4OCH_3$-*p*	250		(307)
p-$HOC_6H_4CH(NHCH_3)CH(NH_2)C_6H_4OH$-*p*	—		(307)
Hydroiodide	259 (d.)		(307)
p-$CH_3OC_6H_4CH(C_2H_5)CH(CN)C_6H_4OCH_3$-*p*	131–133.5	1 mg.	(539)
		0.1 mg. (inactive)	(539)
	130–131		(41, 133)
	Oil (isomeric form)		(41, 539)
p-$HOC_6H_4CH(C_2H_5)CH(CH_2CN)C_6H_4OH$-*p*	—	Active	(475)
p-$CH_3OC_6H_4CH(C_2H_5)CH(COCH_3)C_6H_4OCH_3$-*p*	139–142	0.01 mg.	(539)
		0.001 mg. (inactive)	(539)
	142–143		(41)
	99–101 (isomeric form)	10 mg.	(539)
		1 mg. (inactive)	(539)
	103–104 (isomeric form)		(41)
p-$HOC_6H_4CH(C_2H_5)CH(COCH_3)C_6H_4OH$-*p*	218–220	Active	(41)
	Oil (isomeric form)		(41)
Diacetate	143–144		(41)
Diacetate (isomeric form)	103–104		(41)
p-$CH_3OC_6H_4CH(C_2H_5)CH(CHOHCH_3)C_6H_4OCH_3$-*p*	—	0.1 mg.	(539)
		0.01 mg. (inactive)	(539)

p-$CH_3OC_6H_4CHOHCOC_6H_4OCH_3$-*p*	113	1000 (inactive)	(161)
		100	(63)
p-$CH_3OC_6H_4CHClCOC_6H_4OCH_3$-*p*	81	100	(164)
p-$CH_3OC_6H_4CHBrCOC_6H_4OCH_3$-*p*	104	1000 (inactive)	(161)
p-$CH_3OC_6H_4CHCHC_6H_4OCH_3$-*p* (O bridge)	142	1000 (inactive)	(164)
p-$CH_3OC_6H_4COCOC_6H_4OCH_3$-*p*	133	100 (partial response)	(164)
p-$CH_3OC_6H_4CHOHCHOHC_6H_4OCH_3$-*p*	174	100 (partial response)	(164)
p-$CH_3OC_6H_4CHBrCHBrC_6H_4OCH_3$-*p*	179 (d.)	100 (inactive)	(164)
p-$CH_3OC_6H_4CHClCHClC_6H_4OCH_3$-*p*	184 (d.)	100 (inactive)	(164)
p-$HOC_6H_4COCOC_6H_4OH$-*p*	235	100 (inactive)	(164)
p-$HOC_6H_4CHOHCHOHC_6H_4OH$-*p*	222	100 (inactive)	(164)
p-$CH_3COOC_6H_4C(C_2H_5)(Br)C(C_2H_5)(Br)C_6H_4OCOCH_3$-*p*	156 (d.)	25	(164)
		10 (partial response)	(164)
		1 (inactive)	(164)
	156–156.5 (d.)		(510, 511, 512, 513)
p-$CH_3COOC_6H_4C(C_2H_5)(Cl)C(C_2H_5)(Cl)C_6H_4OCOCH_3$-*p*	156 (d.)	25	(164)
		10 (partial response)	(164)
p-$NaSO_4OC_6H_4COCHOHC_6H_4OSO_3Na$-*p*			(63)
p-$CH_3OC_6H_4COCH_2C_6H_4OCH_3$-*p*		100	(63)
p-$NaSO_3OC_6H_4COCH_2C_6H_4OSO_3Na$-*p*			(63)
p-$CH_3OC_6H_4CH(C_2H_5)COC_6H_4OCH_3$-*p*		10	(63)
p-$NaSO_3OC_6H_4CH(C_2H_5)COC_6H_4OSO_3Na$-*p*			(63)
p-$CH_3OC_6H_4CH(C_2H_5)C(C_2H_5)(OH)C_6H_4OCH_3$-*p*		10	(63)
p-$NaSO_4OC_6H_4CH(C_2H_5)C(C_2H_5)(OH)C_6H_4OSO_3Na$-*p*			(63)
p-$HOC_6H_4SC_6H_4OH$-*p*		100 mg.	(65)
		50 mg. (60%)	(65)
		25 mg. (inactive)	(65)

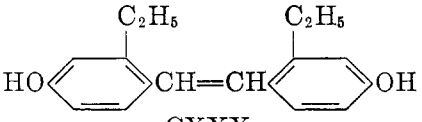
TABLE 14—*Concluded*

Compound	Melting Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
B. Hexestrol analogs—*Continued*			
	°C.		
p-$HOC_6H_4SOC_6H_4OH$-*p*		Inactive	(65)
p-$HOC_6H_4SO_2C_6H_4OH$-*p*			
p-$CH_3OC_6H_4SC_6H_4OCH_3$-*p*		Inactive	(65)
p-$CH_3OC_6H_4CH(C_2H_5)SCH(C_2H_5)C_6H_4OCH_3$-*p*		100 mg.	(65)
		50 mg. (50%)	(65)
		25 mg. (inactive)	(65)
p-$HOC_6H_4SSC_6H_4OH$-*p*		Inactive	(65)
p-$HOC_6H_4SC_6H_4OH$-*p* 		Inactive	(65)

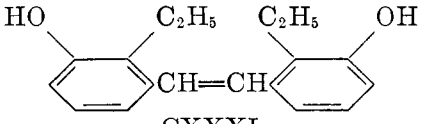
* In mice.
† Orally.
‡ Administered in two portions.
§ Minimal lethal dose.
‖ Administered in five portions.
¶ Administered intravaginally in five portions.
** Administered in aqueous solution.



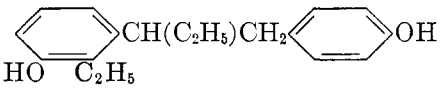
CXXIX



CXXX



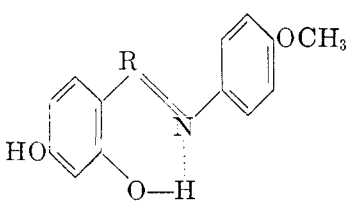
CXXXI



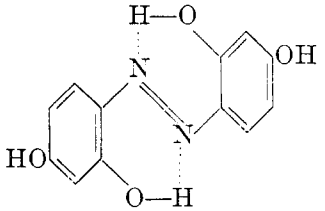
CXXXII

though they resemble CXXV they were much less active. Richtzenhain (352) found 2,2′-diethyl-4,4′-dihydroxystilbene (CXXX) and its dihydro derivative to have only low activity, confirming the result of Linnell and Shaikmahahmud (264). Surprisingly, with the hydroxyl groups in the meta positions the diethylstilbestrol analog (CXXXI) and the hexestrol analog are fairly active, the former giving 87 per cent response at 10 micrograms. After other attempts had failed, CXXXI was obtained by converting 2-ethyl-3-hydroxybenzaldehyde to the thioaldehyde and treating with copper bronze; 2-ethyl-3-methoxybenzaldehyde could not be used, since the final ether could not be demethylated. Hydrogenation of this ether gave the hexestrol analog, which could be demethylated (353). 3-(2-Ethyl-3-hydroxyphenyl)-4-(*p*-hydroxyphenyl)butane (CXXXII) (353) was successfully obtained only by a Friedel–Crafts reaction with 2-ethyl-3-methoxyphenylacetyl chloride and anisole, followed by ethylation of the ketone with sodium ethoxide and ethyl iodide and then by Wolff–Kishner reduction; it was active at 10 micrograms. Neher and Miescher (303) replaced one hydroxyl group of diethylstilbestrol by a carboxyl group and varied the aliphatic portion. 4′-Carboxy-4-hydroxy-α,α'-dipropylstilbene was active at 700–1000 micrograms; the methyl ester of 4′-carboxy-4-hydroxy-α,α'-dimethylstilbene was active at 1 mg., but the free acid was not. This latter result appears to illustrate the idea that a solubilizing carboxyl group tends to aid elimination or a similar process and, depending on the rest of the molecule, may result in inactivity. α'-Carboxy-3-hydroxystilbene, α'-carboxy-3,4′-dihydroxystilbene, and their dihydro compound were inactive at 5 mg. (294).

Nomura (317) prepared a series of azomethines (CXXXIII). The 2-hydroxyl



CXXXIII



CXXXIV

group was introduced in the expectation that intramolecular hydrogen bonding would introduce some rigidity into the molecule, as suggested by Schueler (388). The peak of activity occurred with R = ethyl. Similar compounds were prepared by Keasling and Schueler (228). Takahashi (490) also introduced hydroxyl groups into 4,4′-dihydroxyazobenzene for the purpose of increasing rigidity; the 2,2′,4,4′-tetrahydroxyazobenzene (CXXXIV) was more active than the parent compound. It is difficult to decide whether rigidity in these compounds is responsible for their increased estrogenic activity, since rigidity might be expected to be important only when it affects the relative orientation of the hydrogen-bonding groups. Analogs of diethylstilbestrol, hexestrol, and dienestrol with variation of the aliphatic portion and of aromatic substitution are collected in table 15.

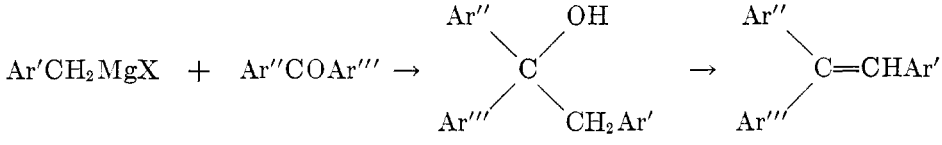
E. TRIPHENYLETHYLENE AND ITS ANALOGS

The discovery of the estrogenic activity of 1,1,2-triphenylethylene and that of certain of its analogs, together with the apparent structural differences in this series compared with diethylstilbestrol, has led to extensive investigation of this class of compounds. Members of the group such as 1,1-bis(*p*-ethoxyphenyl)-2-phenyl-2-bromoethylene (DBE) have been used clinically. Triphenylethylene and its analogs contain the *cis*- and *trans*-stilbene systems and are best considered as variants of diethylstilbestrol.

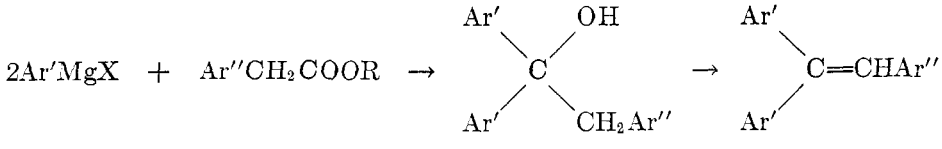
1. Syntheses

Three principal routes have been used for the preparation of estrogenic or potentially estrogenic triphenylethylenes.

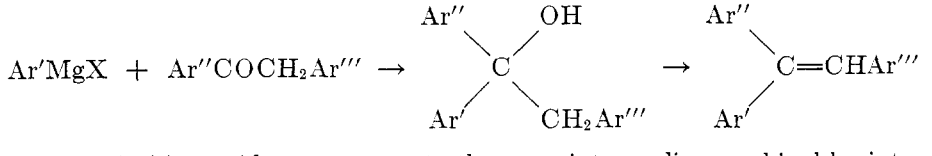
(*a*) From a benzylmagnesium halide and a dialkyl ketone:



(*b*) From an arylmagnesium halide and an arylacetic ester:



(*c*) From an arylmagnesium halide and a desoxybenzoin:



Synthesis (c) provides two routes to the same intermediary carbinol by interchanging Ar′ and Ar″ in the starting materials. The usefulness of the various

syntheses depends on the particular triphenylethylene being prepared. Method (a) is not applicable to *p*-alkoxybenzylmagnesium halides, and in all the methods best results are obtained by the use of an excess of the Grignard reagent. In methods (a) and (c) two molecular proportions of the Grignard reagent are used, while in method (b) it is preferable to use three molecular proportions (59). A wide variety of methods has been found useful for the dehydration step; some tertiary carbinol intermediates undergo dehydration spontaneously (44) or on distillation at low pressures (303). The following chemical methods have been used: treatment with iodine in xylene (303); distillation with dilute sulfuric acid (480); refluxing in acetic acid containing acetyl chloride or a trace of sulfuric acid (480); heating with phosphoric acid (396); heating with 100 per cent formic acid (362); heating with a mixture of acetic and hydrobromic acids (477); heating with *p*-toluenesulfonic acid at low pressures (397).

The 2-chloro and 2-bromo derivatives of triphenylethylenes are an important group of estrogens and have been obtained from the corresponding ethylene or directly from the corresponding intermediate carbinol for the ethylene. Treatment with bromine in carbon disulfide (44) or in carbon tetrachloride, acetic acid, nitrobenzene, or chlorobenzene has been used to obtain the 2-bromo compound. A 2–5 per cent excess of halogen is used (15). The 2-chloro compounds may be similarly obtained or by using sulfuryl chloride in the presence of benzoyl peroxide (477). In the second method the carbinol intermediate may be converted to the halogen compound directly by means of a solution of chlorine or bromine in acetic acid or chloroform (59); water is eliminated in this reaction. The method is valuable for its directness and also in that the carbinols are more easily handled than the ethylenes.

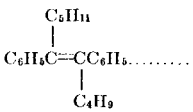
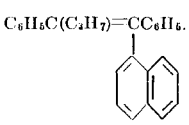
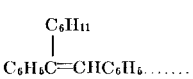
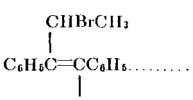
2. Estrogenic activity

The triphenylethylenes, like diethylstilbestrol, hexestrol, and dienestrol, are active by mouth. However, they are distinguished from the latter estrogens in that many of them have the useful property of prolonged action. Only the more important triphenylethylenes, together with some general considerations, will be mentioned here.

The estrogenic activity of triphenylethylene, the parent of the series, was reported almost simultaneously but independently by Robson and Schönberg (364) and by Dodds, Fitzgerald, and Lawson (99). The quite early variations of the parent structure produced some of the most active compounds of the series (457). Triphenylethylene and its 2-chloro and 2-bromo derivatives—provided dosages well above threshold are used—combine sufficiency of estrogenic activity with duration of action, and this characteristic has resulted in clinical interest in this series. However, the introduction of *p*-hydroxyl groups into the aromatic rings removes their property of prolongation of action (483), and it appears that the property is associated with the necessity of *in vivo* hydroxylation. However, their storage in body fat (361) and their low solubility in body fluids are probably important additional factors connected with prolonged action. As previously discussed in connection with the stilbene estrogens, optimum physicochemical

TABLE 15

Analogs of diethystilbestrol, hexestrol, and dienestrol with variation of the aliphatic portion and aromatic substitution

Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
A. Diethylstilbestrol analogs			
	°C.		
$C_6H_5C(C_2H_5)=C(C_3H_7)C_6H_5$		0.1 mg.*	(78)
$C_6H_5CH(C_2H_5)=C(CH_2CH=CH_2)C_6H_5$		0.5 mg.*	(78)
$C_6H_5C(C_2H_5)=C(i\text{-}C_5H_{11})C_6H_5$		0.5 mg.*	(78)
$C_6H_5C(C_2H_5)=C(C_5H_{11})C_6H_5$		2.0 mg.*	(78)
$C_6H_5C(C_3H_7)=C(C_3H_7)C_6H_5$		5.0 mg.*	(78)
$C_6H_5C(C_4H_9)=C(C_3H_7)C_6H_5$		20 mg.*	(78)
		20 mg.*	(78)
		2 mg.*	(78)
	208–210/18 mm. (b.p.)		(44)
	182 (d.)	1 mg. (50%)	(103)
$C_6H_5CH=CHC_6H_4OCH_2CH_2N(C_2H_5)_2\text{-}p$	74		(277)
$C_6H_5C(CH_3)=C(CH_3)C_6H_4OCH_2CH_2N(C_2H_5)_2\text{-}p$	235–238/9.7 mm. (b.p.)		(277)
$C_6H_5C(i\text{-}C_3H_7)=C(i\text{-}C_3H_7)C_6H_4OCH_2CH_2N(C_2H_5)_2$	38		(277)

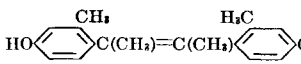
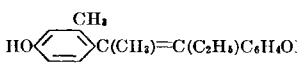
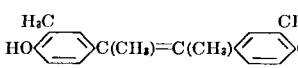
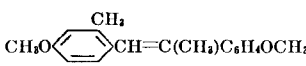
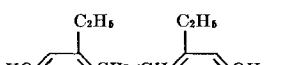
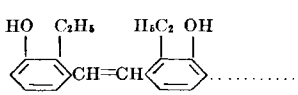
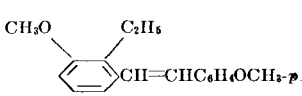
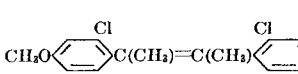
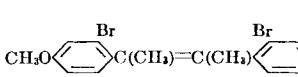
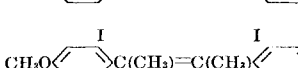
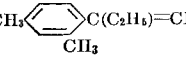
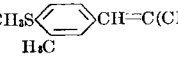
p-$CH_3OC_6H_4C(CH_3)=C(CH_3)C_6H_4OCH_3$-*p*	141.5–143	100*‡	(322)
	208–210		(194, 534)
		1.5§	(37)
	214	6.2†§	(37)
Diacetate	116–117	10,000 (I.U./mg.)	(404, 405)
		5000 (I.U./mg.)	(404, 405)
	153–154		(534)
		1.2§	(37)
		4.8†§	(37)
	197–198	Half the activity of diethylstilbestrol	(404)
	96–97 (trans form)		(534)
	Oil (cis form)		(534)
	151	1 mg.*	(352)
	191–192	10* (87%)	(353)
	81		(353)
	112–113 (trans form)	200*‡	(322)
	117.5–119.5 (trans form)	200*‡	(322)
	159–160 (trans form)	500*‡ (75%)	(322)

