SYNTHETIC ESTROGENS AND THE RELATION BETWEEN THEIR STRUCTURE AND THEIR ACTIVITY

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I. Introduction

In 1933 Cook, Dodds, and Hewett (35) stated that "it seems likely that a whole group of substances of related chemical constitution will be found to have estrus-exciting properties and the synthetic production of such substances would probably be of considerable clinical value." This prediction proved to be fully correct. During the eleven years following this first publication on synthetic

estrogens the field has continually grown in importance as well as in scope, and today there are several hundred substances known to possess estrogenic activity. It is common knowledge that several among these have acquired considerable theoretical and practical importance. The discovery of the estrogenic activity of stilbestrol in 1938 by Dodds, Goldberg, Lawson, and Robinson (58) constitutes by far the most important single advance of this research. Further studies by the same group of investigators as well as by others soon led to the synthesis of a few closely related compounds of similar potency. Since that time research on synthetic estrogens has clearly shown a trend of elaborating and improving over these known structures rather than venturing into entirely new fields. There are a few exceptions to this statement, but even such structures which, strictly speaking, are neither stilbene nor dihydrostilbene derivatives, are nevertheless closely related. Among these are derivatives of diphenylmethane, diphenylpropane, triphenylethylene, and certain ring-closed analogs. Such compounds have also been included in this review because the correlation of chemical structure and biological activity of the stilbenes could not be fully discussed without including them and, conversely, their significance lies in their relationship to the estrogens of the stilbene and dihydrostilbene types. Not included in this review are structures more closely related to the natural hormones than to stilbestrol, as well as other miscellaneous derivatives of benzene, diphenyl, diphenyl ether, acenaphthene, fluorene, phenanthrene, and anthracene. These types of compounds have been treated comprehensively by Masson (118a).

The great amount of painstaking detailed research done in this field lies in the importance of synthetic estrogens as therapeutic agents, an importance which is mainly due to their greater availability and to their efficacy on oral administration. For a number of years a spirited and intense discussion has been under way between those who advocate continued and exclusive use of natural estrogens of the steroid type and those who sponsor their replacement by synthetics of non-steroid structure; however, this discussion concerns therapeutic merits and is beyond the scope of this review, which is concerned with correlating the data on chemical structure and estrogenic activity.

The endeavor to review this field at the present time is prompted mainly by three reasons: firstly, the literature on estrogenic stilbenes and related compounds has become so extensive as to make it desirable to review the chemical facts reported to date; secondly, the research undertaken in the field of synthetic estrogens constitutes one of the most extensive efforts to answer the cardinal question of the correlation between chemical structure and biological activity; and, thirdly, the present state of knowledge in this field appears especially opportune for drawing an intermediary balance.

Necessarily, the discussion of physiological aspects of synthetic estrogens must be limited to those bearing on the correlation of structure and potency. The physiology of synthetic estrogens in its entirety has recently been reviewed by Masson (118a). An earlier review by Wessely (219) covers the literature up to 1940. Partial aspects have since been reviewed in greater detail by Atkinson (4), Morell and Hart (133, 134), and The Council on Pharmacy and Medicine of the American Medical Association (38).

As mentioned earlier, the efficacy on oral administration is one of the main assets of synthetic estrogens. Consequently, assays of oral activity are an important part of the evaluation of any new compound. In order to limit the discussion of physiological aspects and because information on parenteral efficacy is more generally available, comparative oral activities will be omitted from the chemical discussion of the various estrogens; they will be briefly treated in a separate chapter, together with some metabolic conversions intimately related to the oral efficacy.

The question arises if it is feasible to correlate the wealth of information on estrogenic activities. Generally speaking, the physiological results of various authors employing various methods may be compared only with a fairly wide margin of error. This is particularly true for estrogenic activities, where many variations arise from differences in technique as well as in interpretation as practiced in different laboratories. The assay procedure most frequently adopted is based on the method of Allan, Dickens, and Dodds (1a). It consists in the subcutaneous administration of a solution of the test sample in oil, under standardized conditions, to ovariectomized female rats. The rat unit is defined as the minimum amount of an estrogenic substance required to produce full estrous response in 100 per cent of the animals tested. Campbell (21) specified injection in six doses in sesame oil solution during 3 days. A number of investigators modified this standard procedure, used mice or other test animals instead of rats, or based their reported activities on a positive response in less than 100 per cent. The state of "full estrous response" alone, i.e., the degree of cornification of the vaginal smear, requires strict definition. Furthermore, questions of solubility and rates of absorption as well as of excretion need to be considered.

For the purpose of roughly comparing the relative activities of compounds prepared in their own laboratory, Dodds *et al.* (59) reported the activities in approximate rat units per gram of estrogenic substance. This practice has the advantage of expressing the highest degree of potency by the highest numerical value. It has occasionally been adopted by others, though the majority of authors preferred to report the potency in terms of minimal doses in micrograms required for a certain response in a given animal, when the smallest numerical value signifies highest potency. By dividing 1,000,000 by this latter expression it may be converted into the former. One might be tempted thus to evaluate all data reported in the literature by a common expression, but in the opinion of Dodds (147) and other workers in the field it would not be sound to do this with results from different laboratories, and this is quite evident from closer examination of individual data. The quantitative data expressed in various units are reproduced here as reported in the literature and may permit a quantitative comparison within series of compounds reported from *one* laboratory. A comparison of quantitative figures of *various* origins will be useful only for obtaining a rough indication.

Because the unit is expressed in dosage weight irrespective of body weight, naturally the same dose will have the greater effect on the smaller animal. Consequently the rat unit is larger than the mouse unit, but the exact ratio of the two units varies for different estrogens. The relative activity of various estro-

gens in humans is of prime importance, as most of the research was undertaken with the objective of developing new estrogens for clinical use. In view of the marked difference in relative response by species as closely related as rats and mice, it is obvious that animal experiments serve only for the purpose of screening compounds for therapeutic trial. The clinical results will not be discussed here, but some of the problems involved may be illustrated by the fact that one of the more recently developed estrogens was assayed clinically by the almost exclusive use of the "subjective" method, evaluating the subjective reports of patients, when treated at one dose level, regarding the manifestation or lack of certain desirable as well as undesirable symptoms. It was found difficult to correlate symptomatic relief with objective results as found in vaginal smears.