TABLE 15—*Continued*

Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
A. Diethylstilbestrol analogs—*Continued*			
	°C.		
m-$HOC_6H_4CH{=}C(COOH)C_6H_5$	187–188	5 mg.* (inactive)	(294)
m-$HOC_6H_4CH{=}C(COOH)C_6H_4OH$-*p*	230 (d.)	5 mg.* (inactive)	(294)
p-$HOC_6H_4CH{=}CHC_6H_4COOH$-*p*	277–278	1 mg. (inactive)	(303)
	300–302 (isomeric form)		(303)
p-$HOC_6H_4C(CH_3){=}C(CH_3)C_6H_4COOH$-*p*	231–234	1 mg. (inactive)	(303)
Methyl ester	160–162	1 mg.	(303)
		0.5 mg. (inactive)	(303)
p-$HOC_6H_4CH{=}C(C_2H_5)C_6H_4COOH$-*p*	144–146 (from benzene)	1 mg. (inactive)	(303)
	128–133 (from aqueous methanol)		(303)
p-$HOC_6H_4C(C_2H_5){=}CHC_6H_4COOH$-*p*	144–149	1 mg. (inactive)	(303)
	191–196 (polymorphic form)		(303)
p-$HOC_6H_4C(C_3H_7){=}C(C_3H_7)C_6H_4COOH$-*p*	176–178	1000	(303)
		700 (40%)	(303)
p-$H_2NC_6H_4C(CH_3){=}C(CH_3)C_6H_4NH_2$-*p*	145–146		(8, 9)
p-$CH_3SC_6H_4C(CH_3){=}C(CH_3)C_6H_4SCH_3$-*p*	132.5–133.5	300*‡ (50%)	(321)
p-$CH_3SC_6H_4C(C_3H_7){=}C(C_3H_7)C_6H_4SCH_3$-*p*	99–99.5	200*‡ (incomplete)	(321)
p-$CH_3C_6H_4C(C_2H_5){=}CHC_6H_5$	203–204/35 mm. (b.p.)		(44)
p-$CH_3C_6H_4C(C_2H_5){=}C(C_2H_5)C_6H_5$	197–198/29 mm. (b.p.)		(44)
p-$CH_3C_6H_4C(C_2H_5){=}C(C_3H_7)C_6H_5$	202/28 mm. (b.p.)		(44)
p-$CH_3C_6H_4C(C_2H_5){=}C(C_4H_9)C_6H_5$	207–208/25 mm. (b.p.)		(44)
p-$C_2H_5C_6H_4C(C_2H_5){=}CHC_6H_5$	210/30 mm. (b.p.)		(44)
		1 mg.* (inactive)	(78)
p-$(CH_3)_3CC_6H_4C(C_2H_5){=}CHC_6H_5$	205–206/20 mm. (b.p.)		(44)
	198–199/25 mm. (b.p.)		(44)
p-$CH_3SC_6H_4CH{=}C(CN)C_6H_5$	96		(49)
p-$CH_3SC_6H_4CH{=}C(CN)C_6H_4CH_3$-*p*	113		(49)
p-$CH_3SC_6H_4CH{=}C(CN)C_6H_4F$-*p*	117		(49)
p-$CH_3SC_6H_4CH{=}C(CN)C_6H_4Cl$-*p*	100		(49)
p-$CH_3SC_6H_4CH{=}C(CN)C_6H_4Br$-*p*	131		(49)
p-$CH_3SC_6H_4CH{=}C(CN)C_6H_4I$-*p*	135		(49)
	99		(49)

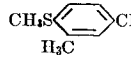
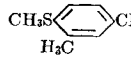
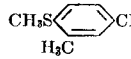
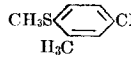
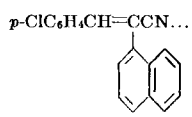
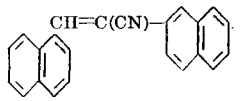
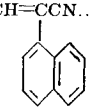
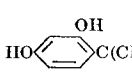
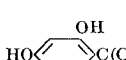
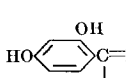
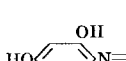
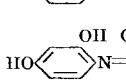
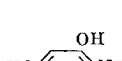
	123		(49)
	134		(49)
	132		(49)
	152		(49)
p-$CH_3OC_6H_4CH{=}C(CN)C_6H_4CH_3$-*p*		10 mg.* (inactive)	(45)
o-$CH_3OC_6H_4CH{=}C(CN)C_6H_4CH_3$-*p*		10 mg.* (inactive)	(45)
p-$ClC_6H_4CH{=}C(CN)C_6H_5$		10 mg.* (inactive)	(45)
		10 mg.* (inactive)	(45)
p-$(CH_3)_2NC_6H_4CH{=}C(CN)C_6H_5$		10 mg.* (inactive)	(45)
p-$(CH_3)_2NC_6H_4CH{=}C(CN)C_6H_4CH_3$-*p*		10 mg.* (inactive)	(45)
o-$CH_3OC_6H_4CH{=}C(CN)C_6H_5$		10 mg.* (inactive)	(45)
p-$ClC_6H_4CH{=}C(CN)C_6H_4CH_3$-*p*		1 mg.* (inactive)	(45)
		5 mg.* (toxic)	(45)
		1 mg.* (inactive)	(45)
o-$CH_3OC_6H_4CH{=}CCN$ 		1 mg.* (inactive)	(45)
p-$(i\text{-}C_3H_7)C_6H_4CH{=}C(CN)C_6H_4CH_3$-*p*		1 mg.* (inactive)	(45)
p-[*p*-$CH_3OC_6H_4$]$C_6H_4C(C_2H_5){=}CHC_6H_5$		1 mg.* (inactive)	(45)
$C_6H_5CH{=}NC_6H_5$	54	25 mg. (inactive)	(228)
$C_6H_5CH{=}NC_6H_4CH_3$-*p*	36	25 mg. (inactive)	(228)
$C_6H_5CH{=}NC_6H_4OCH_3$-*p*	70	25 mg. (inactive)	(228)
$C_6H_5CH{=}NC_6H_4OH$-*p*	185	25 mg. (inactive)	(228)
p-$CH_2C_6H_4CH{=}NC_6H_5$	41	25 mg. (inactive)	(228)

TABLE 15—*Continued*

Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	Reference
A. Diethylstilbestrol Analogs—*Continued*			
	°C.		
p-$CH_3C_6H_4CH{=}NC_6H_4CH_3$-*p*	93	25 mg. (inactive)	(228)
p-$CH_3C_6H_4CH{=}NC_6H_4OCH_3$-*p*	87	25 mg. (inactive)	(228)
p-$CH_3C_6H_4CH{=}NC_6H_4OH$-*p*	200	25 mg. (inactive)	(228)
p-$CH_3OC_6H_4CH{=}NC_6H_5$	57	25 mg. (inactive)	(228)
p-$CH_3OC_6H_4CH{=}NC_6H_4CH_3$-*p*	94	25 mg. (inactive)	(228)
p-$HOC_6H_4CH{=}NC_6H_5$	194	25 mg. (inactive)	(228)
p-$HOC_6H_4CH{=}NC_6H_4CH_3$-*p*	220	25 mg. (inactive)	(228)
	262 (d.)	1 mg.*‡ (inactive)	(317, 318)
	213 (d.)	1 mg.*‡	(317, 318)
	197 (d.)	1 mg.*‡ (40%)	(317, 318)
		20*‡ 10*‡ (60%)	(490) (490)
		1 mg.*‡ (inactive)	(490)
		500*‡ (40%)	(490)

B. Hexestrol analogs

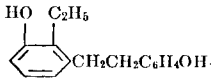
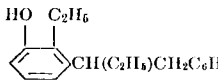
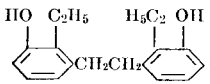
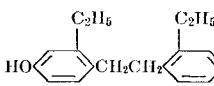
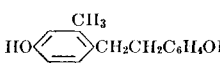
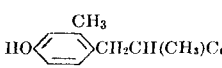
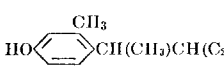
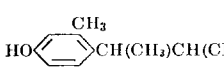
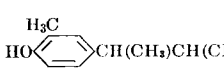
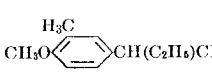
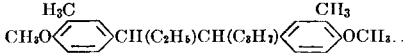
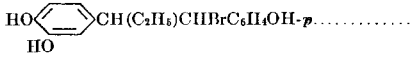
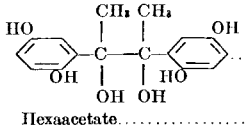
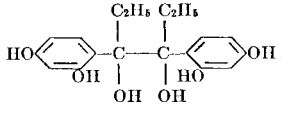
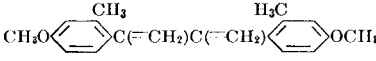
$C_6H_5CH_2CH_2C_6H_5$		100 mg. (incompletely active)	(78)
$C_6H_5CH(C_4H_9)CH(C_4H_9)C_6H_5$	77 (meso form) Oil (racemic form)		(48) (48)
	97–98	0.5 mg.*	(353)
	180/0.3 mm. (b.p.)	10* 5* (75%)	(353) (353)
	154–155	20* (87%) 10* (25%)	(353) (353)
	133	1 mg.*	(352)
	144–145		(534, 535)
	131–133		(534, 535)
	140–141		(534, 535
	189–190		(194, 534, 535)
	174–174.5 (meso form)		(402, 403)
	195–200/2 mm. (b.p.)		(496)

TABLE 15—*Concluded*

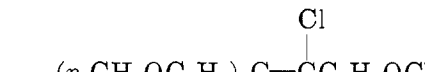
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms Unless Indicated Otherwise	References
B. Hexestrol analogs—*Continued*			
	°C.		
	195–205/2 mm. (b.p.)		(496)
	130–133		(497)
	240–244	50 mg. (inactive)	(140)
Hexaacetate	213–215	50 mg. (inactive)	(140)
	233–234 (α-isomer)	50 mg. (23 days)‖	(140)
		5 mg. (2.5 days)‖	(140)
		2 mg. (inactive)	(140)
	200–201 (β-isomer)	50 mg. (1 day)‖	(140)
		25 mg. (1 day)‖	(140)
		5 mg. (inactive)	(140)
Hexaacetate	227–230 (α-isomer)	5 mg. (2.5 days)	(140)
m-$HOC_6H_4CH_2CH(COOH)C_6H_5$	75	5 mg.* (inactive)	(294)
m-$CH_3OC_6H_4CH_2(COOH)C_6H_4OCH_3$-*p*	104	5 mg.* (inactive)	(294)
p-$CH_3OC_6H_4CH(C_2H_5)CH(CN)C_6H_5$	69–71	10 mg. (inactive)	(539)
	118–119 (isomeric form)	10 mg. (inactive)	(539)
p-$CH_3OC_6H_4CH(C_2H_5)CH(COCH_3)C_6H_5$	108–109.5	0.1 mg.	(539)
		0.01 mg. (inactive)	(539)
	63–66 (isomeric form)		(539)
p-$HOC_6H_4C(C_2H_5)(OH)CH(C_2H_5)C_6H_4NH_2$-*p*	181–182	1 mg.*	(216)
		0.1 mg.* (78%)	(216)
		0.01 mg.* (inactive)	(216)

p-$CH_3SC_6H_4CH(C_3H_7)CH(C_3H_7)C_6H_4SCH_3$-*p*	112		(49)
$C_6H_5SC_6H_5$		Inactive	(65)
p-$O_2NC_6H_4SC_6H_4NO_2$-*p*		Inactive	(65)
p-$H_2NC_6H_4SC_6H_4NH_2$-*p*	107–108	Inactive	(65)
p-$O_2NC_6H_4CH(C_2H_5)SCH(C_2H_5)C_6H_4OH$-*p*		Inactive	(65)
C. Dienestrol analogs			
$C_6H_5CH(CH{=}CH_2)CH(CH{=}CH_2)C_6H_5$	87–87.5 (meso form)	1–10 mg. (50%)	(240)
	Oil (racemic form)		(240)
p-$HOC_6H_4C(=CH_2)C(=CH_2)C_6H_4OH$-*p*	166–167		(1, 178)
Dimethyl ether	108–109		(404)
	108–108.5		(404)

* In mice.
† Orally.
‡ Administered in two portions.
§ Diethylstilbestrol = 1.
‖ Duration of estrus.

properties are apparently essential in the triphenylethylene series. In connection with the concept of proestrogens to be discussed later, Emmens (115) found various triphenylethylenes to be proestrogens. Basford (15) noted that the introduction of *p*-methoxy groups into the 1-phenyl groups of triphenylethylene and its halogen derivatives resulted in estrogens which were more active orally than subcutaneously.

Rothschild and Keys (367) assessed the estrogen tris(*p*-methoxyphenyl)-chloroethylene (CXXXV) (TACE) in the human subject and found that the



CXXXV

minimal effective dose on oral administration for complete cornification of the postmenopausal human female vagina was 24–48 mg., administered as four daily doses of 6–12 mg. each. Administration of the same quantities of this estrogen but on alternate days did not lead to much cornification. This result implies fairly rapid destruction of this estrogen in the body, and it is of interest that Morin, de Clercq, Apelgot, and Daudel (292) showed, using radiobromotriphenylethylene subcutaneously in mice and rabbits, that the substance is rapidly destroyed. The bromine was found to be excreted as inorganic bromide. The ease of destruction of triphenylethylenes, as indicated by these results, may be important when comparing the estrogenic activities of compounds. Rothschild and Keys (367) also showed that with the triphenylethylene TACE in minimal dosage, the duration of estrus was not greatly different from that produced by the stilbene estrogens. However, this estrogen contains potential hydroxyl groups and probably with the exception of massive dosage it is likely that appreciable fat storage is associated with the absence of hydroxyl groups or their equivalents.

Thompson and Werner (504) found TACE more prolonged in action subcutaneously than orally. However, large oral doses in rats did lead to some increased duration of action. The estrogen was in fact found to be stored in body fat, but no such storage was found for diethylstilbestrol or hexestrol; neither did these latter estrogens exhibit prolonged action. As pointed out previously, free hydroxyl groups are unlikely to lead to fat storage, and presumably such storage of TACE at higher dosage is accounted for by the absence of free hydroxyl groups. With monkeys and rats it was found that estrogenic material equivalent in biological activity to more than the administered dose of TACE was eliminated with feces. Dealkylation *in vivo* may account for this. With hexestrol little estrogenic material was excreted. The estrogenic activities found by Thompson and Werner (504) for TACE and the relation to diethylstilbestrol and hexestrol are given in table 16.

3. Structure and estrogenic activity

The extensive investigations in this series make it profitable to consider the effect of structural variation on estrogenic activity along lines similar to those used in discussing diethylstilbestrol, hexestrol, and dienestrol.

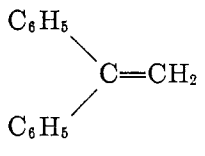
TABLE 16

Estrogenic activities of tris(p-methoxyphenyl)chloroethylene and their relation to diethylstilbestrol and hexestrol

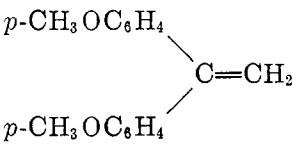
Compound	Dose		Median Duration	
	Subcutaneously	Orally	Subcutaneously	Orally
	mg.	*mg.*	*days*	*days*
Tris(*p*-methoxyphenyl)chloroethylene	1 (18 rat units)	1 (47 rat units)	53	2
		5 (238 rat units)		17
Hexestrol	1 (2857 rat units)	1 (83 rat units)	2	3
		5 (415 rat units)		2
Diethylstilbestrol	1 (2500 rat units)	1 (333 rat units)	3	2
		5 (1666 rat units)		3

(a) Variation of aromatic substitution

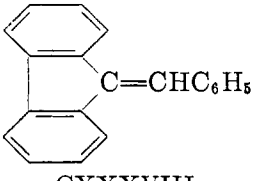
The three phenyl groups in triphenylethylene are essential to higher estrogenic activities; 1,1-diphenylethylene (CXXXVI) (99) is inactive. The related compound 1,1-bis(*p*-methoxyphenyl)ethylene (CXXXVII) (481) is also inactive at 5 mg.



CXXXVI



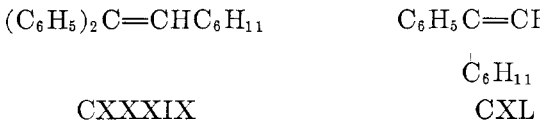
CXXXVII



CXXXVIII

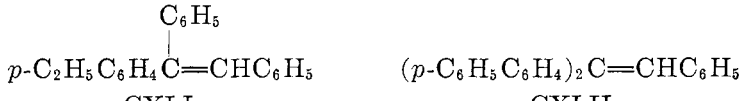
Triphenylethylene itself was reported active in mice subcutaneously at 0.1 mg. by Lacassagne, Buu-Hoï, Corre, Lecocq, and Royer (251); 300 micrograms was reported to give 50 per cent response in mice subcutaneously by Emmens (115); Jacques, Courrier, and Pomeau-Delille (209) reported a subcutaneous activity in rats of 10 mg. in a divided dose. These low activities are reminiscent of those of unhydroxylated stilbene derivatives discussed previously and point to the need for hydroxylation of triphenylethylene before it can exhibit estrogenic function. Triphenylethylene contains both the *cis*- and *trans*-stilbene units, and the well-known *cis*-stilbene steric effect will operate. This steric interaction between a 1-phenyl and the 2-phenyl group will result in rotation of the rings. A 1-phenyl group appears to fulfill a steric function similar to that discussed previously for ethyl groups in diethylstilbestrol. Little steric interaction will presumably occur between the 1-phenyl groups, but the one not hindered by the 2-phenyl group should be capable of orientation, giving the *trans*-stilbene unit the staggered configuration of diethylstilbestrol. Triphenylethylene is more active than *trans*-stilbene and has about the same activity as α-ethyl-α'-propylstilbene previously mentioned. Linking of the two 1-phenyl groups as in 9-benzylidenefluorene (CXXXVIII) (144, 209) results in a weak estrogen, probably owing to the inability of the molecule to adopt appropriate configuration. Apparently this is a case where rigidity of the molecule is disadvantageous.

2-Cyclohexyl-1,1-diphenylethylene (CXXXIX) (362) rather surprisingly is active, while 1-cyclohexyl-1,2-diphenylethylene (CXL) is inactive. The activity of



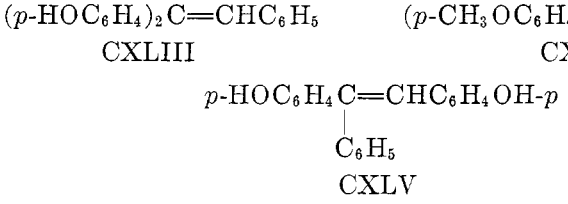
CXXXIX CXL

the former is probably due to its "diphenylmethane" unit, while the latter probably has the cis configuration of aromatic rings (168). 1-(*p*-Ethylphenyl)-1,2-diphenylethylene (CXLI) has low activity (251), suggesting that the rings are trans oriented, since *p*-alkyl groups in the stilbene series abolish activity. 1,1-Bis(4-biphenyl)-2-phenylethylene (CXLII) is inactive (79); here certain blocking of the para positions occurs.



CXLI CXLII

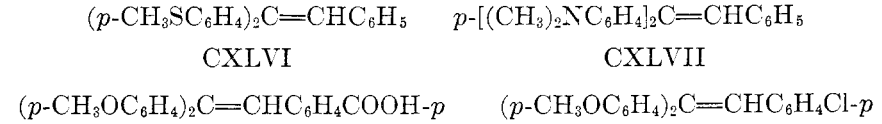
The introduction of a hydroxyl group into the para position of one of the 1-phenyl groups of triphenylethylene considerably enhances the estrogenic activity relative to the parent compound (115). 1,1-Bis(*p*-hydroxyphenyl)-2-phenylethylene (CXLIII) gives 50 per cent response in mice subcutaneously at 8 micro-



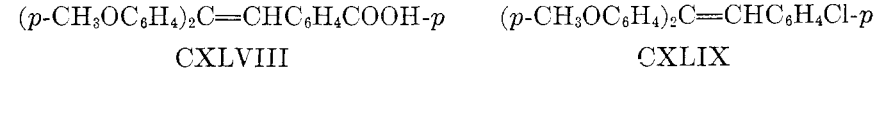
CXLIII CXLIV CXLV

grams. The related compound 1,1-bis(*p*-methoxyphenyl)-2-phenylethane (CXLIV) (45) is active in mice subcutaneously at 2 mg., but its configuration is not definite. 1,2-Bis(*p*-hydroxyphenyl)-1-phenylethylene (CXLV) is also highly active, producing 50 per cent response in mice subcutaneously at 15 micrograms (115). Hydroxyl groups considerably increase the potency of compounds in the triphenylethylene series and in fact are optimum groups for this purpose. However, as indicated previously, they also lead to loss of duration of action.

1,1-Bis(*p*-methylthiophenyl)-2-phenylethylene (CXLVI) (301) and 1,1-bis-(*p*-dimethylaminophenyl)-2-phenylethylene (CXLVII) (78) are inactive. The inactivity of CXLVI is of interest in view of the conflicting reports on the effect of methylthio groups on the activity of the stilbene estrogens mentioned earlier.



CXLVI CXLVII

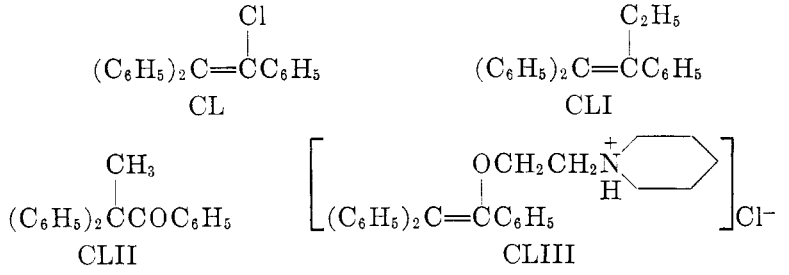


CXLVIII CXLIX

1,1-Bis(*p*-methoxyphenyl)-2-(*p*-carboxyphenyl)ethylene (CXLVIII) is inactive at 1 mg. (303). Some attention has been paid to the introduction of halogen atoms into the triphenylethylene molecule (482); 1,1-bis(*p*-methoxyphenyl)-2-(*p*-chlorophenyl)ethylene (CXLIX) at 1000 micrograms in mice has a median duration of action of 3 days. It appears that the halogen atom, unlike most others, can be replaced *in vivo* by the hydroxyl group.

(b) Variation of the aliphatic portion

Shortly after the discovery of the estrogenic activity of triphenylethylene, Robson, Schönberg, and Fahim (365) showed that 2-chloro-1,1,2-triphenylethylene (CL) is rather more potent than the parent substance. Barbier, Rumpf,



CL CLI

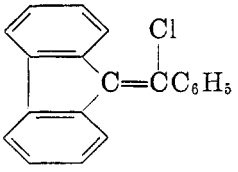
CLII CLIII

and Roland (14) tested the 2-chloro,2-bromo, and 2-iodo compounds and found that the order of effectiveness for estrogenic potency was chlorine > bromine > iodine. Schueler (388) suggested that the inductive effect of the halogen atoms results in the *p*-hydrogen atoms of the 1-phenyl groups acquiring fractional positive charge and hence some hydrogen-bonding capacity. Clark (73), however, considered that the prolonged action of triphenylethylene and its halogen derivatives indicates *in vivo* hydroxylation. Presumably the halogen atom aids this, but in the absence of some information concerning the mechanism of hydroxylation *in vivo* it is not possible to decide whether an inductive or a mesomeric effect of the halogen could aid hydroxylation. In view of what has been said previously concerning the importance of the hydroxyl group to the estrogenic function, the idea of *in vivo* hydroxylation of these triphenylethylenes seems preferable. 2-Ethyl-1,1,2-triphenylethylene (CLI) is quite active (115), suggesting that a steric effect of the ethyl group results in a closer resemblance of this molecule to that of diethylstilbestrol and is responsible for the increased activity relative to triphenylethylene. A steric effect is probably a second function of the halogen atom of the triphenylhalogenoethylenes. Rinderknecht and Rowe (357) prepared a series of 1,1,2-triphenylethylenes and ethanes which were substituted in the aliphatic portion and found CLII to have about 66 per cent of the activity of estrone similarly tested. The piperidino ether (CLIII) was surprisingly active, having about 30 per cent of the activity of estrone.

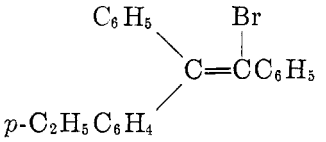
(c) Variation of the aliphatic portion and of aromatic substitution

9,α-Chlorobenzylidenefluorene (CLIV) is much less active than the corresponding chlorotriphenylethylene (144); this result would appear to emphasize

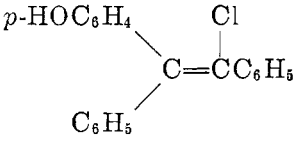
the importance of the halogen as a steric factor. 2-Bromo-1-(*p*-ethylphenyl)-1,2-diphenylethylene (CLV) is active at 0.1 mg. (251); in view of the previous discussion this suggests that the unsubstituted rings have a trans relation and will presumably be hydroxylated *in vivo*. As for triphenylethylene itself, the introduc-



CLIV

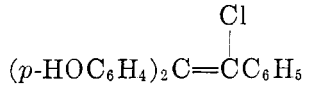


CLV

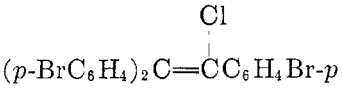


CLVI

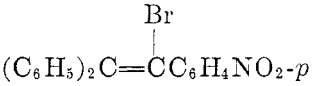
tion of hydroxyl groups into triphenylhalogenoethylenes enhances the estrogenic potency of the latter (115). Both geometrical isomers of 2-chloro-1-(*p*-hydroxyphenyl)-1,2-diphenylethylene (CLVI) are quite active (115) and of the same order. However, this is not necessarily unexpected, since the 2-phenyl group in both isomers will probably need to be hydroxylated; in view of the suggested function of a halogen atom this ring is probably most difficult to hydroxylate biochemically. 1,1-Bis(*p*-hydroxyphenyl)-2-chloro-2-phenylethylene (CLVII)



CLVII



CLVIII

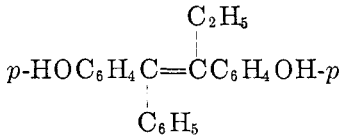


CLIX

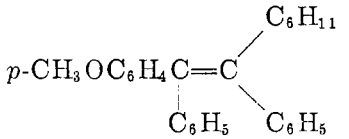
(115) gives 50 per cent response in mice subcutaneously at 0.2 microgram, an increase in potency over the corresponding monohydroxy compound. The dimethyl ether of CLVII in accordance with generality is two hundred times less active than the free phenol. 1,2-Tris(*p*-bromophenyl)-2-chloroethylene (CLVIII) is active, and its action is prolonged (480). This compound, however, is less prolonged in action than the corresponding 1,1,2-tris(*p*-bromophenyl)ethylene (480). This conclusion seems to apply to various similar halogen derivatives. Again it would seem that the para halogen atoms in CLVIII and related compounds are replaced biochemically by hydroxyl groups.

2-Bromo-1-(*p*-methylthiophenyl)-1,2-diphenylethylene is active at 1 mg. (301), but 2-bromo-1,1-bis(*p*-methylthiophenyl)-2-phenylethylene is inactive at 5 mg. (558); apparently in this series methylthio groups are unsuitable. It is interesting that 2-bromo-2-(*p*-nitrophenyl)-1,1-diphenylethylene (CLIX) is active (52) at 1 mg.; it would be valuable to have a comparison with the corresponding amino acompound. 1,2-Bis(*p*-hydroxyphenyl)-2-ethyl-2-phenylethylene (CLX) (115) is very potent, giving 50 per cent response in mice subcutaneously at 0.9 microgram; it is apparently the most potent triphenylethylene derivative known. Its high activity is hardly surprising, since it must have a

close structural resemblance to diethylstilbestrol. The highly substituted compound 2-cyclohexyl-1-(*p*-methoxyphenyl)-1,2-diphenylethylene (CLXI) and the corresponding ethoxy compound have slight activity (168). The reported triphenyl-



CLX



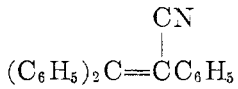
CLXI

ethylenes of estrogenic interest are collected in tables 17 and 18. It may be pointed out that the estrogenic activities of many triphenylethylenes have been reported in terms of the duration of estrus produced by a given dosage of estrogen (359).

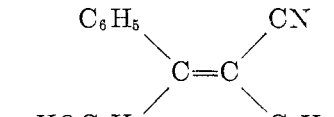
F. TRIPHENYLACRYLONITRILE AND ITS ANALOGS

Although triphenylacrylonitrile and related compounds are closely related structurally to the triphenylethylenes, the extensive work in this field justifies their separate consideration. The study of the estrogenic triphenylacrylonitriles is of more recent origin and is almost wholly due to the efforts of Buu-Hoï, Lacassagne, and their collaborators.

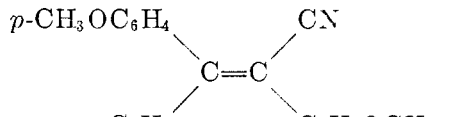
Triphenylacrylonitrile (CLXII) itself has been reported, by the same group (251), as having the same activity as triphenylethylene when used subcutane-



CLXII



CLXIII



CLXIV

ously in mice, 0.1 mg. of each giving full response. The reports of other workers appear to indicate that triphenylacrylonitrile is more active (209) than triphenylethylene. The linear cyano group can have no steric effect on the triphenylethylene system, and it seems that it can only have an effect on some physical property of the molecule.

Replacement of the cyano group by the carboxyl group decreases estrogenic potency (251) and use of the amido group abolishes activity (78). In contrast to the effect in the triphenylethylene series the introduction of a hydroxyl or potential hydroxyl group into triphenylacrylonitrile has little effect on activity. β-(*p*-Hydroxyphenyl)-α,β-diphenylacrylonitrile (CLXIII) (45) and *trans*-α,β-bis(*p*-methoxyphenyl)-β-phenylacrylonitrile (CLXIV) (78) have the same activity in mice as the parent compound. Various modifications of triphenylacrylonitrile may be made without removing estrogenic activity.

TABLE 17

Triphenylethylene analogs with variation of aromatic substitution

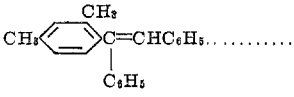
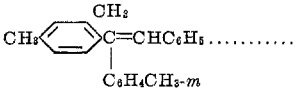
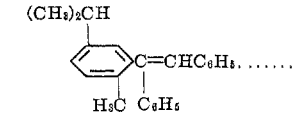
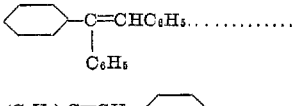
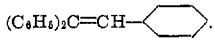
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
	°C.		
$(C_6H_5)_2C{=}CHC_6H_5$		300* (50%) > 200*§ (50%) 0.1 mg.* 10 mg.‖	(115) (115) (251) (209)
p-$CH_3C_6H_4C(C_6H_5){=}CHC_6H_5$	238–240/20 mm. (b.p.)		(44)
m-$CH_3C_6H_4C(C_6H_5){=}CHC_6H_5$	240–242/20 mm. (b.p.)		(44)
m-$CH_3C_6H_4C(C_6H_4CH_3\text{-}p){=}CHC_6H_5$	248–250/22 mm. (b.p.)		(44)
	198–200/1.8 mm. (b.p.)		(44)
		1 mg.*	(251)
p-$C_2H_5C_6H_4C(C_6H_5){=}CHC_6H_5$	200–202/2 mm. (b.p.)		(44)
		1 mg.*	(251)
	245–248/15 mm. (b.p.)	> 1 mg.*	(251)
p-$(CH_3)_3CC_6H_4C(C_6H_5){=}CHC_6H_5$	260–262/22 mm. (b.p.)		(44)
	245–248/1 mm. (b.p.)		(44)
p-$(CH_3)_3CC_6H_4C(C_6H_4CH_3\text{-}m){=}CHC_6H_5$	218–220/2.1 mm. (b.p.)		(44)
p-$C_6H_5C_6H_4C(C_6H_5){=}CHC_6H_5$	177.5		(44)
$(p\text{-}C_6H_5C_6H_4)_2C{=}CHC_6H_5$		10 mg.* (inactive)	(70)
	141/0.14 mm. (b.p.) 137–138/0.3 mm. (b.p.)	Inactive	(168) (362)
$(C_6H_5)_2C{=}CH$– 		Active*	(362)

TABLE 17—*Continued*

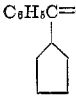
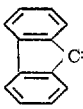
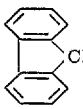
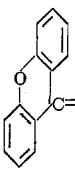
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
	°C.		
$(C_6H_{11})_2C{=}CHC_6H_5$	39		(372)
$C_6H_5C{=}CHC_6H_5$ 	118–120/9 × 10^{-2} mm. (b.p.)	Inactive	(168)
 $C{=}CHC_6H_5$	75–76	100 mg. (inactive) 50 mg. (weakly active)	(209) (144)
 CH_2		100 mg. (inactive)	(144)
 $C{=}CHC_6H_5$	114–114.5	100 mg. (inactive)	(209)
$p\text{-}HOC_6H_4C(C_6H_5){=}CHC_6H_5$		20* (50%) 44*§ (50%)	(115) (115)
$(p\text{-}HOC_6H_4)_2C{=}CHC_6H_5$	178	50* (slight effect) 75* (2 days) ¶ 100* (2 days) ¶ 200* (3 days) ¶ 375* (3 days) ¶ 750* (4 days) ¶ 1000*† (nil) ¶ 8* (50%) 20*§ (50%)	(483) (483) (483) (483) (483) (483) (483) (115) (115)
	178		(477)
	179–181	(266)	(266)
Methyl ethyl ether	240–250/15 mm. (b.p.)		(15)
Diethyl ether	74–75		(16)
Di-*n*-propyl ether	76–77		(477)
Diisopropyl ether	83–84		(477, 478)
Diallyl ether	71–73		(477, 478)
Dibenzyl ether	94		(477, 478)
Diacetate	84	1000* (9 days) ¶	(483)
Dipropionate	65–66	100* (6 days) ¶	(483)
$(p\text{-}CH_3OC_6H_4)_2CHCH_2C_6H_5$	98	2 mg.*	(45)
$p\text{-}HOC_6H_4C(C_6H_5){=}CHC_6H_4OH\text{-}p$		15* (50%) 10*§ (50%)	(115) (115)
$(p\text{-}HOC_6H_4)_2C{=}CHC_6H_4OH\text{-}p$	189–191		(396)
Triacetate	135–137		(396)
Trimethyl ether	100–101		(396, 397)
Triethyl ether	88		(480)

TABLE 17—*Continued*

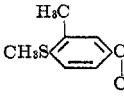
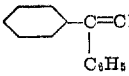
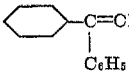
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
	°C.		
$(p\text{-}HOC_6H_4)_2C{=}CHC_6H_4OCH_3\text{-}p$	184–185		(396)
$(p\text{-}CH_3OC_6H_4)_2C{=}CHC_6H_4OH\text{-}p$			(396)
$p\text{-}CH_3OC_6H_4C(C_6H_4OH\text{-}p){=}CHC_6H_4OH\text{-}p$			(396)
$(p\text{-}C_6H_5CH_2OC_6H_4)_2C{=}CHC_6H_4OCH_3\text{-}p$	80–82		(396)
$(p\text{-}CH_3OC_6H_4)_2C{=}CHC_6H_4OCH_2C_6H_5\text{-}p$	139–141		(396)
$(p\text{-}C_6H_7OC_6H_4)_2C{=}CHC_6H_4OC_2H_5\text{-}h$	76		(59)
$p\text{-}CH_3SC_6H_4C(C_6H_5){=}CHC_6H_5$	100		(49)
$(p\text{-}CH_3SC_6H_4)_2C{=}CHC_6H_5$	106	1 mg.* (inactive)	(301)
		1 mg.*† (inactive)	(301)
	112		(558)
	280/17 mm. (b.p.)		(49)
$[p\text{-}(CH_3)_2NC_6H_4]_2C{=}CHC_6H_5$		5 mg.* (inactive)	(78)
$[p\text{-}(CH_3)_2NC_6H_4]_2C{=}CHC_6H_4OCH_3\text{-}p$	125–126		(397)
$(p\text{-}CH_3OC_6H_4)_2C{=}CHC_6H_4COOH\text{-}p$	204.5–205.5	1 mg. (inactive)	(303)
$(C_6H_5)_2C{=}CHC_6H_4CN\text{-}p$	107–109	1 mg.* (weakly active)	(480)
$(p\text{-}CNC_6H_4)_2C{=}CHC_6H_5$	151	5 mg.* (∞) ¶	(480)
$p\text{-}C_6H_5CH_2COC_6H_4C(C_6H_5){=}CHC_6H_5$	110–111	5 mg.* (∞) ¶	(480)
$(C_6H_5)_2C{=}CHC_6H_4COCH_3\text{-}p$	125	0.1 mg.	(52)
$(C_6H_5)_2C{=}CHC_6H_4COC_2H_5\text{-}p$	85	1 mg.	(52)
$p\text{-}HOC_6H_4C(C_6H_5){=}CHC_6H_4Cl\text{-}p$	139–140		(266)
$(p\text{-}CH_3OC_6H_4)_2C{=}CHC_6H_4Cl\text{-}p$	91	1000* (3 days) ¶	(482)
$(p\text{-}C_2H_5OC_6H_4)_2C{=}CHC_6H_4Cl\text{-}p$	76	1000* (weakly active)	(482)
$(p\text{-}CH_3OC_6H_4)_2C{=}CHC_6H_4Br\text{-}p$	107		(480)
$(p\text{-}C_2H_5OC_6H_4)_2C{=}CHC_6H_4Br\text{-}p$	110	1 mg.* (<125 days) ¶	(480)
$(C_6H_5)_2C{=}CHC_6H_4Cl\text{-}p$	76–77		(482)
$p\text{-}ClC_6H_4C(C_6H_5){=}CHC_6H_5$	89		(52)
$(C_6H_5)_2C{=}CHC_6H_4Br\text{-}p$	77	1000* (2 days) ¶	(482)
$(p\text{-}ClC_6H_4)_2C{=}CHC_6H_4Cl\text{-}p$	90–91		(482)
$(p\text{-}ClC_6H_4)_2C{=}CHC_6H_4Br\text{-}p$	118	5 mg.* (∞) ¶	(480)
$(p\text{-}ClC_6H_4)_2C{=}CHC_6H_4CH_3\text{-}p$	94	5 mg.* (∞) ¶	(480)
$(p\text{-}BrC_6H_4)_2C{=}CHC_6H_4Cl\text{-}p$	84		(482)
$(p\text{-}BrC_6H_4)_2C{=}CHC_6H_4Br\text{-}p$	101	5 mg.* (∞) ¶	(480)
$(p\text{-}IC_6H_4)_2C{=}CHC_6H_4Cl\text{-}p$	102–103		(482)
	79	Inactive	(168)
	57–58	Inactive	(168)