The sequence of topics in discussing the various compounds has been chosen for didactic reasons. The historical development and stimulation of research by the discovery and identification of hexestrol among the demethylation products of anethole made it desirable to treat hexestrol before stilbestrol; nevertheless, the latter may be considered the central topic. While the more important substances are discussed in detail, an attempt has been made to summarize in tabular form all compounds relevant to the subject. The methyl ethers of the phenolic hydroxyl derivatives have been omitted from the tables wherever they were obtained as intermediates only, without being of special interest as estrogens.

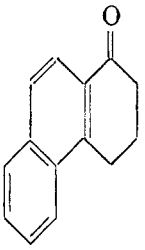
A few words will be in order regarding adoption of the abbreviated name "stilbestrol" instead of "diethylstilbestrol" as originally proposed by Dodds, Robinson, and coworkers (58). These authors gave the name "stilbestrol" to the "mother-substance" of the series, 4,4′-dihydroxystilbene, and consequently called the diethyl derivative "diethylstilbestrol." Actually, the basic name "stilbestrol" has been used only rarely in conjunction with homologs of 4,4′-dihydroxy-α,β-diethylstilbene. The Council for Pharmacy and Medicine of the American Medical Association (38) designated "diethylstilbestrol" as the officially accepted name. On the other hand, for the same compound, the abbreviated name "stilbestrol" has been increasingly used in the medical as well as in the chemical literature, including its use by Dodds *et al.* (26, 52, 56). Therefore, and for the sake of briefness, this practice has been extended to this review.

II. Historical

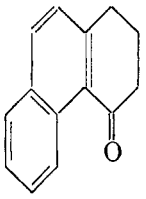
Even before the structure of the natural female sex hormones had been fully elucidated, Cook and Dodds with their collaborators (32, 34, 35) undertook to synthesize more readily accessible estrogenic substances of simpler structure. This endeavor was encouraged by the fact that estrogenic activity, being shared by a group of sterols, was apparently less specific than other hormonal activity. It was therefore not unreasonable to expect this lack of specificity even to extend to other classes of compounds. However, quoting the British authors, "... it would have been difficult to imagine that so complicated a series of effects involving an orderly sequence such as that of the estrous phenomena can be induced by anything other than the appropriate hormone."

This work was undertaken for the additional reason of studying the correlation between estrogenic and carcinogenic substances. The structural side of this relationship will be discussed later. Cook, Dodds, and Hewett (32, 35) first examined compounds containing the same ring system as carcinogenic hydrocarbons but with one or more rings hydrogenated and with polar groups present.

The first compounds of non-steroid structure reported in 1933 by these authors to possess estrogenic activity were 1-keto-1,2,3,4-tetrahydrophenanthrene (I) and the corresponding 4-keto derivative (II).

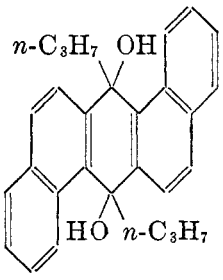


I



II

Their activity is low compared with that of estrone, and it was later recognized that activities of such low order are common to a very large number of compounds. The same authors found considerably higher activity for a series of 9,10-dihydroxy-9,10-dialkyl-9,10-dihydrobenzanthracenes. Cook, Dodds, Hewett, and Lawson (34) studied the effect of various alkyl groups on estrogenic activity; in this series the optimal activity is reached with the di-*n*-propyl derivative (III).

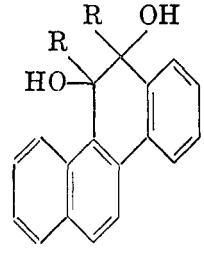


III

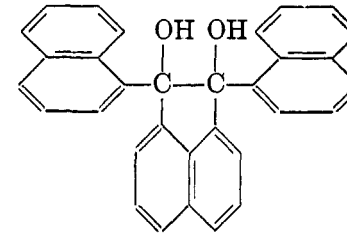
Extending the biological assays to other species, Cook, Dodds, and Greenwood (33) contributed to the recognition of the fundamental fact that there exist practically no qualitative differences between natural and synthetic estrogens. Among the great number of physiological reactions due to natural estrogens only isolated instances (130) have been reported of a qualitative difference between the two types of estrogens.

Between 1933 and 1938 Dodds and his collaborators (36, 50, 55, 61, 62, 64), as well as others, synthesized a large number of compounds, many of which were found to possess weak activity. Among these, only the following compounds

may be mentioned as being representative of the development away from structures still containing the phenanthrene skeleton and towards the simpler, yet infinitely more potent, stilbene derivatives: 11,12-dihydroxy-11,12-dialkyl-11,12-dihydrochrysene (IV), 1,3-dihydroxy-1,2-di-α-naphthylacenaphthene (V), diphenyl-α-naphthylcarbinol (VI), triphenylethylene (VII), bis(4-hydroxyphenyl)methane (VIII), 4,4′-dihydroxydiphenyl (IX), stilbene (X), 4,4′-dihydroxystilbene (XI).



IV



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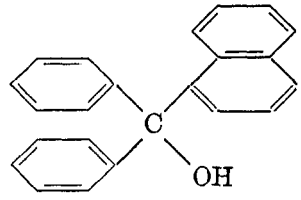
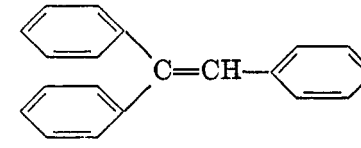
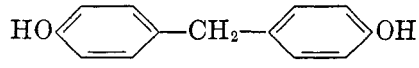


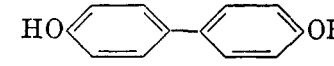
VI



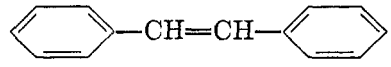
VII



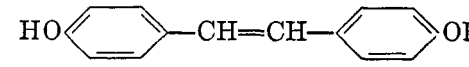
VIII



IX



X



XI

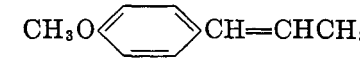
At this stage of the work, it became apparent that simple phenols and phenolic stilbene derivatives were worthy of special attention.