TABLE 17—*Continued*

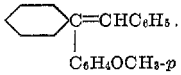
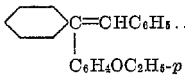
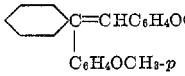
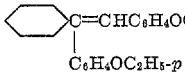
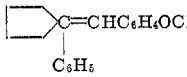
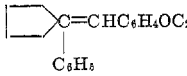
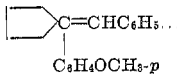
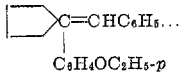
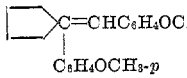
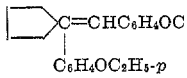
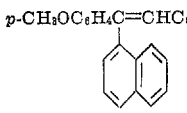
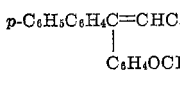
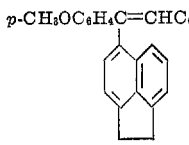
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
	°C.		
	108/4.7 × 10^{-5} mm. (b.p.)	Inactive	(168)
	118/1.3 × 10^{-4} mm. (b.p.)	Inactive	(168)
	168–174/5 × 10^{-2} mm. (b.p.)		(168)
	168/3 × 10^{-2} mm. (b.p.)		(168)
	78–79	Inactive	(168)
	100–102/2 × 10^{-3} mm. (b.p.)	Inactive	(168)
	104/1.3 × 10^{-4} mm. (b.p.)	Inactive	(168)
	114/7 × 10^{-4} mm. (b.p.)	Inactive	(168)
	165/1.5 × 10^{-3} mm. (b.p.)		(168)
	164/4.7 × 10^{-3} mm. (b.p.)		(168)
	102	1 mg.*	(47) (79)
	102	10 mg.* 2 mg.* (incompletely active)	(47) (79) (79)
		2 mg.*	(79)

TABLE 17—*Continued*

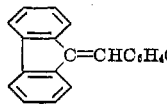
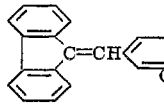
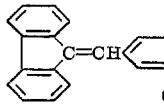
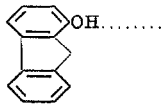
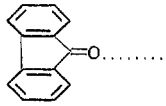
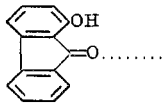
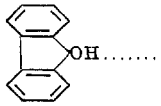
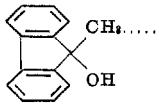
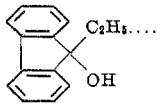
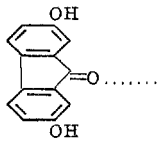
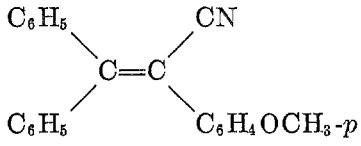
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
	°C.		
	128–128.5	100 mg. (inactive) 50 mg. (weakly active)	(209) (144)
		50 mg. (weakly active)	(144)
		50 mg. (weakly active)	(144)
		100 mg. (inactive)	(144)
		100 mg. (inactive)	(144)
		100 mg. (inactive)	(144)
Benzoate		100 mg. (inactive)	(144)
		100 mg. (inactive)	(144)
		100 mg. (inactive)	(144)
		100 mg. (inactive)	(144)
		100 mg. (weakly active)	(144)

TABLE 17—*Concluded*

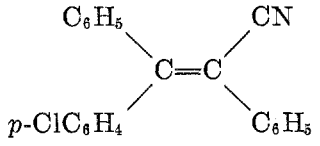
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
	°C.		
Dibenzoate		100 mg. (weakly active)	(144)
Dimethyl ether		100 mg. (inactive)	(144)
(p-$CH_3OC_6H_4$)$_2$C=CH_2	142–143		(341)
		5 mg.* (inactive)	(481)
(p-$C_2H_5OC_6H_4$)$_2$C=CH_2	142		(481)
(p-$C_3H_7OC_6H_4$)$_2$C=CH_2	54		(481)
(p-$C_6H_5CH_2OC_6H_4$)$_2$C=CH_2	186		(481)
(p-$C_2H_5OC_6H_4$)$_2$C=CHCOOH	134		(480)
(p-$C_3H_7OC_6H_4$)$_2$C=CHCOOH	128–129		(480)

* In mice.
† Orally.
§ Administered intravaginally.
‖ Administered in divided dosage over a period of 2.5 days.
¶ The period of median duration of estrus.

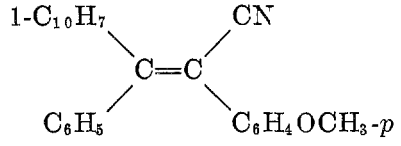
β,β-Diphenyl-α-(p-tolyl)acrylonitrile (CLXV) (251) is active at 1 mg. in mice subcutaneously; *trans*-β-(p-chlorophenyl)-α,β-diphenylacrylonitrile (CLXVI) is active at the same level (251). Replacement of a β-phenyl group by various



CLXV



CLXVI



CLXVII

polycyclic groups is possible without destroying activity, and *cis*-α-(p-methoxyphenyl)-β-(1-naphthyl)-β-phenylacrylonitrile (CLXVII) is one of the most active acrylonitriles, being active in the rat subcutaneously at 0.01 mg. (46).

The data relating to the estrogenic activities of the various acrylonitriles are collected in table 19.

VII. Ring-closed Analogs of Diethylstilbestrol, Hexestrol, and Dienestrol

Various chrysene, phenylnaphthalene, and phenylindene derivatives (462) were synthesized earlier as ring-closed analogs of the stilbene estrogens. It was thought that these ring-closed structures would more closely simulate the general

TABLE 18

Triphenylethylene analogs with variation of the aliphatic portion and aromatic substitution

Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
A. Variation of the aliphatic portion			
	°C.		
$(C_6H_5)_2C{=}C(C_6H_5)Cl$		77* (50%)	(115)
		0.89*§ (50%)	(115)
		29	(14)
$(C_6H_5)_2C{=}C(C_6H_5)Br$		<0.01 mg.*	(251)
		33.5 (incomplete)	(14)
$(C_6H_5)_2C{=}C(C_6H_5)I$	125	38.2 (incomplete)	(14)
$(C_6H_5)_2C{=}C(C_6H_5)C_2H_5$		12* (50%)	(115)
		4.4*§ (50%)	(115)
$(C_6H_5)_2CHCOC_6H_5$		10‖ (I.U./mg.)	(357)
		40** (I.U./mg.)	(357)
$(C_6H_5)_2C(CH_3)COC_6H_5$		6000 (I.U./mg.)	(357)
$(C_6H_5)_2C(C_2H_5)COC_6H_5$		1000 (I.U./mg.)	(357)
$(C_6H_5)_2C(CH_2CH_2\overset{+}{N}H\text{-}O)COC_6H_5\ Cl^-$		<100 (I.U./mg.)	(357)
$(C_6H_5)_2C{=}C(C_6H_5)OCOCH_3$		400‖ (I.U./mg.)	(357)
		400** (I.U./mg.)	(357)
$(C_6H_5)_2C{=}C(C_6H_5)OC_2H_5$		5000 (I.U./mg.)	(357)
$(C_6H_5)_2C{=}C(C_6H_5)OC_3H_7$		500 (I.U./mg.)	(357)
$(C_6H_5)_2C{=}C(C_6H_5)(OCH_2CH_2\overset{+}{N}H\text{-})\ Cl^-$		3000 (I.U./mg.)	(357)
$(C_6H_5)_2C{=}C(C_6H_5)(OCH_2CH_2\overset{+}{N}H(CH_3)_2)\ Cl^-$		200 (I.U./mg.)	(357)
$(C_6H_5)_2C{=}C(C_6H_5)(OCH_2CH_2\overset{+}{N}H\text{-}O)\ Cl^-$		100 (I.U./mg.)	(357)
$(C_6H_5)_2C{=}C(C_6H_5)(OCH_2CH_2\overset{+}{N}(CH_3)\text{-}O)\ Cl^-$		<400‖ (I.U./mg.) <100** (I.U./mg.)	
$(C_6H_5)_2CHCH(C_6H_5)(OCH_2CH_2\overset{+}{N}H\text{-}O)\ Cl^-$		<400 (I.U./mg.)	(357)

TABLE 18—*Continued*

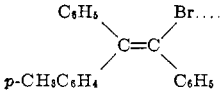
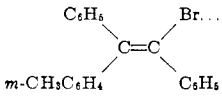
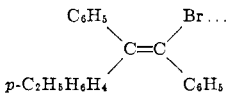
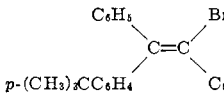
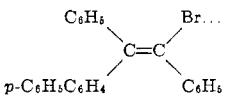
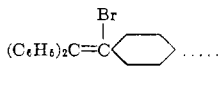
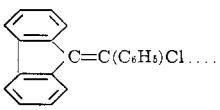
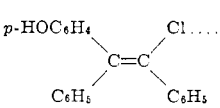
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
B. Variation of the aliphatic portion and aromatic substitution			
	°C.		
	113.5–114		(44)
		0.01 mg.*	(251)
	Cis-trans mixture		(44)
	112.5–113		(44)
		0.1 mg.*	(251)
		1 mg.*	(251)
	181–182 (d.)		(44)
		0.1 mg.*	(251)
	112	1 mg.*	(362)
		20 mg.* (15 days)¶	(362)
		50 mg. (strongly active)	(144)
	101–103		
	136–138 (β-form)		
			(266)
			(266)
		2.3* (50%)	(115)
		0.0014*§ (50%)	(115)
		1.6* (50%) (isomeric form)	(115)
		0.0013§ (50%) (isomeric form)	(115)
$(p\text{-HOC}_6H_4)_2C{=}C(C_6H_5)Cl$		0.2* (50%)	(115)
		0.0010*§ (50%)	(115)
Dimethyl ether		40* (50%)	(115)
		1.2*§ (50%)	(115)
Ethyl methyl ether	210–220/1 mm. (b.p.)		(15)
Diethyl ether	86–88		(477)
Dipropyl ether	102		(477)
Diisopropyl ether	106		(477)

TABLE 18—*Continued*

Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
B. Variation of the aliphatic portion and aromatic substitution—*Continued*			
	°C.		
$(p\text{-}CH_3OC_6H_4)_2C{=}CC_6H_4OCH_3\text{-}p$ Cl	113–114		(397)
		1 mg.† (2 days) ¶	(504)
		5 mg.† (17 days) ¶	(504)
		1 mg. (53 days) ¶	(504)
		6 mg.††	(367)
$(p\text{-}CH_3OC_6H_4)_2C{=}CC_6H_4OC_2H_5\text{-}p$ Cl	82		(166)
$(p\text{-}ClC_6H_4)_2C{=}CC_6H_4Br\text{-}p$ Cl	170–171	5 mg.* (12 days) ¶	(480)
$(p\text{-}BrC_6H_4)_2C{=}CC_6H_4Br\text{-}p$ Cl	189	1 mg.* (11 days) ¶	(480)
		5 mg.* (15 days) ¶	(480)
$(p\text{-}C_2H_5OC_6H_4)_2C{=}CHCl$	76		(481)
$(p\text{-}C_3H_7OC_6H_4)_2C{=}CHCl$	Oil		(481)
$(p\text{-}C_6H_5CH_2OC_6H_4)_2C{=}CHCl$	98–99		(481)
C_6H_5, Br; $p\text{-}HOC_6H_4$, C_6H_5	158–160		(266)
		2.7* (50%)	(115)
		0.011*§ (50%)	(115)
		3.0* (50%) (isomeric form)	(115)
		0.01*§ (50%) (isomeric form)	(115)
Methyl ether		105* (50%)	(115)
		0.70*§ (50%)	(115)
		100* (50%) (isomeric form)	(115)
		0.49*§ (50%) (isomeric form)	(115)
Ethyl ether	91–92		(59)
	83–84 (polymorphic form)		(59)
	111 (isomeric form)		(59)
Propyl ether	118		(59)
$(C_6H_5)_2C{=}CC_6H_4OCH_3\text{-}p$ Br	130		(59)
$(C_6H_5)_2C{=}CC_6H_4OC_2H_5\text{-}p$ Br	95		(59, 166)
$(C_6H_5)C{=}CC_6H_4OC_3H_7\text{-}p$ Br	92		(59, 166)

TABLE 18—*Continued*

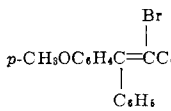
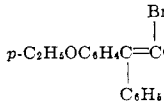
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
B. Variation of the aliphatic portion and aromatic substitution—*Continued*			
	°C.		
$(p\text{-}HOC_6H_4)_2C{=}C(C_6H_5)Br$	205–207	1* (nil)	(483)
		2* (weakly active)	(483)
		10* (4 days)¶	(483)
		15* (5 days)¶	(483)
		100* (8 days)¶	(483)
		10*† (weakly active)	(483)
		20*† (3 days)¶	(483)
		25*† (3 days)¶	(483)
		50*† (3 days)¶	(483)
		100*† (3 days)¶	(483)
		0.54* (50%)	(115)
		0.0014*§ (50%)	(115)
	209–210 (d.)		(266)
	205–207		(477)
Diacetate	157–159	0.2* (weakly active)¶	(483)
		0.5* (5 days)¶	(483)
		1* (5 days)¶	(483)
		2* (5 days)¶	(483)
		10* (9 days)¶	(483)
		1000* (24 days)¶	(483)
		10*† (3 days)¶	(483)
		50*† (6 days)¶	(483)
Dimethyl ether		51* (50%)	(115)
		1.0*§ (50%)	(115)
			(387)
Ethyl methyl ether	78		(15)
Diethyl ether	96–97		(16)
	97		(59)
	87 (polymorphic form)		(59)
		10*† (7 days)¶	(482, 483)
		50*† (21 days)¶	(482, 483)
		500*† (38 days)¶	(482, 483)
		42.3 (incomplete)	(14)
Ethyl propyl ether	ca. 70 (isomer mixture)		(59, 167)
Dipropyl ether	101		(477)
Diisopropyl ether	119–120		(477)
		100* (6 days)	(483)
		1000* (128 days)	(483)
	100.5		(167)
Di-*sec*-butyl ether	88		(167)
			
$p\text{-}CH_3OC_6H_4C{=}CC_6H_4OC_2H_5\text{-}p$	106		(59, 166)
	153 (isomeric form)		(59, 166)
			
$p\text{-}C_2H_5OC_6H_4C{=}CC_6H_4OC_2H_5\text{-}p$	133–134		(16)

TABLE 18—*Continued*

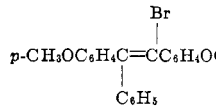
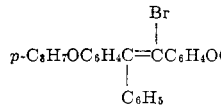
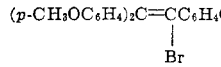
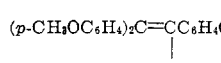
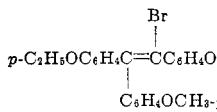
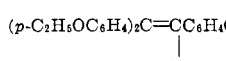
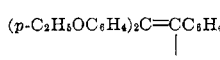
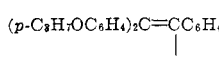
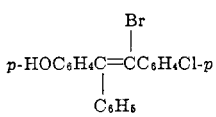
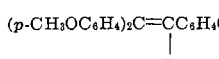
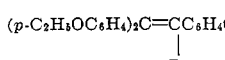
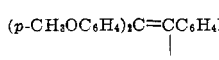
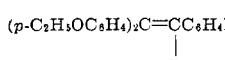
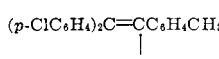
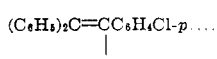
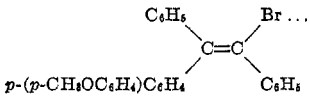
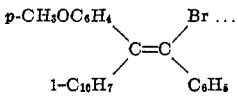
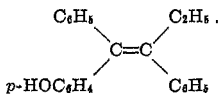
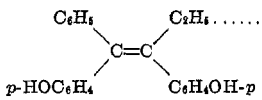
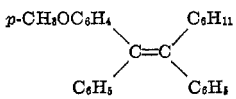
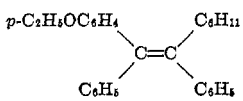
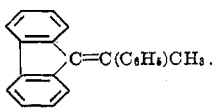
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
B. Variation of the aliphatic portion and aromatic substitution—*Continued*			
	°C.		
	85		(59, 166)
	71		(59)
	119–120.5		(397)
	76		(59, 166)
	136–138		(15)
	81		(59)
	81–82		(59, 166)
	86		(59, 166)
	141–143		(266)
	112	100* (5 days) ¶ 10*† (weakly active) 100*† (16 days) ¶	(482) (482) (482)
	98	100* (3 days) ¶ 10*† (3 days) ¶ 100*† (16 days) ¶	(482) (482) (482)
	114		(480)
	99	0.1 mg.* (8 days) ¶ 0.5 mg.* (>130 days) ¶	(480) (480)
	158	5 mg.* (>90 days) ¶	(480)
	114–115	100* (11 days) ¶	(482)

TABLE 18—*Continued*

Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
B. Variation of the aliphatic portion and aromatic substitution—*Continued*			
	°C.		
$C_6H_5C(Br)=CC_6H_5$ C_6H_4Cl-*p*	157	5 mg.	(52)
$(C_6H_5)_2C(Br)=CC_6H_4Br$-*p*	114-115	1000* (56 days) ¶	(482)
(*p*-$ClC_6H_4)_2C(Br)=CC_6H_5Cl$-*p*	166	5000* (5 days) ¶	(443)
(*p*-$ClC_6H_4)_2C(Br)=CC_6H_4Br$-*p*	174		(480)
(*p*-$BrC_6H_4)_2C(Br)=CC_6H_4Cl$-*p*	168	5000* (10 days) ¶	(482)
(*p*-$BrC_6H_4)_2C(Br)=CC_6H_4Br$-*p*	183	1 mg.* (7 days) ¶	(480)
(*p*-$IC_6H_4)_2C(Br)=CC_6H_4Cl$-*p*	158-160	5000* (10 days) ¶	(482)
(*p*-$CH_3OC_6H_4)_2C(Br)=CC_6H_4COOH$-*p*	197-198	1 mg. (inactive)	(303)
p-$ClC_6H_4C(Br)=CC_6H_4NO_2$-*p* C_6H_5	163		(52)
$(C_6H_5)_2C(Br)=CC_6H_4NO_2$-*p*	180	0.1 mg.	(52)
p-$CH_3SC_6H_4C(Br)=CC_6H_5$ C_6H_5	131		(49)
	105	1 mg.*	(301)
(*p*-$CH_3SC_6H_4)_2C=C(C_6H_5)Br$	133	5 mg. (inactive)	(558)
(*p*-$C_2H_5SC_6H_4)_2C=C(C_6H_5)Br$	74		(362)
C_6H_5, Br, $C=C$, C_6H_5, CH_3S, CH_3	124		(49)
p-$CH_3OC_6H_4$, Br, $C=C$, *p*-$C_6H_5C_6H_4$, C_6H_5	138-140		(47)
		0.1 mg.*	(79)

TABLE 18—*Concluded*

Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
B. Variation of the aliphatic portion and aromatic substitution—*Concluded*			
	°C.		
		1 mg.*	(79)
			(47)
		7.7* (50%) 0.015*§ (50%)	(115) (115)
		0.9* (50%) 0.00065*§ (50%)	(115) (115)
	127–127.5	Weakly active	(168)
	127.5–129.5	Weakly active	(168)
		50 mg. (weakly active)	(144)
$(p\text{-}CH_3OC_6H_4)_2C{=}CHBr$	84	5 mg.* (inactive)	(481)
$(p\text{-}C_2H_5OC_6H_4)_2C{=}CHBr$	64		(481)
$(p\text{-}C_3H_7OC_6H_4)_2C{=}CHBr$	42		(481)
$(p\text{-}C_6H_5CH_2OC_6H_4)_2C{=}CHBr$	119–120		(481)

* In mice.
† Orally.
§ Administered intravaginally.
‖ Administered in aqueous ethanol.
** Administered in peanut oil.
¶ The period of median duration of estrus.
†† Administered in four daily doses; produced cornification of the human female vagina.

TABLE 19

Estrogenic activities of triphenylacrylonitrile and its analogs

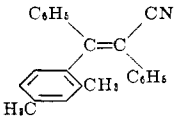
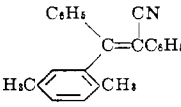
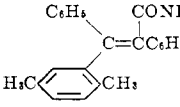
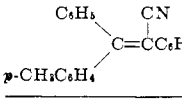
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose	References
	°C.		
$(C_6H_5)_2C{=}C(C_6H_5)CN$		0.1 mg.*	(251)
$(C_6H_5)_2C{=}C(C_6H_5)COOH$	213		(50)
		5 mg.*	(251)
$(C_6H_5)_2C{=}C(C_6H_5)CONH_2$		10 mg.* (inactive)	(78)
$p\text{-}CH_3C_6H_4C{=}C(C_6H_5)CN$ $\vert$ C_6H_5	123		(50)
$p\text{-}CH_3C_6H_4C{=}C(C_6H_5)COOH$ $\vert$ C_6H_5	208–210		(50)
$(C_6H_5)_2C{=}CC_6H_4CH_3\text{-}p$ $\vert$ CN	153		(50)
		1 mg.*	(251)
$(C_6H_5)_2C{=}CC_6H_4CH_3\text{-}p$ $\vert$ $COOH$	237–238		(50)
		1 mg.*	(78)
$(C_6H_5)_2C{=}CC_6H_4CH_3\text{-}p$ $\vert$ $CONH_2$	216		(50)
$(C_6H_5)_2C{=}CC_6H_4CH_3\text{-}m$ $\vert$ CN	122		(50)
		1 mg.*	(251)
$(C_6H_5)_2C{=}CC_6H_4CH_3\text{-}m$ $\vert$ $CONH_2$	177		(50)
	134		(47)
	133		(47)
	ca. 203–204		(47)
	114–115		(50)
		1 mg.*	(78)

TABLE 19—*Continued*

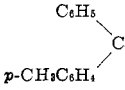
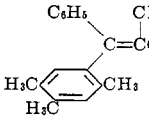
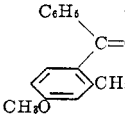
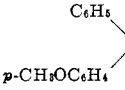
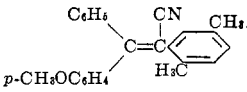
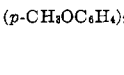
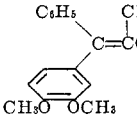
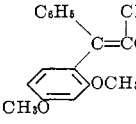
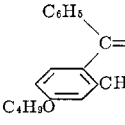
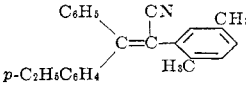
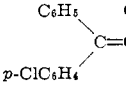
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose	References
	°C.		
	237		(50)
	>230/10 mm. (b.p.)		(47)
	134–135		(47)
	113–115		(51)
		1 mg.* (inactive)	(45)
	110–111	0.1 mg.*	(50) (78)
	165–166		(51)
	200–202 (cis form)		(51)
		1 mg.*	(45)
		2 mg.* (inactive)	(45)
	147–148		(50)

TABLE 19—*Continued*

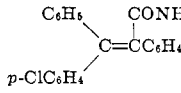
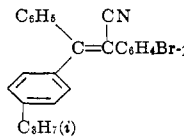
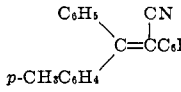
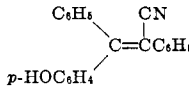
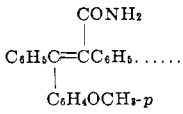
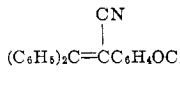
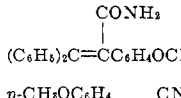
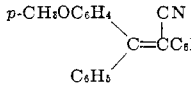
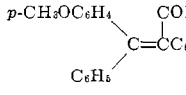
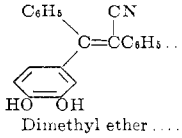
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose	References
	°C.		
	197		(50)
		1 mg.* (inactive)	(45)
		2 mg.*	(45)
		0.1 mg.*	(45)
Methyl ether	166 (cis form)		(50)
	124–125 (trans form)		(50)
n-Propyl ether	129–130		(47)
		0.1 mg.*	(79)
		1 mg.* (1 month) ¶	(79)
	105 (isomeric form)		
n-Butyl ether	114		(47)
		0.1 mg.*	(79)
	196–198 (cis form) 176–180 (trans form)		(50)
	149		(50)
		0.1 mg.*	(251)
	198		(50)
	122–125 (trans form)		(50)
		0.1 mg.*	(78)
	243 (trans form)		(50)
		2 mg.* (incomplete)	(45)
Dimethyl ether	181 (cis form)		(50)

TABLE 19—*Continued*

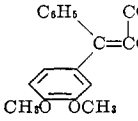
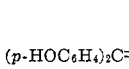
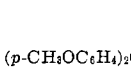
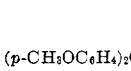
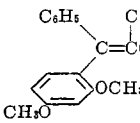
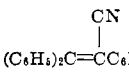
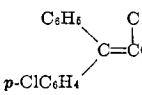
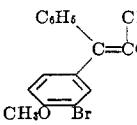
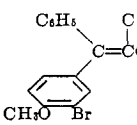
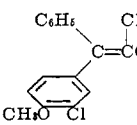
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose	References
	°C.		
		1 mg.*	(78)
	143–145 (trans form)		(50)
	198 (trans form)		(50)
			
(*p*-$HOC_6H_4)_2C{=}CC_6H_5$		<0.75 mg.*	(45)
Dimethyl ether	159		(50)
		0.01 mg.*	(251)
Diethyl ether	130–131		(51)
			
(*p*-$CH_3OC_6H_4)_2C{=}CC_6H_5$	209		(50)
		3 mg.* (inactive)	(78)
			
(*p*-$CH_3OC_6H_4)_2C{=}CC_6H_5$	169		(51)
		1 mg.*	(251)
	146–148		(50)
		1 mg.*	(78)
			
$(C_6H_5)_2C{=}CC_6H_4Br$-*p*	152–153		(51)
	139–140 (trans form)		(50)
		1 mg.*	(251)
	135		(51)
	159		(51)
	160		(51)

TABLE 19—*Continued*

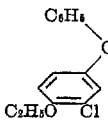
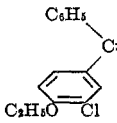
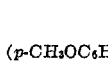
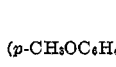
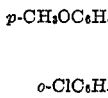
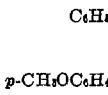
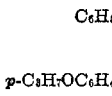
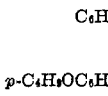
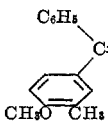
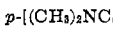
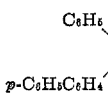
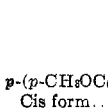
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose	References
	°C.		
	158		(51)
	173		(51)
	175–176		(51)
	223–225		(51)
		0.1 mg.*	(45)
		1 mg.*	(45)
		1 mg.*	(45)
		0.1 mg.*	(45)
			
Cis form		2 mg.* (incomplete)	(45)
Trans form		2 mg.* (incomplete)	(45)
	185		(50)
	210		(47)
		0.1 mg.*	(79)
	184 (isomeric form)		(47)
			(45)
Cis form		1 mg.*	(45)
Trans form		1 mg.*	(45)

TABLE 19—*Continued*

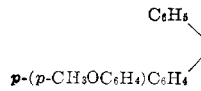
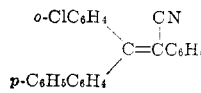
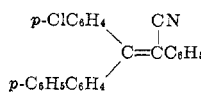
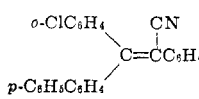
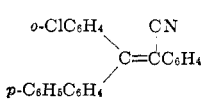
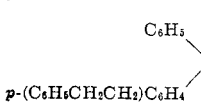
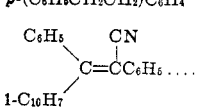
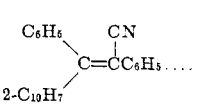
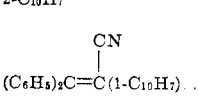
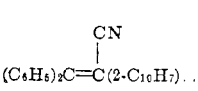
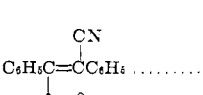
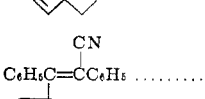
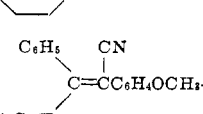
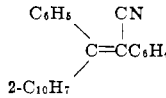
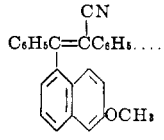
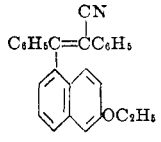
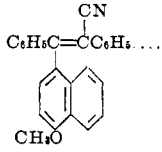
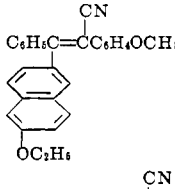
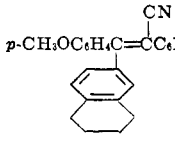
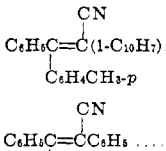
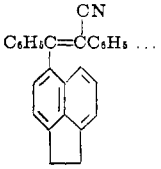
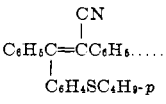
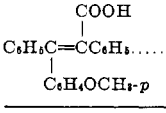
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose	References
	°C.		
		2 mg.* (inactive)	(45)
	177		(47)
		1 mg.*	(45)
		1 mg.* (inactive)	(45)
		2 mg.* (inactive)	(45)
	295–320/12 mm. (b.p.)		(47)
			
	176–178 (cis form)		(47, 51)
		0.1 mg.	(46)
	ca. 129–130 (trans form)		(47)
	180–181		(47)
		1 mg. (inactive)	(46)
	170–172		(51)
		1 mg.	(46)
	164–165		(51)
		0.1 mg.	(46)
		1 mg.*	(79)
	128–130		(47)
	140–141 (isomeric form)		(47)
	166–167 (cis form)		(51)
		0.01 mg.	(46)
		1 mg. (8 days) ¶	(46)

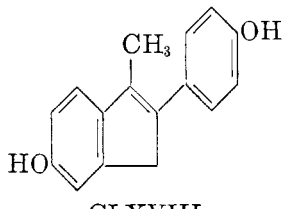
TABLE 19—*Concluded*

Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose	References
	°C.		
		1 mg.*	(45)
Methyl ether	202		(47)
		0.01 mg.	(46)
	160 (cis form)		(47)
	146 (trans form)		(47)
			
Cis form		0.1 mg.	(46)
		1 mg. (36 days) ¶	(46)
Trans form		0.1 mg.	(46)
		1 mg. (16 days) ¶	(46)
	166–167		(47)
		2 mg. (inactive)	(46)
	185		(47)
		0.01 mg.	(46)
		0.1 mg. (3 weeks) ¶	(46)
	184		(47)
	171 (isomeric form)		(47)
	126–127		(51)
		2 mg. (inactive)	(46)
	232		(47)
	194 (isomeric form)	1–2 mg.* (incomplete)	(79)
			(47)
		10 mg.* (strongly active)	
		5 mg.*	

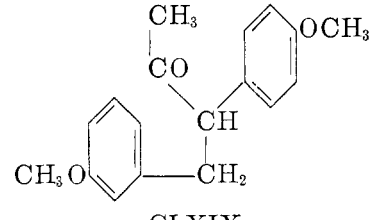
* In mice. † Orally. ¶ The period of duration of estrus.

structure of natural estrogens. The activity in this field has continued and highly potent estrogens have been encountered.

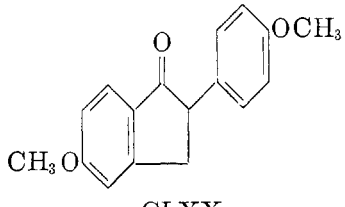
The compound 6-hydroxy-2-(*p*-hydroxyphenyl)-3-methylindene (CLXVIII), obtained by Salzer (377, 378), has presented a structural and biological problem. Salzer found a high estrogenic activity for the substance, but Adler and Hagglund (4) found it inactive at 100 micrograms and the inactivity has been confirmed by Solmssen and Wenis (466). Salzer obtained CLXVIII by cyclization of the ketone CLXIX, followed by demethylation. The cyclization was considered to proceed in the position para to the methoxyl group, but in the patent reference Salzer



CLXVIII



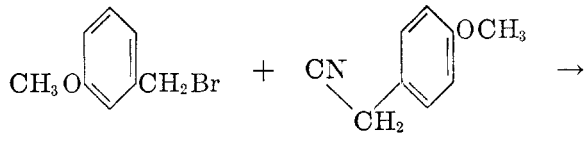
CLXIX

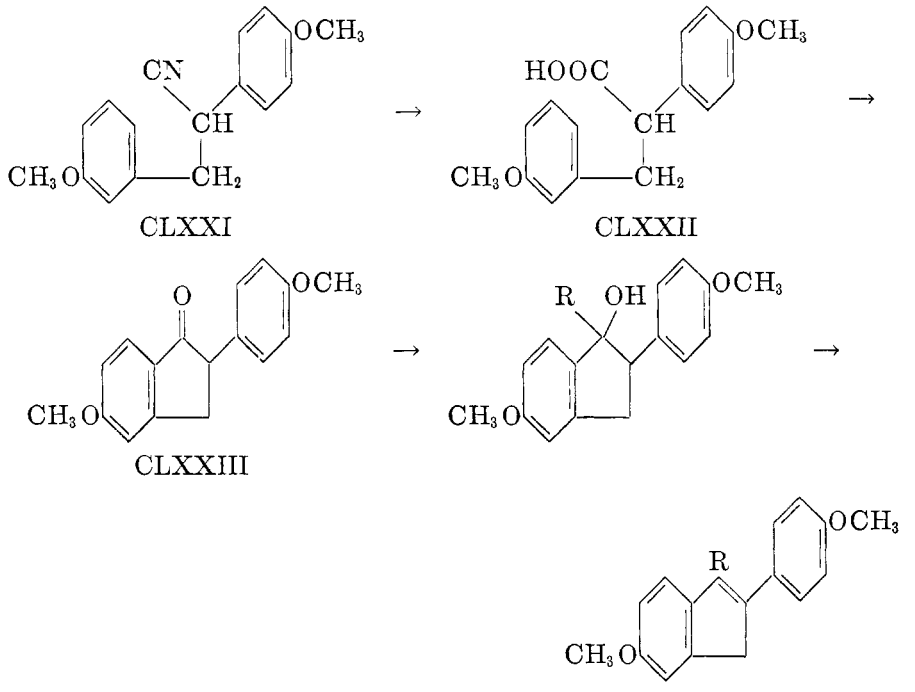


CLXX

indicated that cyclization may occur ortho to this group. By a different route Solmssen (463) obtained two isomeric indanone intermediates melting at 96°C. and 172°C. The lower-melting isomer only could be reacted with a Grignard reagent and so was considered to be the para cyclized product (CLXX); however the evidence is not final. Silverman and Bogert (413) obtained additional evidence of the structure of Solmssen's indanone intermediates by a new synthesis. *m*-Methoxybenzyl bromide was condensed with *p*-methoxybenzyl cyanide by means of sodium amide in liquid ammonia and subsequent reaction in benzene solution, giving a 71 per cent yield of α-(*p*-methoxyphenyl)-β-(*m*-methoxyphenyl)-propionitrile (CLXXI). Hydrolysis of the nitrile gave an 85 per cent yield of the corresponding acid (CLXXII), which was cyclized to 6-methoxy-2-(*p*-methoxyphenyl)-3-indanone (CLXXIII) in 82 per cent yield by the action of stannic chloride on the acid chloride in benzene solution.

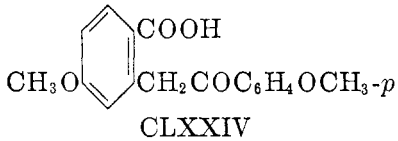
This cyclization failed with sulfuric acid, phosphorus oxychloride, or in an intramolecular Friedel–Crafts reaction using aluminum chloride.



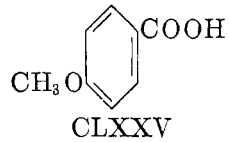


CLXXI CLXXII CLXXIII

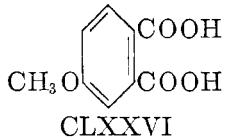
The indanone CLXXIII melted at 96–97°C. and was identical to the lower-melting compound obtained by Solmssen. The constitution of CLXXIII as the para cyclized compound was established by oxidation, 2-(*p*-methoxyphenacyl)-anisic acid (CLXXIV), anisic acid (CLXXV), and 4-methoxyphthalic acid (CLXXVI) being obtained. Conclusive evidence of the structures of these inter-



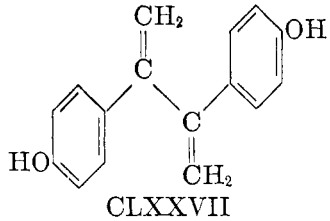
CLXXIV



CLXXV



CLXXVI

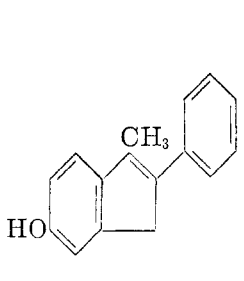


CLXXVII

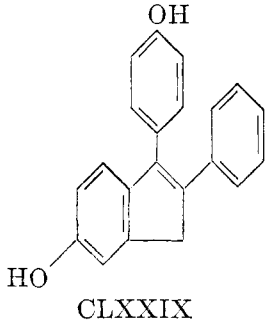
mediates and the indenes derived from them was provided by Adler and Hagglund (4), who cyclized the symmetrical 2,3-bis(*p*-hydroxyphenyl)butadiene (CLXXVII) and its diacetate, using boron trifluoride in chloroform, and obtained CLXVIII and its diacetate.

By their synthesis Silverman and Bogert obtained 6-methoxy-2-(*p*-methoxyphenyl)-3-methylindene in 60 per cent yield by a Grignard reaction on CLXXIII.