III. Hexestrol

A. Discovery

In 1937 Dodds and Lawson (62, 64) observed that different preparations of *p*-propenylphenol (anol) (XII) gave contradictory biological results. Their prepara-

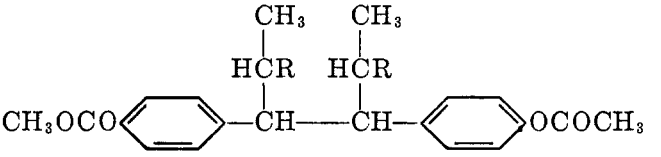
XII
Anol



XIII
Anethole

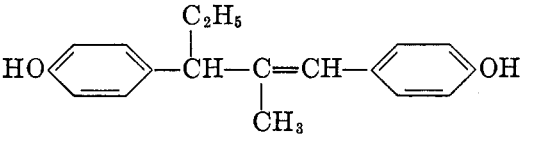
tion had been obtained from the biologically inactive anethole (XIII) by demethylation with potassium hydroxide and alcohol. Shortly thereafter, Serini

and Steinruck (177, 187) described the demethylation of anethole by means of Grignard reagents and, after acetylation of the resulting phenols, the production of crystalline products of considerable potency. With ethylmagnesium iodide, the product $C_{26}H_{34}O_4$, m.p. 186°C., was obtained; with propylmagnesium iodide, the product $C_{28}H_{38}O_4$, m.p. 175°C. It was postulated that the two products were formed by dimerization of two molecules of anol with simultaneous addition of two ethyl (propyl) groups, resulting in compounds most likely of the structure shown in formula XIV.



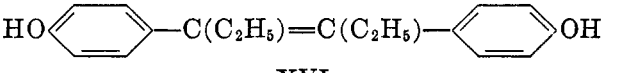
XIV

These products were active in doses of 5–10 micrograms (in rats), and were not identical with those obtained by Dodds and Lawson (62), who had observed substantially higher activities, though one product may have been the diacetate of the demethylation product of the latter workers. Dodds and Lawson (63), after being informed of an observation by Serini and Steinruck, confirmed that the mother liquors of their crystallized product contained the extremely potent fractions, while pure anol is only weakly active. This result was corroborated by Zondek and Bergmann (233), while Supniewski and Hano (209) apparently assayed crude preparations and found high activity. Campbell, Dodds, and Lawson (23) showed that the high potency of their crude compound could not be due to the presence of dianol (XV), which showed activity only in 100-microgram doses.



XV
Dianol

Shortly thereafter, in 1938, Dodds, Goldberg, Lawson, and Robinson (58) in a preliminary report published their synthesis of stilbestrol (4,4′-dihydroxy-α,β-diethylstilbene) (XVI). This investigation marked the opening of a new

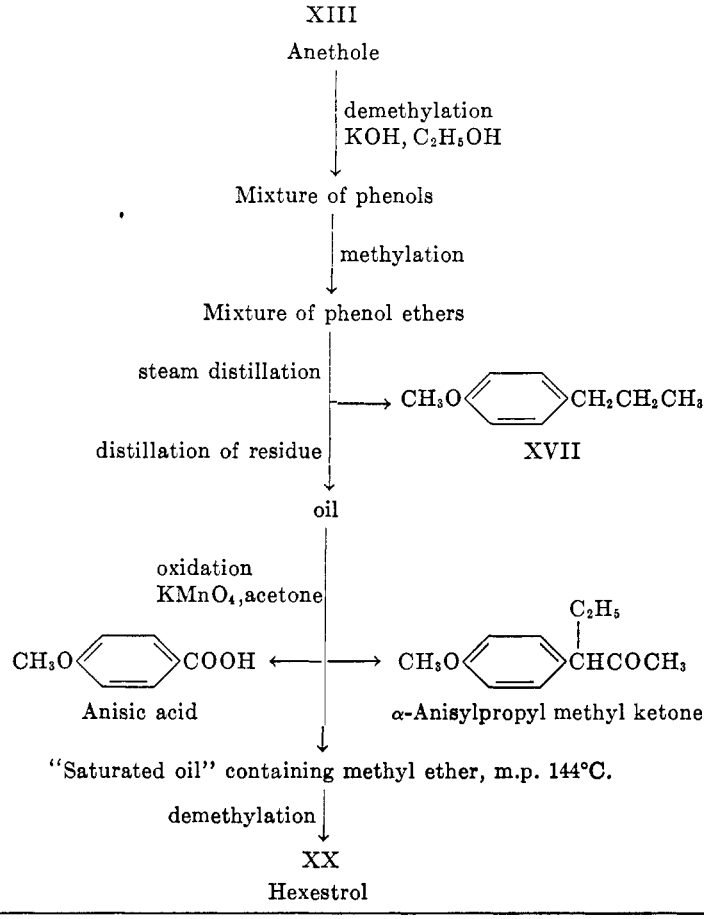


XVI
Stilbestrol

field of research with the objective of elaborating on the stilbestrol structure and possibly attaining even higher activities. Yet it still remained to identify the nature of the compound responsible for the activity of impure anol prepara-

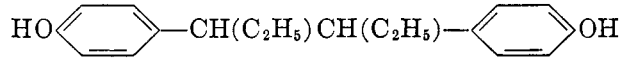
tions. Campbell, Dodds, and Lawson (24) solved this problem by careful fractionation of the demethylation products of anethole according to the scheme shown in table 1.