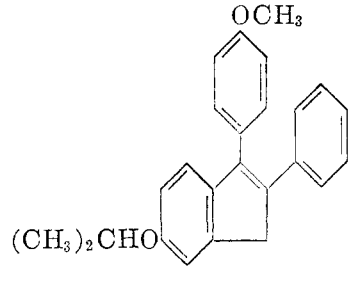
Similarly, the 3-ethyl, 3-cyclohexyl, and 3-phenyl analogs were obtained in 61, 55, and 45 per cent yields, respectively. In agreement with previous experience these compounds proved difficult to demethylate; the method used was refluxing with 48 per cent hydrobromic acid in acetic acid in a carbon dioxide atmosphere, as previously described by Solmssen (463). By this method 3-ethyl-6-hydroxy-2-(*p*-hydroxyphenyl)indene (m.p. 176–177°C.) was obtained but only in 2–3 per cent yield; it was unstable except as the diacetate. Solmssen's earlier preparation of this hydroxyindene, melting at 136°C., was apparently impure. The intermediate in the Solmssen and Silverman–Bogert synthesis was CLXXII; this was obtained by Davies and Morris (86) and by an improved procedure by Morris (294). A Perkin condensation with *p*-nitrophenylacetic acid and *m*-nitrobenzaldehyde gave *m*-nitro-α-(*p*-nitrophenyl)cinnamic acid, which on reduction with ammoniacal hydrogen sulfide or catalytically using Raney nickel gave the diamine. The diazo reaction followed by hydrogenation and methylation gave the propionic acid CLXXII, melting at 104°C. By the use of the appropriate reactants *m*-methoxy-, *m*-isopropoxy-, and *m*-benzyloxy-α-phenylcinnamic acids were obtained, and similarly the *m*-hydroxy analog was obtained. The isopropoxy and benzyloxy compounds were prepared in the hope that the indenes finally obtained might be more easily dealkylated than the methyl ethers. The cinnamic acids were hydrogenated as their sodium salts in aqueous solution, using Raney nickel; catalytic hydrogenation in alcohol failed. The *m*-methoxy and *m*-isopropoxy acids were reduced smoothly to the propionic acid, but hydrogenolysis accompanied hydrogenation of the *m*-benzyloxy acid and β-(*m*-hydroxyphenyl)-α-phenylpropionic acid was obtained. This acid was also prepared by hydrogenation of the *m*-hydroxy-α-phenylcinnamic acid. β-(*m*-Methoxyphenyl)-α-phenylpropionic acid and the *m*-isopropoxy analog were readily cyclized to the indanones by the action of stannic chloride in benzene on their acid chlorides. The *m*-benzyloxy analog was, however, debenzylated under these conditions, and phosphorus pentoxide in benzene or sulfuric acid failed to cyclize the corresponding propionic acid. The β-(*m*-hydroxyphenyl)-α-phenylpropionic acid could not be benzoylated, and although the acetate was obtained this could not be cyclized.



CLXXVIII



CLXXIX

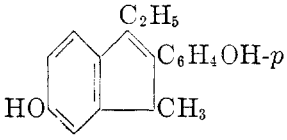


CLXXX

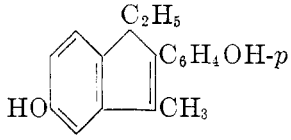
Attempts to dealkylate 6-methoxy-3-methyl-2-phenylindene and the 6-isopropoxy analog using hydrogen iodide–acetyl iodide and hydrogen bromide–acetic

anhydride failed, as apparently water is necessary; hydrobromic acid–acetic acid did produce some dealkylation. Morris found 6-hydroxy-3-methyl-2-phenylindene (CLXXVIII) active at 5 mg.; presumably the higher dosage is due to the 2-phenyl group lacking a hydroxyl group. The indene CLXXIX is also active at the 5 mg. level, but this is a much smaller activity than that of the corresponding triphenylethylene. The related ether (CLXXX) is inactive at 5 mg. While 6-hydroxy-2-(*p*-hydroxyphenyl)-3-methylindene (CLXVIII), previously discussed, is inactive at 100 micrograms in rats, the 3-ethyl analog at 1.2 micrograms subcutaneously in mice results in 50 per cent response. These results suggest an important steric function of the 3-alkyl group.

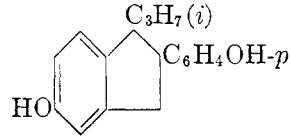
Hausmann and Wilder Smith (158) observed that losses of dienestrol occurred when dienestrol containing urines was refluxed with hydrochloric acid. These losses were accounted for when it was found that dienestrol itself, when refluxed under nitrogen with hydrochloric acid, gave good yields of a compound identified as 3-ethyl-6-hydroxy-2-(*p*-hydroxyphenyl)-1-methylindene (CLXXXI).



CLXXXI



CLXXXII

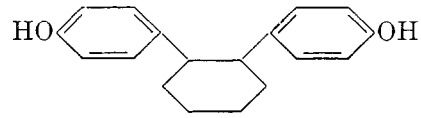


CLXXXIII

This compound, also referred to as indenestrol A, had been obtained previously in 92 per cent yield by Adler and Hagglund (4) by cyclizing dienestrol with boron trifluoride in chloroform. By the same method isodienestrol gave a 70–80 per cent yield of CLXXXI. An 82 per cent yield of the compound was obtained by Hausmann and Wilder Smith by refluxing dienestrol in acetic acid containing a drop of sulfuric acid; phosphoric acid also effected the cyclization. Adler and Hagglund (4) found that the diacetate of CLXXXI was reversibly isomerized by heating with pyridine, yielding after hydrolysis the isomer CLXXXII. Both isomers are highly active, but the biological results, which come from different sources, make it difficult to decide whether the introduction of a 1-methyl group into 3-ethyl-6-hydroxy-2-(*p*-hydroxyphenyl)indene is beneficial to estrogenic activity.

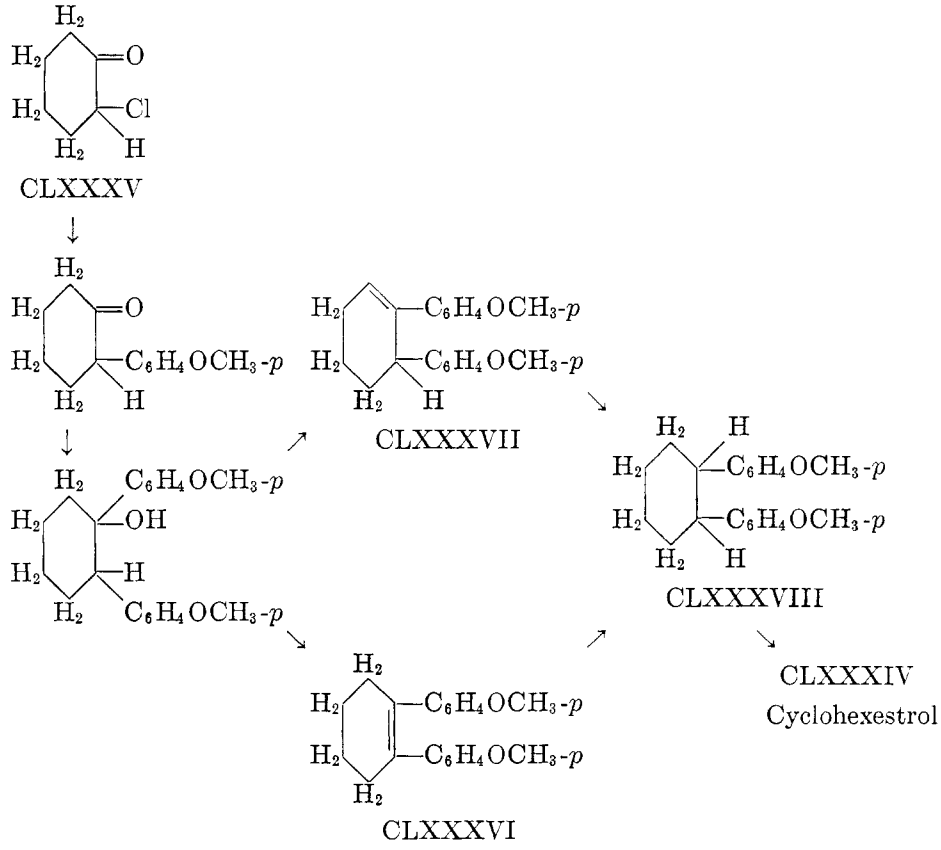
Salzer (377) hydrogenated CLXVIII to the indan but reported this hexestrol analog inactive; Solmssen (463), however, found the corresponding 3-ethylindan only slightly less active than its indene. Unlike the estrogenic indenes, the indans have satisfactory stability, a characteristic which adds further to their interest. In view of these biological results Solmssen and Wenis (466) extended the series of 3-alkylindans. The key intermediate was prepared in improved yield by a Perkin reaction between *m*-methoxybenzaldehyde and *p*-methoxyphenylacetic acid. Reduction of the cinnamic acid followed by ring closure with anhydrous hydrogen fluoride gave almost exclusively the desired indanone and in 81.4 per cent yield. Treatment with the appropriate Grignard reagent followed by dehydration with hydrochloric acid gave the 3-alkylindenes. Hydrogenation of these over 10 per cent palladium on charcoal gave the series of 3-alkyl-6-methoxy-2-(*p*-methoxyphenyl)indans; these were demethylated by 48 per cent hydro-

bromic acid–acetic acid. Optimum activity was found with the 3-isopropyl compound (CLXXXIII), 0.7 microgram of which gave 50 per cent response subcutaneously in rats. However, as the authors pointed out, comparison within the



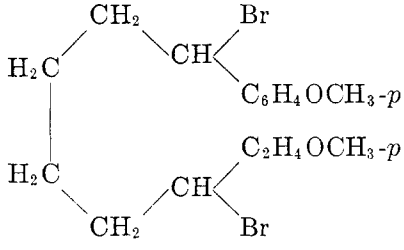
CLXXXIV

series and with other compounds is difficult, since only one isomer was isolated in each case and the configurations are unknown. Reaction of these indans with paraformaldehyde in alcoholic alkali gave the 1-methylene derivatives, which on reduction over Raney nickel gave a series of 3-alkyl-6-hydroxy-2-(*p*-hydroxyphenyl)-1-methylindans. In this series maximum activity was again found with the 3-isopropyl compound, although it was less active than its analog lacking the 1-methyl group. 3-Ethyl-1-methylindan required more than 16 micrograms for 50 per cent response subcutaneously in rats; Hausmann and Wilder Smith (159) obtained the same compound and reported 200 micrograms for 50 per cent re-

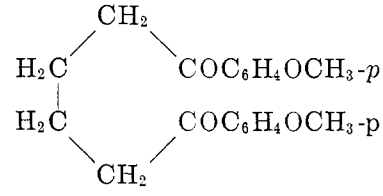


sponse under the same conditions. An isomer isolated by the latter workers gave 50 per cent response similarly tested at 3 micrograms, illustrating the importance of configuration in this series.

After an earlier failure by Price and Mueller (343), Mueller and May (295) succeeded in synthesizing 1,2-bis(*p*-hydroxyphenyl)cyclohexane (CLXXXIV) (cyclohexestrol), an analog of hexestrol in which the two ethyl groups are united to form a new ring. *p*-Methoxyphenylmagnesium bromide was reacted with 2-chlorocyclohexanone (CLXXXV) to give a mixture of 1,2-bis(*p*-methoxyphenyl)cyclohexene (CLXXXVI) and 2,3-bis(*p*-methoxyphenyl)cyclohexene (CLXXXVII), the former greatly in preponderance. Both halogen and carbonyl sites are attacked (305), followed by spontaneous elimination of water from the intermediate carbinol. The substituted cyclohexenes were formed when the molar ratio of 2-chlorocyclohexanone to Grignard reagent was 1:2; with a ratio of 1:1, 2-*p*-methoxyphenylcyclohexanone was the chief product. Hydrogenation of the mixture of cyclohexenes or the separate isomers over palladium on charcoal yielded 1,2-bis(*p*-methoxyphenyl)cyclohexane (CLXXXVIII), which was demethylated by alcoholic potassium hydroxide to cyclohexestrol. By relation to the hydrogenation of diethylstilbestrol, cyclohexestrol was considered to have the trans configuration. It was weakly active estrogenically. Dodds, Huang, Lawson, and Robinson (103) also prepared cyclohexestrol and found it inactive at 10 mg.; they considered it to be the cis compound. Other attempts by Mueller and May to obtain cyclohexestrol by a Wurtz or Grignard–cobaltous chloride reaction using 1,6-bis(*p*-methoxyphenyl)-1,6-dibromohexane (CLXXXIX)

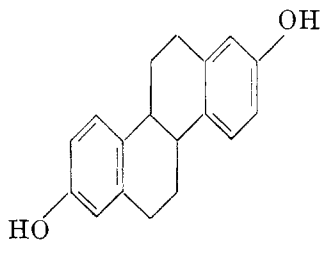


CLXXXIX

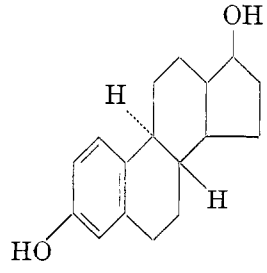


CXC

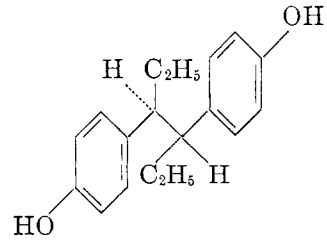
failed. An attempt to obtain a pinacol, as intermediate, from 1,4-bis(*p*-methoxybenzoyl)butane (CXC) failed, although an interesting polymer was produced.



CXCI



CXCII

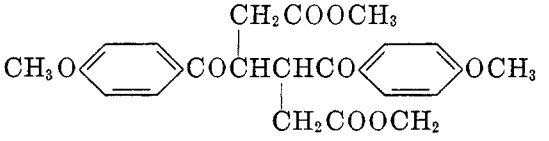


CXCIII

Nazarov and Kotlyarevskiĭ (302) prepared 1,2-bis(*p*-hydroxyphenyl)-3-methylcyclopentane as a further variation of the union of the ethyl groups of hexestrol; it was inactive at 100 micrograms.

Wilds and Sutton (555) reëxamined the problem of the estrogenic activity of 2,8-dihydroxy-4*b*,5,6,10*b*,11,12-hexahydrochrysene, the trans form (CXCI) of which had been reported previously as active at 1000 micrograms (102).

This activity of the trans compound is surprising in view of the structural similarity to "α"-estradiol (CXCII) and hexestrol (CXCIII). Reduction of methyl *p*-methoxycinnamate with amalgamated aluminum in moist ether gave a 24 per cent and an 18 per cent yield, respectively, of the meso and racemic forms of dimethyl β,γ-dianisoyladipate (CXCIV).

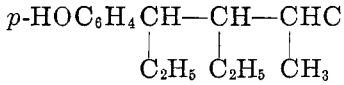


CXCIV

The meso acid chloride was cyclized in benzene with aluminum chloride and gave 88 per cent of the trans diketo compound; the cis diketo compound was obtained in 99 per cent yield by the same method. Catalytic reduction of the diketo compounds in acetic acid over palladium–charcoal gave a 90 per cent yield of the *trans*-chrysene and 70–75 per cent of the cis compound. Demethylation with 48 per cent hydrobromic acid–acetic acid gave the *trans*- and *cis*-2,8-dihydroxyhexahydrochrysenes in 94 per cent and 91 per cent yield, respectively. The trans compound gave 90 per cent response in rats subcutaneously at 500 micrograms, whereas the cis compound gave 40 per cent response at the same dosage; the trans diacetate was slightly less active than the cis diacetate. Apparently factors other than the purely structural are responsible for the activities of these isomers. The ring-closed analogs of diethylstilbestrol, hexestrol, and dienestrol are collected in table 20.

VIII. Diphenylpropanes and Analogs

The earlier work of Blanchard, Stuart, and Tallman (25, 474) on the diphenylpropane estrogens led to the discovery of the active compound 2,4-bis(*p*-hydroxyphenyl)-3-ethylhexane (CXCV), known as benzestrol. The estrogenic ac-



CXCV

Benzestrol

tivity of this compound lies between that of estrone and "α"-estradiol, and it is claimed to be less toxic than the stilbene type of artificial estrogen. As yet, however, it has not attained extensive usage. More recently the work in this series has been extended, largely by Stuart and Tallman and their collaborators, but

TABLE 20

Ring-closed analogs of diethylstilbestrol, hexestrol, and dienestrol

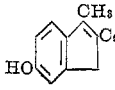
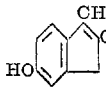
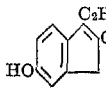
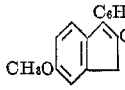
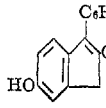
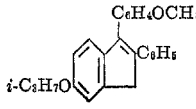
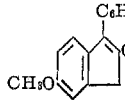
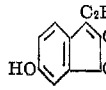
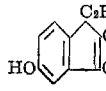
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
	°C.		
	76–77		(159)
	46–47		(159)
	154–155	1 mg.* (inactive) 5 mg.*	(294) (294)
Methyl ether	98–99	1 mg.* (inactive) 5 mg.*	(294) (294)
	197–198	100 (inactive)	(4)
	176–177		(413)
	115–117		(413)
	225–230	1 mg.* (inactive) 5 mg.*	(294) (294)
	145–146	5 mg.* (inactive)	(294)
	137–139		(413)
	175–176 175 175–176	3 (50%) 1	(158, 159) (4) (5, 182)
	128–129	1	(4) (5, 182)

TABLE 20—*Continued*

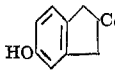
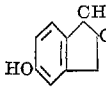
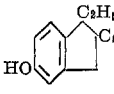
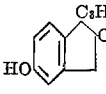
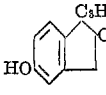
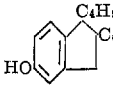
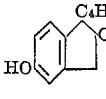
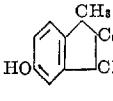
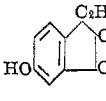
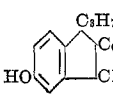
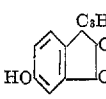
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
	°C.		
 C_6H_4OH-*p*		>60 (50%)	(466)
 C_6H_4OH-*p*	165–166 166–167	>200 (50%)	(466) (4)
 C_6H_4OH-*p*	162–163	15 (50%)	(464, 466)
 C_6H_4OH-*p*	145–147	2.1 (50%)	(466)
 C_6H_4OH-*p*	192–194	0.7 (50%) 10† (50%)	(466) (466)
 C_6H_4OH-*p*	187–188	>16 < 150 (50%)	(466)
 C_6H_4OH-*p*	197–200	2.8 (50%)	(466)
 C_6H_4OH-*p*	195–196	>16 (50%)	(465, 466)
 C_6H_4OH-*p*	195–198 198–199 (d.) 196–197 74 (isomeric form)	>16 (50%) 200 (50%) 3 (50%)	(465, 466) (159) (4, 182) (159)
 C_6H_4OH-*p*	184–185	>32 (50%)	(465, 466)
 C_6H_4OH-*p*	174–181	1 (50%)	(465, 466)

TABLE 20—*Continued*

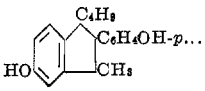
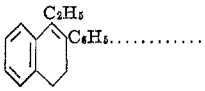
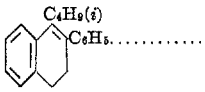
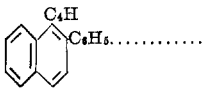
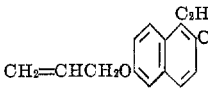
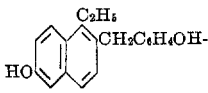
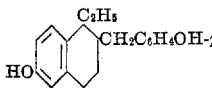
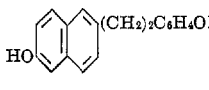
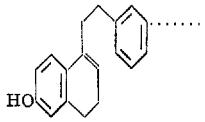
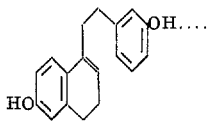
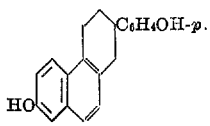
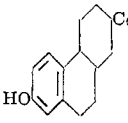
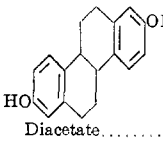
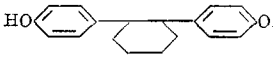
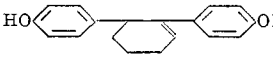
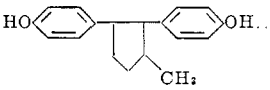
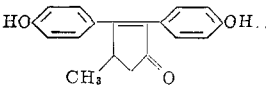
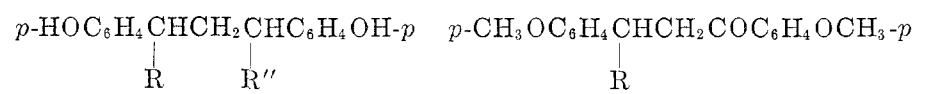
Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
	°C.		
	174–182	>32 (50%)	(465, 466)
	222–223/34 mm. (b.p.)		(44)
	62		(44)
	57		(44)
	130–132		(413)
	164–166	0.5 mg. (inactive) 1 mg. (20%)	(219) (219)
	116–120	0.5 mg. (37%) 1 mg. (36%)	(219) (219)
	201–202	<0.001 (diethylstilbestrol = 1)	(193)
	197–198/0.8 mm. (b.p.)	1 mg. (inactive)	(38)
	185–186	1–2 (weakly active)	(38)
	228.5–230.3	0.5 mg. (10%) 1 mg. (20%)	(219) (219)

TABLE 20—*Concluded*

Compound	Melting Point or Boiling Point	Estrogenic Activity in Rats, Subcutaneously (100% Response Unless Indicated Otherwise); Minimal Effective Dose in Micrograms, Unless Indicated Otherwise	References
	°C.		
 C_6H_4OH-*p*	194–196	0.5 mg. (inactive) 1 mg. (10%)	(219) (219)
	269–271 (vac.) (trans form) 223.8–224.6 (cis form)	350 (60%) 500 (90%) 500 (40%)	(555) (555) (555)
Diacetate	201–202 (trans form) 213–214 (cis form)	500 (77%) 400 (80%)	(555) (555)
	177.5–179.5 176–177	200 (I.U./mg.) 10 mg. (inactive)	(295) (103)
	171–173.5	300 (I.U./mg.)	(295)
	226.6–228.6	150 (I.U./mg.)	(295)
	215–220/0.06 mm. (b.p.)	100* (inactive)	(302)
	268	100* (inactive)	(302)

* In mice.
† Orally.

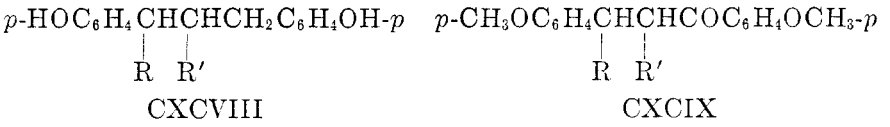
no estrogen superior to benzestrol has been encountered. The earlier work (458) showed that monoalkylated 1,3-diphenylpropanes had only low activities. Stuart, Shukis, and Tallman (472) prepared a series of dialkylated 1,3-diphenylpropanes of the type shown in formula CXCVI and observed maximum activity,



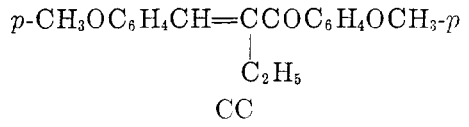
CXCVI CXCVII

of 0.2 milligram, with R = CH_3 and R″ = C_3H_7. These compounds were prepared by reacting the starting ketone (CXCVII: R = CH_3, C_2H_5, C_3H_7) with methylmagnesium iodide, followed by dehydration of the carbinol obtained by heating at 150–200°C. in a vacuum with a drop of hydrochloric acid. Yields

of 80–90 per cent of the corresponding alkenes were obtained. In the same way the diethyl, ethylpropyl, and dipropyl compounds were obtained. Hydrogenation of the alkenes in acetic acid over platinum oxide and at atmospheric pressure gave practically quantitative yields of the alkanes, which were demethylated. The demethylation products were assayed without separation of isomers, a procedure which makes structural interpretation of their estrogenic activities difficult. In a second series of dialkylated 1,3-diphenylpropanes (CXCVIII)

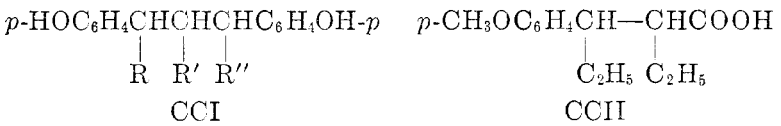


CXCVIII CXCIX



CC

the starting ketone (CC) was obtained by the condensation of anisaldehyde and *p*-methoxybutyrophenone. Reaction of this chalcone with three moles of a Grignard reagent at −10°C. gave 80 per cent yields of the ketones (CXCIX). Reaction of methylmagnesium iodide with CC failed to give a ketone of type CXCIX; instead indene-type products were obtained. The ketones (CXCIX) were separated into their two racemates and these hydrogenated over copper chromite at 230°C. and 200–250 atm. pressure; subsequent demethylation gave the racemates (CXCVIII). The B racemates (CXCVIII) (table 21) were obtained from the higher-melting racemates of the ketones. Again only the racemic products were tested biologically; the highest potency, at 0.03 milligram, was found with the racemate in which R = C_2H_5 and R′ = C_3H_7, while the racemate in which R = C_2H_5 and R′ = C_2H_5 had a closely similar activity. In a further paper (473) a series of trialkylated 1,3-diphenylpropanes (CCI) was prepared.



CCI CCII

The starting materials were the racemic ketones CXCIX, which by treatment with a Grignard reagent and dehydration of the carbinols as described previously gave 80 per cent yields of alkenes. Reduction using platinum oxide in ethyl alcohol and at 100°C. and 100–150 atm. pressure gave a mixture of two racemates in about equal amounts; with Raney nickel as catalyst the product consisted largely of one racemate. Demethylation yielded the racemates of CCI given in table 21; A and B, as before, refer to the racemic ketones CXCIX. When the mixture of racemates (CCI) was separated, the lower-melting, more soluble one was designated as 1 and the other as 2. When only one crystalline product was obtained, this was arbitrarily considered to be the less soluble form and was designated as 2; in other cases a mixture is assumed. Benzestrol is the B-2 race-

TABLE 21

Diphenylpropane analogs

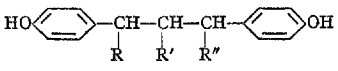
Compound			Melting Point	Estrogenic Activity in Rats, Subcutaneously; Rat Units‡ in Milligrams Unless Indicated Otherwise	References
					
R	R′	R″			
			°C.		
C_2H_5	H	H	Glass		(492, 493, 495)
H	C_2H_5	H			(492, 493, 495)
CH_3	H	CH_3	144	10	(472)
CH_3	H	C_2H_5	Resin	5	(472)
CH_3	H	C_3H_7	116	0.2	(472)
C_2H_5	H	C_2H_5	86–88	1	(472)
					(492, 493, 495)
C_2H_5	H	C_3H_7	Resin	1	(472)
C_3H_7	H	C_3H_7	Resin	5	(472)
C_2H_5	CH_3	H	A 128	2.5	(472)
			B 138	5	(472)
C_2H_5	C_2H_5	H	A 52	5	(472)
					(493, 495)
			B 109	0.04	(472)
					(493, 495)
C_2H_5	C_3H_7	H	A Resin	0.25	(472)
			B Resin	0.03	(472)
C_3H_7	CH_3	H	A 84–86	7.5	(472)
			B 115	10	(472)
C_3H_7	C_2H_5	H	A 111	7.5	(472)
			B 91–93	0.2	(472)
C_3H_7	C_3H_7	H	A 57–59	10	(472)
			B Resin	0.25	(472)
C_2H_5	CH_3	CH_3	B-2 141–143	0.5	(473)
C_2H_5	CH_3	C_2H_5	A Resin	1.0	(473)
			B-2 126–127	5.0	(473)
C_2H_5	C_2H_5	C_3H_7	A-2 102	2.0	(473)
			B-2 143–144	2.0	(473)
C_2H_5	C_3H_7	C_2H_5	A Resin	0.60	(473)
			B Resin	1.0	(473)
C_2H_5	C_2H_5	C_2H_5	A-2 144	1.0	(473)
					(492, 493, 495)
			B-1 138–139	0.50	(473)
			B-2 154–155	0.10	(473)
			160–170/ 0.05 mm. (b.p.)	0.1 mg. (100%)	(103)
				0.01 mg. (inactive)	(103)
C_3H_7	C_2H_5	CH_3	A-2 132	0.40	(473)
			B-2 155	0.013	(473)
C_2H_5	C_3H_7	CH_3	A-2 68–72	0.10	(473)
			B-2 121–122	0.005	(473)
C_2H_5	C_2H_5	CH_3	A-1 Resin	0.010	(473)
			A-2 75	0.005	(473)
			B-1 144	0.035	(473, 494)
			B-2 162	0.0008	(473, 494)
			170–180/ 0.08 mm. (b.p.)	0.01 mg. (80%)	(103)

TABLE 21—*Concluded*

Compound	Melting Point	Estrogenic Activity in Rats, Subcutaneously; Rat Units‡ in Milligrams Unless Indicated Otherwise	References
	°C.		
o-$HOC_6H_4CH_2CH_2CH(C_2H_5)C_6H_4OH$-*p*			(493, 495)
m-$HOC_6H_4CH_2CH_2CH(C_2H_5)C_6H_4OH$-*p*			(493, 495)
p-$HOC_6H_4CH_2CH_2CH(C_3H_7)C_6H_4OH$-*o*			(493, 495)
p-$HOC_6H_4CH_2CH(C_2H_5)CH(C_2H_5)C_6H_4OH$-*o*			(493, 495)
p-$HOC_6H_4CH(C_2H_5)CH_2CH(C_2H_5)C_6H_4OH$-*o*			(493, 495)
o-$HOC_6H_4CH(CH_3)CH(C_2H_5)CH(C_2H_5)C_6H_4OH$-*p*			(493, 495)
o-$HOC_6H_4CH(C_2H_5)CH_2CH(C_2H_5)C_6H_4OH$-*o*			(493, 495)
m-$HOC_6H_4CH(C_3H_7)CH_2CH_2C_6H_4OH$-*m*	Glass	10 mg. (inactive)	(103)
m-$HOC_6H_4CH_2CH_2CH(C_3H_7)C_6H_4OH$-*p*	80–82	<0.001§	(37, 192)
m-$HOC_6H_4CH_2CH_2CC_6H_4OH$-*p* $\parallel$ CHC_2H_5	250/5 mm. (b.p.)	<0.001§	(37, 192)
p-$HOC_6H_4CH(C_2H_5)CH{=}CHC_6H_4OH$-*p* $\mid$ CH_3	98–99	100 micrograms*	(273, 275)
HO, $CH_2CH_2CH_2C_6H_4OH$-*p*	126–128	<0.001§	(193) (37)
Diacetate	96	<0.001§	(193) (37)
p-$HOC_6H_4CH_2CH{-}CHC_6H_4OH$-*p*; H_2C, CH_2, CH_2			
Trans form	138–139	10 mg. (inactive)	(103)
Cis form	100.5–103	10 mg. (inactive)	(103)
$(p\text{-}ClC_6H_4)_2CHCCl_3$		45 mg. (inactive)	(127)
$(p\text{-}CH_3OC_6H_4)_2CHCCl_3$		45 mg. (inactive)	(127)
$(p\text{-}HOC_6H_4)_2CHCCl_3$		20 mg.	(127)
		15 mg. (75%)	(127)
		10 mg. (50%)	(127)
p-$HOC_6H_4CC_6H_4OH$-*p*; $COCH_3$, CH_3	130–131	10 mg. (inactive)	(103)
p-$HOC_6H_4CCH_2CC_6H_4OH$-*p*; C_2H_5, CH_3, $CHCH_3$	135	0.25 microgram (= 1 unit of estrone)	(384)

* In mice.

† Orally.

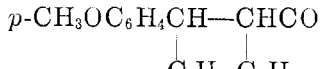
‡ The rat unit is defined as the minimum amount of material needed to produce complete vaginal cornification in 80 per cent of rats on single subcutaneous injection.

§ Diethylstilbestrol = 1.

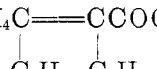
mate, m.p. 162°C. The highest activities were found with the compounds in which R = C_2H_5, R′ = C_2H_5, R″ = CH_3 and R = C_2H_5, R′ = C_3H_7 and R″ = CH_3.

Shukis and Ritter (412) substantiated the structure of benzestrol by another synthesis. The key intermediate was the known racemic α-ethyl-β-(*p*-methoxy-

phenyl)valeric acid (CCII), which was prepared by the condensation of anisaldehyde and methyl propyl ketone (28), followed by addition of ethylmagnesium bromide across the double bond of the unsaturated ketone. A 97 per cent yield of the ketone CCIII was obtained. The haloform reaction on this gave 21 per

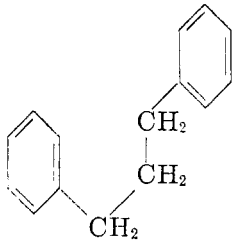


CCIII

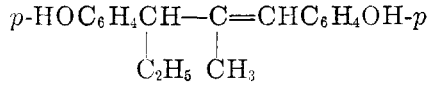


CCIV

cent of CCII. A second route (263) to CCII was via a Reformatsky reaction with *p*-methoxypropiophenone and ethyl α-bromobutyrate; an 86 per cent yield of the unsaturated ester CCIV was obtained. Reduction using platinum oxide–platinum black gave a 97 per cent yield of the dihydro compound, which on hydrolysis gave a 42 per cent yield of CCII. Conversion of racemic CCII to its acid chloride, followed by a Friedel–Crafts reaction with anisole, gave the ketone CXCIX (R = R′ = C_2H_5); the latter with methylmagnesium iodide, dehydration, and reduction gave a 61 per cent yield of benzestrol dimethyl ether. A further procedure leading to CCII due to Rubin and coworkers (368, 369) was considered inferior. Yoshida and Akagi (559) also obtained CCII as an intermediate for use in the synthesis of benzestrol. Anisaldehyde was condensed with diethyl malonate, and ethylmagnesium iodide was added across the unsaturated ester obtained. Ethylation of the product by ethyl iodide and sodium in benzene, followed by hydrolysis and decarboxylation, gave CCII. In view of the stereoisomer problem, as indicated, it is difficult to interpret estrogenic activity in the diphenylpropane series in structural terms. However, in view of the concept of the spacing of hydrogen-bonding groups, it is probable that these compounds are adsorbed in the configuration CCV or a related configuration. The introduction



CCV



CCVI

of alkyl groups into the aliphatic portion could enhance activity by steric or adsorption means and by influencing physical properties. The polymerization of *p*-anol and *p*-anethole (459) has recently been restudied (275), and 3,5-bis(*p*-hydroxyphenyl)-4-methyl-4-pentene (CCVI), also called dianol, has been synthesized (273). In the synthesis a mixture of 3,5-bis(*p*-hydroxyphenyl)-4-methylpentenes was obtained, and this was claimed to show activity in mice subcutaneously at 0.5 microgram; dianol is active only at 100 micrograms. Metanethole, 3-ethyl-6,4′-dimethoxy-2-methyl-1-phenylindan, whose estrogenic activity has not previously been reported, was found inactive at 10 mg.

Little work on other diphenylalkanes has been reported recently, presumably since no compounds of high activity had been found previously (460, 461). However, Fisher, Keasling, and Schueler (127) investigated the activity of DDT and related compounds. 2,2′-Bis(*p*-hydroxyphenyl)-1,1,1-trichloroethane was found rather more active than its dimethyl ether or DDT. Of interest is the finding that 2,2′-bis(*p*-hydroxyphenyl)ethane is only one-seventh as active as the 1,1,1-trichloro compound. The importance of the trichloromethyl group was interpreted as increasing the hydrogen-bonding capacity of the hydroxyl groups by the operation of an inductive or direct field effect and as sterically inhibiting free rotation and so introducing rigidity into the molecule.

IX. Some Physiological Considerations

A. Some General Factors Affecting Estrogenic Activity

Some general factors known to affect the potency of an estrogenic substance were mentioned in the introduction. Their bearing on correlations of chemical constitution and estrogenic activity was stressed. The factor of the test animal has been exemplified previously, and this factor may lead to the frustration of an attempt to use a promising estrogen clinically. Tissue response to an estrogen is a multiple effect, and action on the vagina, the uterus, the breast, bone, and other tissues is established. The test object, therefore, is of importance in the assay of a substance, and relative activity may even be reversed by using different test objects as the criterion of activity (81). The route of administration is important, and the potency exhibited, for a particular route, depends on the rate of absorption of the estrogen (98). Oral potency is in general less than subcutaneous potency. The importance of rate of absorption is presumably due to the fact that estrogens take several days to act; easy absorption should make for ease of elimination. As indicated previously, many practical uses of this factor have been explored. Different vehicles affect potency (566); e.g., the administration of estrone with subtosan doubles its duration of action (257). Water solubility permits more rapid action of an estrogen, though a smaller physiological response will be expected. Water solubility, however, may be an asset to an estrogen which is easily inactivated. Other factors being satisfied, appropriate physicochemical properties together with chemical stability are apparently necessary for optimum activity. Unfortunately, as yet little can be said about either of these factors. For some triphenylethylene estrogens fat storage in the body after administration is established and in part at least is responsible for prolonged action (148, 503, 504). Thompson and Werner (505) found, using TACE in humans, that duration of therapy and size of dose governed the level of estrogenic material in the fat. Little information is available for other estrogens, but Koch and Heim (241, 242) demonstrated, using pigs and cows, the storage of dienestrol in fat.

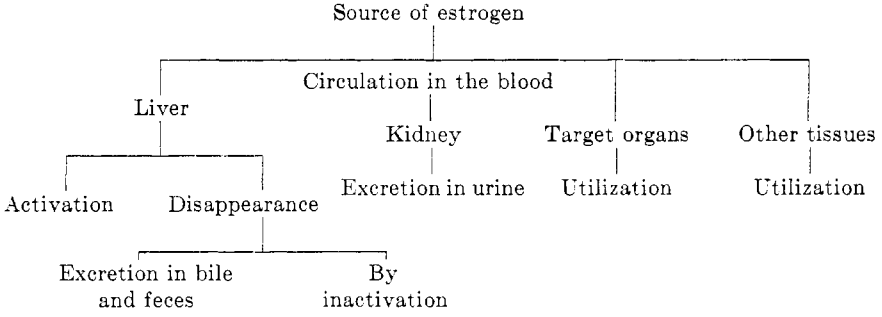
The toxicity of diethylstilbestrol has been mentioned (373); it can also cause liver and kidney damage in rats (526) and dogs (528). Nicol and Helmy (306) tested several artificial and natural estrogens and found diethylstilbestrol most toxic. The compound was more toxic orally than intramuscularly. Adminis-

tration of dienestrol followed by diethylstilbestrol dipropionate gave a less toxic effect than either alone. Dodds (97) considers that the potency of a substance, not its molecular features, is responsible for toxic effects. Nicol and Helmy (306) found several artificial estrogens more toxic in smaller than larger dosage and suggested the development of body resistance by overdosage. There is evidence for cooperative and antagonistic interaction between estrogen, androgen, and progestogen (80, 87, 136, 197, 245, 246, 296, 297, 408).