TABLE 1
Demethylation of anethole



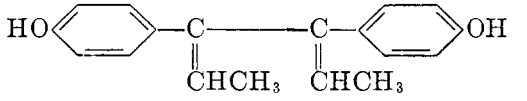
The phenol (XX), m.p. 184–185°C., proved fully active in doses of 0.2 microgram and thus accounted for the relatively high activities occasionally observed with impure preparations of anol. The compound was called hexestrol and remains to this day one of the most potent estrogens known.

The structure of hexestrol as 3,4-di(*p*-hydroxyphenyl)hexane (XX) was established by the proof of its identity with the hydrogenation products of stil-



XX
Hexestrol

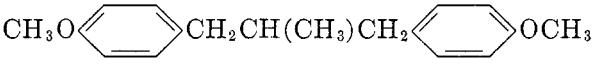
bestrol and of 3,4-di(*p*-hydroxyphenyl)-2,4-hexadiene (XXI), synthesized by Dodds *et al.* (59, 60) and to be discussed later. The occurrence of hexestrol



XXI
Dienestrol

among the demethylation products of anethole was studied in greater detail by Campbell, Dodds, and Lawson (25). In addition to hexestrol (m.p. 184–185°C.) another saturated phenol was found with m.p. 122°C. (also 128°C.), later identified as the optical isomer of hexestrol and found to be considerably less active.

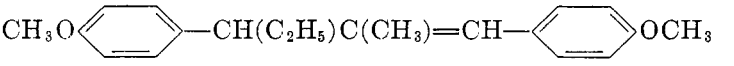
Two hydrogen atoms are required for the formation of hexestrol during the demethylation of anethole as well as for the simultaneous formation of 1-(*p*-anisyl)propane (XVII), as isolated by Campbell *et al.* (24); the origin of these hydrogen atoms is not yet fully understood, disproportionation being one possible explanation. Another saturated dimerization product formed by prolonged heating of anethole has been more recently obtained by Campbell (20) and identified as 1,3-di(*p*-anisyl)-2-methylpropane (XXII); it is only feebly active.



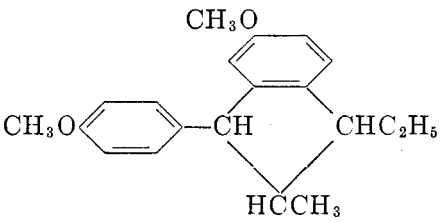
XXII

The isolation and structure elucidation of hexestrol are a remarkable feat in view of the fact that this product of linkage between two α-carbon atoms of anethole occurs among the demethylation products in 0.01 to 0.02 per cent yield only.

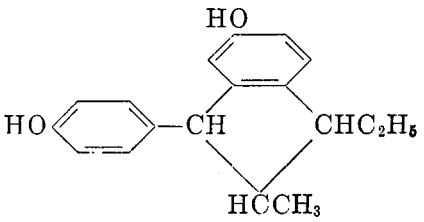
In this connection it may be of interest to note two other dimerization products of anethole (XIII) which have been the subject of recent studies. One of them is an oil, called isoanethole, and its structure (XXIII) was established by Goodall and Haworth (87); thus, isoanethole is the dimethyl ether of dianol (XV) mentioned earlier, and is formed by the linkage of one α- and one β-carbon atom. The other dimerization product of anethole is crystalline and is called metanethole; it is, according to Baker and Enderby (7) and confirmed by Mueller and Richl (137), the phenylindane derivative (XXIV) formed by linkage involving α- as well as β-carbon atoms. No assays of estrogenic activity of the demethylated metanethole ("metanethol") (XXV) have been reported, but the compound is of interest in connection with other active phenylindane derivatives to be discussed later. According to Polak (201) metanethole exists in a sublimable and a non-sublimable form; this may indicate the presence of still another isomer.



XXIII



XXIV



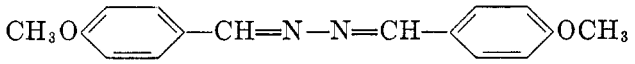
XXV

Sempronj *et al.* (186) described a product of unknown structure formed by spontaneous polymerization of anol (XII) and active in doses between 14 and 20 micrograms.

B. SYNTHESES (METHODS OTHER THAN HYDROGENATION)

For didactic reasons direct syntheses of hexestrol, i.e., synthetic methods other than hydrogenation of stilbene derivatives, will be discussed here separately.

Simultaneously with the hydrogenation of dienestrol (XXI) to hexestrol by Campbell, Dodds, and Lawson (25), the same authors reported the first direct synthesis in the course of their work on the identification of hexestrol among the demethylation products of anethole. Anisaldazine (XXVI) was reacted with two moles of ethylmagnesium bromide to yield hexestrol dimethyl ether (XXVII).



XXVI

Anisaldazine

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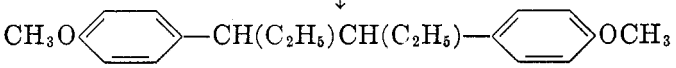
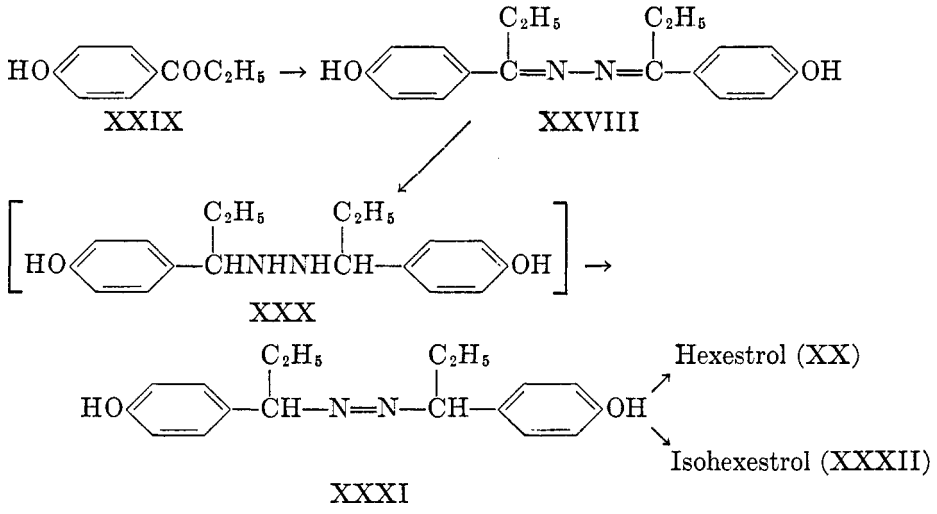