Heat, Höhn, and Robson (161) found that estrogen–progesterone antagonism occurred in the target organ. Arhelger and Huseby (12) found antagonism between steroid androgen and estrogen but none using diethylstilbestrol as estrogen. The results indicate competition for an intermediary or receptor; probably the hydrogen-bonding capacity of the hydroxyl groups in diethylstilbestrol make steroid androgen unable to compete. Férin (125), however, found that very large doses of testosterone acetate did inhibit the action of diethylstilbestrol in women; this supports the above conclusion.

B. INACTIVATION OF ESTROGENS

In considering estrogenic potency the possibility of metabolic inactivation is important. The pathways of estrogen in the body are indicated in the chart below:



Only a fraction of the estrogen administered is excreted (107, 210). Tissue storage cannot account for the rest (563). It was assumed that destruction or inactivation occurred in the body. Much experimental work has indicated that liver tissue is the main site of estrogen inactivation, both for natural and for artificial estrogens in rabbits, rats, guinea pigs, and dogs (22, 24, 56, 117, 147, 163, 207, 265, 339, 342, 380, 392, 564).

In humans hepatic damage has been shown to impair the inactivating ability of the liver (141, 145, 153, 381, 416, 491).

Partial hepatectomy impairs the ability of the liver to inactivate "α"-estradiol (393). Liebermann, Tagnon, and Schulman (262) recorded high inactivating ability *in vitro* to rat liver with "α"-estradiol, estrone, and estriol. The average human liver was found to be capable of metabolizing 11.5 g. of "α"-estradiol in 25 hr. (484), but there is no proved relationship for *in vivo* inactivating ability. Apparently the ability of liver to inactivate an estrogen depends on the animal;

human (514) and monkey (184) liver is inferior to rat liver. The ability of liver to inactivate an estrogen is destroyed by heating; this indicates that, at least *in vitro*, enzyme systems are involved. De Meio, Rakoff, Cantarow, and Paschkis (88) found complete inactivation of "α"-estradiol by rat liver slices under oxygen; under nitrogen or with boiled slices no inactivation occurred. Under nitrogen but in the presence of methylene blue 60 per cent inactivation occurred. It was suggested that, in part at least, a dehydrogenation mechanism was responsible for inactivation. The inactivating ability of rat liver homogenate is augmented by the addition of diphosphopyridine nucleotide (DPN) and nicotinamide (76, (88), indicating that the postulated dehydrogenation mechanism is in part linked to DPN. Heller (163) and Levy (259) found that cyanide inhibited the ability of liver to inactivate estrogen, but De Meio, Rakoff, Cantarow, and Paschkis (88) found only a limited inhibition by cyanide. This was interpreted as a limited participation of cytochrome oxidase in the inactivating process. While liver slices inactivate "α"-estradiol, liver mince was found inefficient (77), and it was concluded that cozymase participated in inactivation. Riegel and Meyer (356) attempted localization of the enzyme factors associated with inactivation by differential centrifugation of rat liver homogenate. The fractions were tested by incubation with estrogen in the presence of DPN and nicotinamide. No single fraction of nuclei, mitochondria, microsomes, or supernatant inactivated "α"-estradiol, but the microsomes and supernatant combined were as effective as homogenate; estrone behaved similarly. With diethylstilbestrol supernatant was almost as effective as homogenate; riboflavin monophosphate (RMP) alone, as well as boiled homogenate, inactivated the compound. Apparently a nonenzymatic process can inactivate diethylstilbestrol. Serchi and Principe (395) interpreted the activity of 17-ethynylestradiol and 1-ethynylcyclopentan-1-ol as indirect, arising from the liberation of acetylene from them by liver enzymes. The acetylene was postulated as destroying phenol oxidases in liver by combination with their copper component. Destruction of the functioning of phenol oxidases permits a temporary rise of estrogen in the normal circulation. Zimmerberg (562) found diethylstilbestrol incubated with rat liver slices to be partially oxidized and partially conjugated, the latter being preferred. The mechanisms were enzymatic. The problem of the nature of the metabolites remains largely to be solved, but Pearlman and De Meio (338) showed the conversion of "α"-estradiol into estrone by rat liver. There is evidence of enterohepatic circulation of estrogen with ultimate inactivation (155); during circulation small amounts of substances are lost via feces. Fishman (128) pointed out that it is not established that liver inactivation is functioning under physiological conditions regulating the metabolism of estrogens. Liver inactivation is reduced by various colloidal substances such as gelatin or methylcellulose (118, 119). Biskind and Biskind (23) found that the liver of rats on a diet deficient in vitamin B complex lost its ability to inactivate estrogens. Segaloff and Segaloff (394) concluded that thiamine and riboflavin were the important constituents of the B complex. However, Drill and Pfeiffer (109) and Jailer (211) claimed that concomitant inanition accompanying B deficiency is the factor responsible. Gyorgy (153) found that methionine or protein digests corrected B complex deficiency. Zondek and

Finkelstein (565) reported that B-deficient rats could inactivate estrone *in vivo* but that *in vitro* their liver tissue cannot. Jailer and Seaman (212) reported that the liver of rats on a 50 per cent casein diet is able to inactivate "α"-estradiol in spite of B avitaminosis or inanition. On a 15 per cent diet this ability is lost. Mentz, Odendaal, and Steyn (283) found the B vitamins essential for liver to inactivate estrogen; for optimum inactivation a certain balance between the various members of the B complex is necessary. It appears that, directly or indirectly, vitamins are associated with the capacity of the liver to inactivate estrogens (165). Folic acid is apparently not the factor associated with the vigorous capacity of the liver to inactivate estrogens *in vitro* (244). There is evidence of inactivation by blood (543).

The work described above has been done largely with steroid estrogens, although the general conclusions probably apply to many artificial estrogens. Metabolic conjugation has, however, been studied with several artificial estrogens. Wilder Smith (419) found indirectly that of estrogen administered to humans 50 per cent was excreted in urine as the monoglucuronide, 6 per cent as the sulfate ester, and less than 1 per cent in the free form. Using rabbits, Wilder Smith and Williams (421) found that 35 per cent of the diethylstilbestrol administered was excreted as the monoglucuronide; no sulfate was detected and little free estrogen. The latter fact is in agreement with the results of Mazur and Shorr (281) but in disagreement with the findings of Stroud (471). Rabbits were found to metabolize the monoglucuronide further to inactive substances. The recovery of estrogen depended on the animal; much lower recovery was found for cats. Simpson and Wilder Smith (415) attempted to elucidate the significance of estrogen conjugates and determined the activities of the monoglucuronides of diethylstilbestrol, hexestrol, and dienestrol subcutaneously and intravaginally. Activities of the order of 5–10 per cent of those of the parent substances were found, and it was concluded that their conversion to free estrogen could not explain their activities. Using diethylstilbestrol and hexestrol in rabbits, Dodgson, Garton, Stubbs, and Williams (105) found 70 per cent as monoglucuronides in urine; no sulfate was found. This was suggested as being due to the acidity of the hydroxyl groups, which is closer to that of alcoholic then phenolic hydroxyl. These authors drew attention to the different ease of hydrolysis of the monoglucuronides of diethylstilbestrol, hexestrol, and dienestrol and pointed out that only one monoglucuronide of diethylstilbestrol can exist, whereas two enantiomorphs of hexestrol can exist. Using diethylstilbestrol at the therapeutic dosage in women, Dodgson and Williams (106) obtained 35 per cent recovery as the benzylamine salt of the monoglucuronide; as indicated previously, earlier methods had been indirect. Evidence points to the liver as the site of conjugation (82, 83). Triphenylchloroethylene has been recovered from feces unchanged (215). The significance of estrogen conjugates is not yet clear, although previous discussion supports the liberation of estrogen from esters and ethers prior to biological functioning. Cohen and Marrian (74) accounted for the activity of sodium estriol glucuronide in terms of estriol content. Robson and Adler (360) found estriol glucuronide effective intravaginally, indicating a direct action. Fishman (129) considers that conjugation is a step in the utilization of estrogen by tissues and

that β-glucuronidase participates in the conjugation process (128). Hanahan, Daskalakis, Edwards, and Dauben (155), however, regard conjugates as a storage form of estrogen from which free estrogen is liberated as required. In view of the low estrogenic activities of estrogen conjugates, their widespread occurrence, their stereochemistry, and their structural similarity to other esters and ethers, it does seem reasonable to view them as inactivation products.

C. ACTIVATION OF ESTROGENS

During previous discussions mention has been made of the possibility of *in vivo* modification of an administered substance with the production of an active estrogen. The concept of activation of substances and their conversion to estrogenically active metabolites has been developed largely by Emmens and his collaborators (114, 115, 116). Various compounds were given subcutaneously in oil and intravaginally in 50 per cent aqueous glycerol and the dosage needed to produce cornified smears in 50 per cent of animals determined; for each route the ratio of subcutaneous or systemic to local dosage, the S/L ratio, was found of the order of unity for some compounds and for others between 50 and 400. Compounds of the first type with an S/L ratio of unity were considered to be modified *in vivo*. Such compounds were considered unable to act directly on the vagina but were absorbed into the general circulation, metabolized, and returned to the vagina in about the same concentration as would be obtained on injection. These compounds were called proestrogens. Compounds of high S/L ratio were called true estrogens; owing to their direct action on the vagina only a small intravaginal dose was needed. The proestrogens are collected in table 22 and those considered to be true estrogens in table 23. In view of the apparent importance of hydrogen-bonding groups the proposal that compounds lacking one or more hydroxyl groups, such as α,α′-diethyl-4-hydroxystilbene, should be classified as proestrogens is understandable. Presumably *in vivo* hydroxylation occurs. However, that compounds such as α-ethyl-4,4′-dihydroxy-α-methylstilbene should be proestrogens is more difficult to understand. None of the proestrogens rigorously satisfy the structural requirements of a potent estrogen as illustrated by diethylstilbestrol, and it is possible that of an intravaginal dose only a small portion can act before delocalization of the substance occurs. Emmens examined esters of estrone, "α"-estradiol, and diethylstilbestrol and found them to be true estrogens (table 24); this surprising result was attributed to their ease of hydrolysis intravaginally. 1,1-Bis(*p*-ethoxyphenyl)-2-bromo-2-phenylethylene was found to be a proestrogen by Robson and Ansari (361); according to Emmens the dimethoxy compound is a true estrogen. 2-Chloro-1,1,2-tris(*p*-methoxyphenyl)-ethylene was found by Thompson and Werner (503) to be a proestrogen. Of interest is the report by Heat, Höhn, and Robson (161) that *trans*-androstenediol and *trans*-stilbene, classified as proestrogens by Emmens, can exert a direct estrogenic action on the atrophic rabbit.

D. THE MODE OF ACTION OF ESTROGENS

In spite of the accumulation of data in many directions, the mechanism by which a hormone acts has yet to be elucidated. It seems probable, however, that

TABLE 22

Estrogenic activities and S/L ratio for some proestrogens

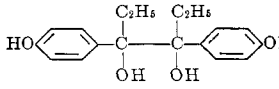
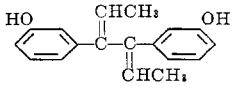
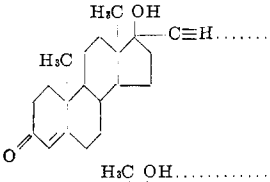
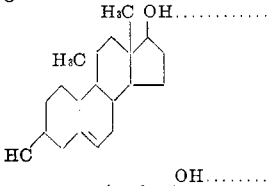
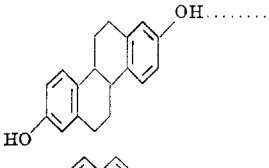
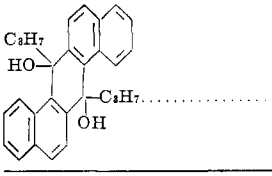
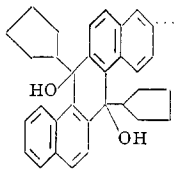
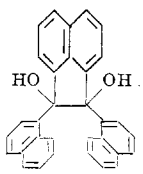
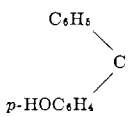
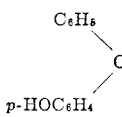
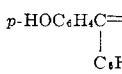
Compound	Estrogenic Activities in Mice		S/L Ratio
	Subcutaneously	Intravaginally	
	micrograms	*micrograms*	
p-$HOC_6H_4CH_2C(CH_3)_3$	40,000	>20,000	<2.0
p-$HOC_6H_4COC_2H_5$	8,000	ca. 2,000	ca. 4.0
p-$HOC_6H_4C_6H_5$	120,000	>10,000	<12.0
p-$HOC_6H_4C_6H_4OH$-*p*	15,000	>2,000	<7.0
p-$HOC_6H_4OC_6H_5$	30,000	>4,000	<7.0
p-$HOC_6H_4OC_6H_4OH$-*p*	30,000	>2,000	<15.0
$C_6H_5CH{=}CHC_6H_5$	3,200	>2,000	<1.6
p-$HOC_6H_4CH{=}CHC_6H_5$	2,000	>2,000	<1.0
p-$HOC_6H_4CH{=}CHC_6H_4OH$-*p*	2,200	>2,000	<1.0
p-$HOC_6H_4C(CH_3){=}CHC_6H_5$	700	>200	<3.5
p-$HOC_6H_4C(C_2H_5){=}C(C_2H_5)C_6H_4OH$-*p*	20	>30	<0.6
p-$HOC_6H_4C(CH_3){=}C(C_2H_5)C_6H_4OH$-*p*	0.44	2.2	0.2
p-$HOC_6H_4C(i\text{-}C_3H_7){=}CHC_6H_4OH$-*p*	75	65	1.1
p-$HOC_6H_4C(C_3H_7){=}CHC_6H_4OH$-*p*	60	>60	<1.0
p-$HOC_6H_4C(C_2H_5){=}CHC_6H_4OH$-*p*	90	>80	<1.0
o-$HOC_6H_4C(C_2H_5){=}C(C_2H_5)C_6H_4OH$-*o*	320	165	2.0
p-$HOC_6H_4CH(C_2H_5)CH_2C_6H_4OH$-*p*	650	>100	<6.5
	30	60	0.5
	300	220	1.4
	1,200	1,000	1.2
	700	800	0.9
	150	ca. 200	ca. 0.7
	18	20	0.9

TABLE 22—*Concluded*

Compound	Estrogenic Activities in Mice		S/L Ratio
	Subcutaneously	Intravaginally	
	micrograms	*micrograms*	
	490	300	1.6
	200	ca. 600	ca. 0.33
	6,000	>2,000	<3.0
$(C_6H_5)_2C{=}CHC_6H_5$	300	>200	<1.5
	20	44	0.45
$(p\text{-}HOC_6H_4)_2C{=}CHC_6H_5$	8	20	0.4
	12	4.4	2.7
	15	10	1.5

the various identical physiological responses produced by natural and artificial estrogens proceed by the same mechanism for each hormone type. There is certainly considerable evidence showing that estrogens do affect enzyme systems both *in vitro* and *in vivo* (40, 128, 284). However, the alternative possibility of action by participation in specific transfer mechanisms through cytostructural barriers cannot be excluded (162).

TABLE 23

Estrogenic activities and S/L ratios for some true estrogens

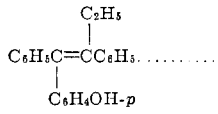
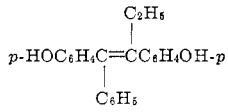
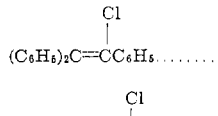
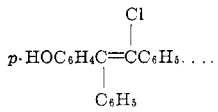
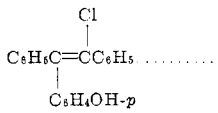
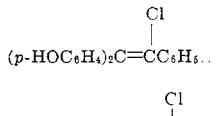
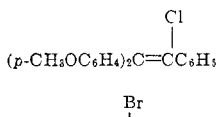
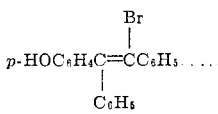
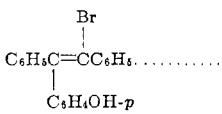
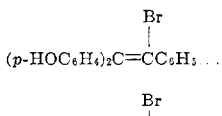
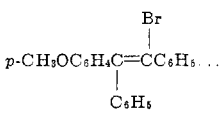
Compound	Estrogenic Activities in Mice		S/L Ratio
	Subcutaneously	Intravaginally	
	micrograms	*micrograms*	
	7.7	0.015	510
	0.9	0.00065	1,400
	77	0.89	86
	2.3	0.0014	1,600
	1.6	0.0013	1,200
	0.2	0.0010	200
	40	1.2	33
	2.7	0.011	250
	3.0	0.010	300
	0.54	0.0014	390
	105	0.70	150

TABLE 23—*Concluded*

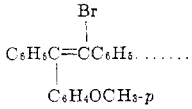
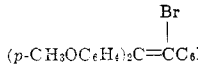
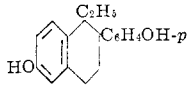
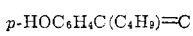
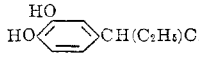
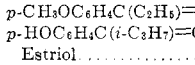
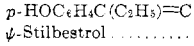
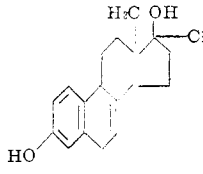
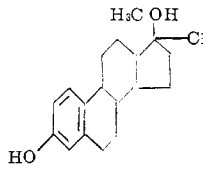
Compound	Estrogenic Activities in Mice		S/L Ratio
	Subcutaneously	Intravaginally	
	micrograms	*micrograms*	
	100	0.49	200
	51	1.0	51
	ca. 1,000	ca. 8.0	ca. 125
	50	0.16	310
	12.5	0.2	63
Hexestrol (racemic)	8.9	0.025	360
	8.0	0.02	400
	4.7	0.015	310
Estriol	2.0	0.001	2,000
Estrone methyl ether	0.9	0.015	60
	0.6	0.0035	170
ψ-Stilbestrol	0.45	0.001	450
Hexestrol (meso)	0.16	0.0009	180
Diethylstilbestrol	0.12	0.00037	320
Dienestrol	0.1	0.00058	170
Estrone	0.075	0.00029	260
	0.045	0.005	90
Estradiol	0.025	0.0005	50
	0.03	0.00025	120

TABLE 24

The effect of esterification on the S/L ratio

Compound	Estrogenic Activities in Mice		S/L Ratio
	Subcutaneously	Intravaginally	
	micrograms	*micrograms*	
Estrone	0.075	0.00029	260
Estrone butyrate	0.070	0.0003	230
Estrone caproate	0.15	0.0003	500
Estradiol	0.025	0.0005	50
Estradiol benzoate	0.08	0.0005	160
Diethylstilbestrol	0.12	0.00037	320
Diethylstilbestrol dipropionate	0.14	0.00075	190
Diethylstilbestrol dicaproate	0.45	0.0015	300
Diethylstilbestrol dipalmitate	6.0	0.0012	3,000

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