XXVII

Hexestrol dimethyl ether

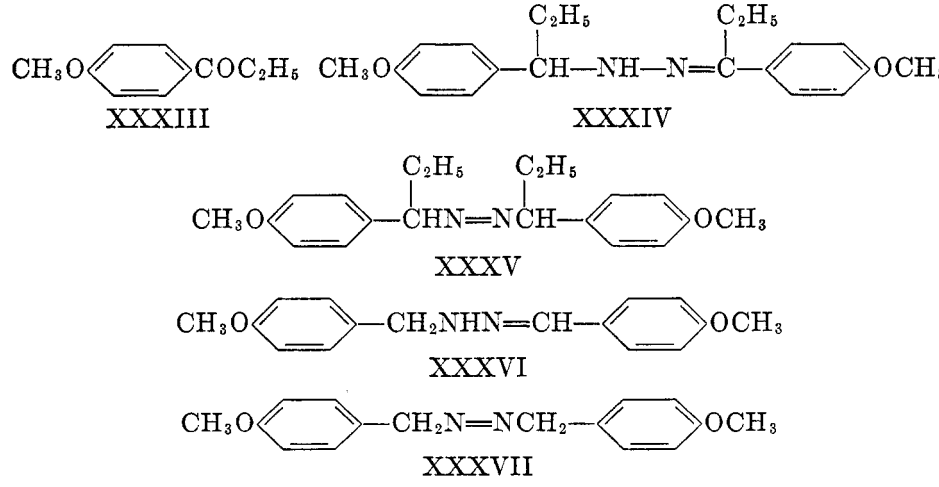
By demethylation hexestrol was obtained in poor over-all yield, but this synthesis confirmed the structure of hexestrol as 3,4-bis(*p*-hydroxyphenyl)hexane (XX). Bretschneider *et al.* (16, 17) later improved the yield of this synthesis (25); nevertheless the method remains without practical significance. Bretschneider *et al.* (16, 29) also developed another original synthesis with an over-all yield of 10 per cent. The ketazine (XXVIII) of *p*-hydroxypropiophenone (XXIX) is hydrogenated with palladium on charcoal to a tetrahydro derivative (XXX) (not isolated), which was oxidized with iodine, air, or simply by vacuum distillation (30) to a dihydro derivative (XXXI), possibly existing in two forms; on heating this compound above 120°C. nitrogen is lost to give a mixture of hexestrol and an optical isomer of the same, called isohexestrol (XXXII).



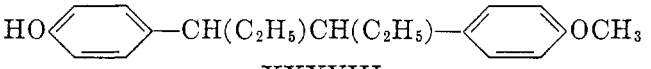
The success of this synthesis is interesting in view of the negative attempts of Linnell and Sharma (115) to remove nitrogen directly from the ketazine (XXVIII).

Foldi and Fodor (81, 160) in collaboration with Bretschneider applied the same method to the ketazine of *p*-methoxypropiophenone (XXXIII). The dihydroketazine (XXVIII) was isolated in two isomeric forms. Both isomers on thermal decomposition gave equal parts of hexestrol dimethyl ether and isohexestrol dimethyl ether.

Fodor and Szarvas (79) investigated the absorption spectra of the two intermediate dihydroketazines, in order to decide between the two formulas (XXXIV and XXXV), by comparison with the spectra of anisal anisylhydrazone (XXXVI) and 4,4′-dimethoxy-α,α'-azotoluene (XXXVII).

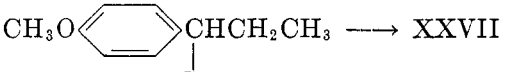


The absorption spectra of the two isomeric dehydroketazines coincide with each other as well as with that of compound XXXVII, while compound XXXVI shows an entirely different spectrum. This excludes formula XXXIV, but no decision can be made between the possibility of either *cis–trans* isomerism or *meso–dl* isomerism. By simultaneous decomposition of a mixture of *p*-hydroxy- and *p*-methoxy-propiophenone dihydroketazines, the monomethyl ether (XXXVIII) of hexestrol has been prepared (16). This method is of considerable theoretical interest, representing one of the rare cases of an association of unsymmetrical radicals formed by decomposition of two different substances.



XXXVIII

Peak and Short (13, 145, 190) synthesized hexestrol by a shorter method, starting from the known (124, 143) anethole hydrobromide (XXXIX) which is readily accessible from anethole (XIII) and hydrobromic acid. By the action of sodium, magnesium, aluminum, zinc, or the liquid alloy of potassium and sodium, two molecules undergo the Wurtz reaction and yield hexestrol dimethyl ether (XXVII).

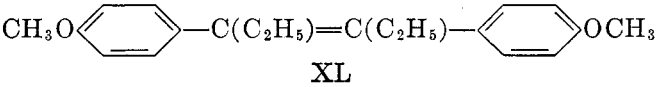


XXXIX Hexestrol

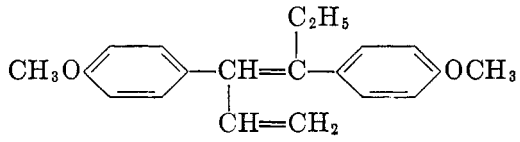
Anethole hydrobromide dimethyl ether

Instead of anethole hydrobromide, the hydrochloride or hydroiodide may be used and the reaction may be catalyzed by iodine, ethyl bromide, or Grignard reagent. Docken and Spielman (49) independently, though later, arrived at the identical method and reported an over-all yield of 10 to 15 per cent. Braker and Pribyl (15) obtained a United States patent on the same synthesis. This route was also followed independently by Bernstein and Wallis (11, 214), who prepared *p*-(α-bromopropyl)anisole (anethole hydrobromide) (XXXIX) in a longer, though inexpensive way from *p*-hydroxypropiophenone (XXIX) and then continued in essentially the same manner. Anethole hydrobromide has also been prepared (13) from anisaldehyde by reaction with ethylmagnesium bromide, followed by bromination with phosphorus tribromide.

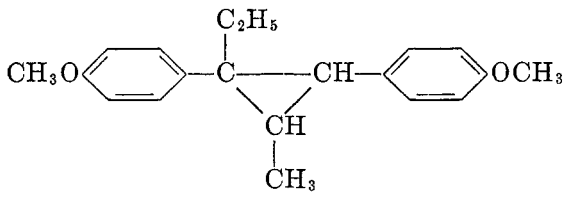
Kharasch and Kleiman (99) effected the dehydrobromination of anethole hydrobromide by means of sodium amide in liquid ammonia. In this case an unsaturated dimethyl ether isomeric, but not identical, with stilbestrol dimethyl ether (XL) is obtained and is believed to be represented by either one of the two structural formulae XLI or XLII.



XL

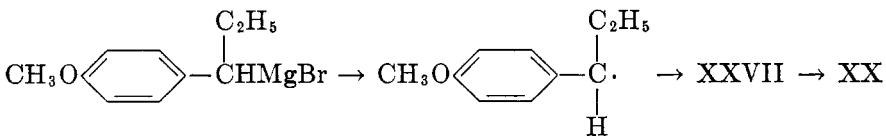


XLI



XLII

Hydrogenation with platinum black gives a theoretical yield of a hexestrol dimethyl ether (XXVII). The same authors (100) devised an even shorter synthesis with a 42 per cent over-all yield which may be superior to all others. By means of cobaltous chloride the Grignard compound (XLIII) of anethole hydrobromide is reduced to a free radical (XLIV), which dimerizes to hexestrol dimethyl ether (XXVII).



XLIII XLIV

Of theoretical interest only is a synthesis found by Price and Mueller (154), who subjected 3,4-dichlorohexane (XLV) to a Friedel–Crafts reaction with anisole and obtained a very small yield of hexestrol dimethyl ether (XXVII).

$$\underset{\text{XLV}}{C_2H_5CHClCHClC_2H_5} \longrightarrow \text{XXVII}$$

C. OPTICAL ISOMERISM

Dodds, Goldberg, Lawson, and Robinson (59) obtained two isomeric forms of 3,4-bis(*p*-hydroxyphenyl)hexane (XX), one melting at 185°C., the other at 128°C. The relationship of these two isomers to stilbestrol and its isomer will be treated in a subsequent chapter. The higher melting form was called hexestrol by Campbell, Dodds, and Lawson (24), who also reported its superior estrogenic activity as compared with the lower melting form, called isohexestrol by Peak and Short (145). Wessely and Welleba (224, 225) reported that the purest preparations of hexestrol do not have a clear melting point at 186°C., and even after purification by way of the diacetate, hexestrol contains an impurity melting at 230°C. with decomposition. These authors succeeded in assigning the *meso*-form to hexestrol through resolution of isohexestrol into two

TABLE 2

Homologs of hexestrol

FORMULA  R	R′	MELTING POINT	NAME	ESTROGENIC ACTIVITY IN RATS SUBCUTANEOUSLY (100 PER CENT RESPONSE, UNLESS OTHERWISE INDICATED) Minimum effective dose	Rat units per gram	REFERENCES
		°C.		*micrograms*		
H	H	198–199	1,2-Bis(*p*-hydroxyphenyl)ethane	100,000		(64)
CH_3	CH_3	138–139	2,3-Bis(*p*-hydroxyphenyl)butane	0.5	2,000,000	(56)
		139–139.5		10		(1, 75a)
		231–232		1,000		(1)
C_2H_5	C_2H_5		3,4-Bis(*p*-hydroxyphenyl)hexane			
		186	*Meso*-form ("hexestrol")	0.2	5,000,000	(24, 56)
				2.0		(223)
		129	Racemate ("isohexestrol")	1,000		(25)
		130		500		(223, 225)
		80	+Antipode	100		(225)
		80	−Antipode	1,000 (40%)		(225)
C_3H_7	C_3H_7		4,5-Bis(*p*-hydroxyphenyl)octane			
		165	(a)	5	200,000	(56)
		b.p. 185/0.1 mm.	(b)	100	10,000	(56)
$C_{16}H_{33}$	H	86–87	1,2-Bis(*p*-hydroxyphenyl)-octadecane	100,000	10	(56)

antipodes by means of α-bromocamphor-π-sulfonic acid. Equal parts of the two antipodes (m.p. 80°C., $[\alpha]_D^{17} = +17.7°$ and $-17.6°$, respectively) mixed together showed the melting point, 129°C., of the racemate. The two antipodes and the racemate possess entirely different activities, the *d*-form being five times more active than the racemate, and ten to twenty times more active than the *l*-form (see table 2). The following point might illustrate the limitations in comparing estrogenic potencies, even those reported from the same laboratory. Unless the *l*-antipode should have an inhibitory effect on the activity of the *d*-form, an extremely remote possibility, it is not clear why the racemate should be less than one-half as active as the *d*-form.

Interesting rearrangements have been observed for the pair of dimethyl ethers; hexestrol dimethyl ether melts at 145–146°C. and isohexestrol dimethyl ether melts at 56°C. (see table 6).

Bretschneider *et al.* (15a, 16), while attempting unsuccessfully to dehydrogenate the isomeric hexestrols to stilbestrol derivatives, observed that both dimethyl ethers are attacked when heated in the presence of palladium on charcoal. Hexestrol dimethyl ether remains unchanged to the extent of 28 per cent, while the remainder is converted into a substance not yet identified. When isohexestrol dimethyl ether is treated under similar conditions 42 per cent is converted into hexestrol dimethyl ether, or 70 per cent on the basis of recovered unchanged material. The authors pointed out the practical significance of thus converting an estrogen of medium into one of highest potency.

Peak and Short (145) observed a 50 per cent conversion of the racemate into the *meso*-form and partial conversion in the reverse direction by heating to 300°C. in an atmosphere of hydrogen sulfide. Peak and Short remarked that "it is difficult to envisage the observed isomerizations except on the basis either of reversible dehydrogenation or of fission and of recombination." However, this isomerization is reminiscent of the well-known partial racemization of tartaric acid, leading to an equilibrium between the *meso*-form and the racemate.

The assignment of the *meso*-form was confirmed by Carlisle and Crowfoot (27), who undertook a study of x-ray crystallographic measurements of a series of *p,p'*-substituted diphenylhexane derivatives. For *p,p'*-dihydroxy derivatives (hexestrol and isohexestrol), as well as for the 4,4'-diamino and the 4,4'-dicarbomethoxy derivatives, it could be shown that the higher melting isomers possess the molecular symmetry characteristic of the *meso*-form, while the lower melting forms are racemic.

IV. Stilbestrol

A. Syntheses

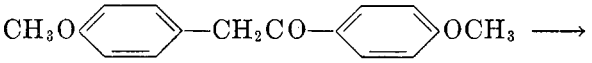
The first synthesis from desoxyanisoin (XLVI) was published in 1938 by Dodds, Goldberg, Lawson, and Robinson (58) simultaneously with the disclosure of the potency of stilbestrol. The relatively poor yield and the increasing demands for therapeutic use were incentives for many workers to develop new syntheses. The structure of stilbestrol lends itself to a large number of

synthetic approaches. Several among the syntheses represent definite advances over Dodds's original method and appear suitable for production on a larger scale. Other procedures are of only theoretical interest; nevertheless they demonstrate interesting relationships between the intermediates of various syntheses.

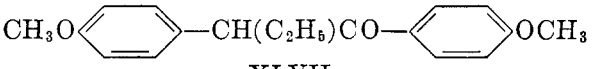
In the following discussion the synthetic methods have been broken down into types of approaches irrespective of their practical usefulness.

1. Syntheses from anisoin

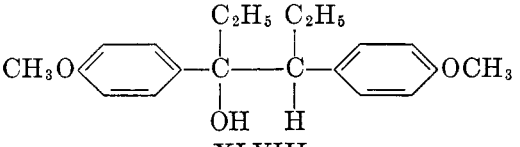
Dodds and coworkers (58, 59) reacted desoxyanisoin (XLVI) with ethyl iodide and sodium ethoxide to give ethyldesoxyanisoin (XLVII). Introduction of the second ethyl group by a Grignard reaction resulted in one of the two racemic forms, m.p. 117°C., of 3,4-dianisyl-3-hexanol (XLVIII). The other isomeride, m.p. 85°C., was later isolated by Braker *et al.* (14) and by Wessely and coworkers (222). Dehydration of the carbinol (XLVIII) to a stilbene derivative was originally (58) effected by means of phosphorus tribromide, potassium bisulfate, or a mixture of acetic anhydride and acetyl chloride; later Kuwada *et al.* (107) used hydrochloric acid, and Wessely *et al.* (222) used potassium pyrosulfate. These reactions led to a mixture of the liquid *cis*- and the crystalline *trans*-forms of 4,4′-dimethoxy-α,β-diethylstilbene (XL).



XLVI
Desoxyanisoin



XLVII
Ethyldesoxyanisoin



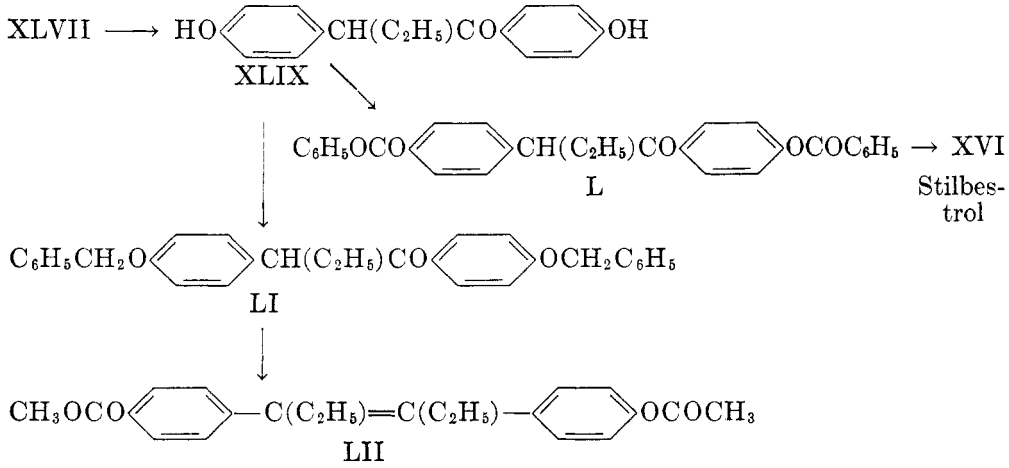
XLVIII
3,4-Dianisyl-3-hexanol

Subsequent studies, discussed later, provided the evidence for the respective assignment of configuration. Rohrmann (168a, 168b) found that iodine in various solvents or the complex of boron trichloride (or, preferably, the trifluoride) with ethyl ether reacts with the carbinol (XLVIII) in carbon tetrachloride to give almost exclusively the desired *trans*-form. Wilds and Biggerstaff (228a) obtained the same result with *p*-toluenesulfonic acid.

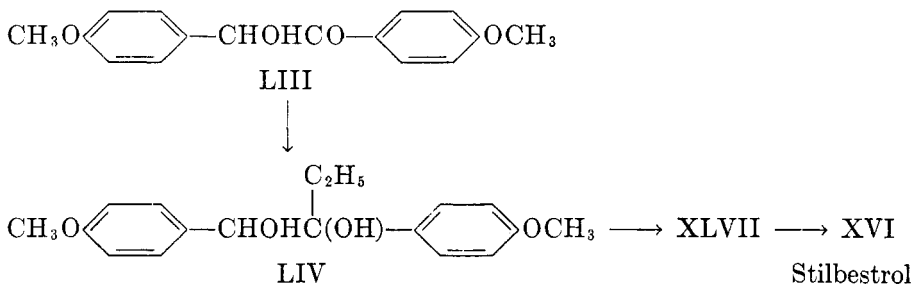
The last step in the synthesis, demethylation of the methoxyl groups, caused considerable difficulties. Dodds *et al.* (58) used potassium hydroxide and ethanol at 228°C., Zajik and Wessely (230) Grignard reagent at elevated temperatures,

and Corse (37, 68a), hydroxides of sodium, potassium, or lithium dissolved in ethylene, diethylene, dipropylene, or triethylene glycols at 190–235°C. Rubin *et al.* (170) found that the demethylation by sodium or sodium hydroxide in boiling diethylene glycol monoethyl ether (Carbitol) yields a mixture of stilbestrol and its monomethyl ether, with the latter predominating.

Dodds *et al.* (59) further reported two modifications of their original synthesis. The difficult demethylation of the phenolic methoxyl groups is effected at an earlier stage by treating ethyldesoxyanisoin (XLVII) with hydriodic acid to give 4,4′-dihydroxy-α-ethyldesoxybenzoin (XLIX). Therefrom the dibenzoic ester (L) was prepared which was reacted with 5 moles of ethyl Grignard reagent to give stilbestrol (XVI) directly. The other modification is by way of the dibenzyl ether (LI), followed by Grignard reaction and acetylation to stilbestrol diacetate (LII).

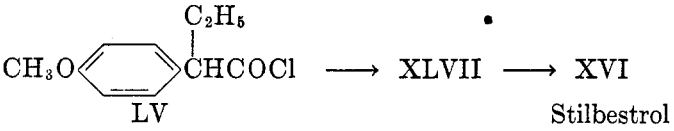


Kuwada and Sasagawa (106) modified the original synthesis by introducing the first ethyl group into anisoin (LIII) by means of a Grignard reaction to give 3,4-bis(*p*-anisyl)-3,4-butanediol (LXIV); dehydration with sulfuric acid led to ethyldesoxyanisoin (XLVII), the key intermediate of Dodds's synthesis.



2. Introduction of anisyl group by Friedel–Crafts reaction

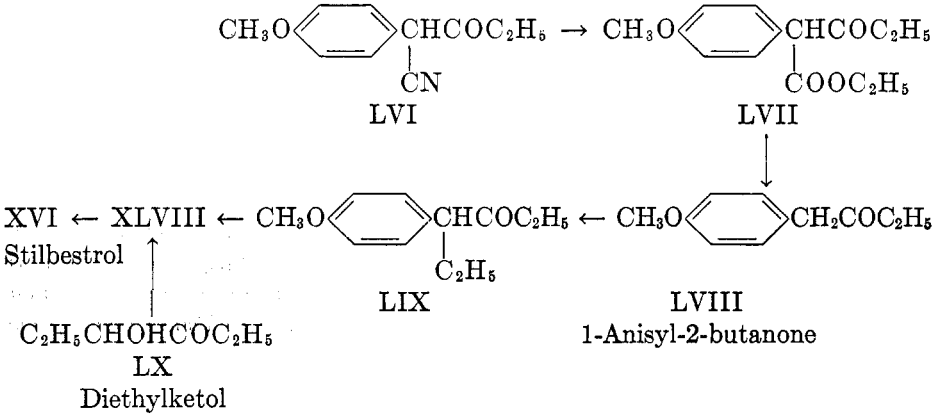
The same intermediate (XLVII) of the preceding syntheses was obtained by Andersag and Salzer (2) from α-anisyl-α-ethylacetyl chloride (LV), by a Friedel–Crafts reaction with anisole.



While this Friedel–Crafts synthesis has not yet been reported in detail, Wilds and Biggerstaff (228a) independently arrived at essentially the same method. These authors obtained the acid chloride (LV) from the readily available α-phenylbutyric acid by a series of standard reactions.

3. Introduction of anisyl group by Grignard reaction

Wessely and coworkers (222) devised a stilbestrol synthesis starting from *p*-methoxybenzyl cyanide, which was subjected to a Claisen condensation to give α-propionyl-*p*-methoxybenzyl cyanide (LVI) and, by way of the imido ether, ethyl α-propionyl-α-*p*-methoxyphenyl acetate (LVII). After hydrolysis and decarboxylation to 1-anisyl-2-butanone (LVIII), the second ethyl group was introduced by means of ethyl iodide and sodium ethoxide, resulting in 3-(*p*-anisyl)-4-hexanone (LIX). The Grignard reaction of the hexanol with anisylmagnesium bromide gave predominantly the carbinol (XLVIII), m.p. 117°C., described by Dodds *et al.* (58, 59), in addition to a new isomer melting at 85°C. The synthesis was completed by dehydration to stilbestrol dimethyl ether, followed by demethylation.



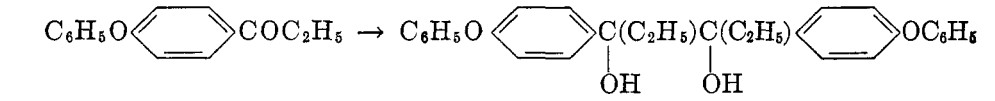
The same synthesis is a subject of a patent claim by Fieser and Christiansen (78). Kuwada *et al.* (107) introduced both anisyl groups by Grignard reactions into diethylketol (LX), arriving at the carbinol (XLVIII).

4. Syntheses involving retro-pinacolin rearrangements

A number of syntheses are based on the intermediate formation of asymmetric α,α-dianisylethane derivatives, which are subject to the retro-pinacolin rearrangement to stilbene derivatives. Part of this work is based on investigations by Orekhoff (142) on the corresponding phenyl analogs.

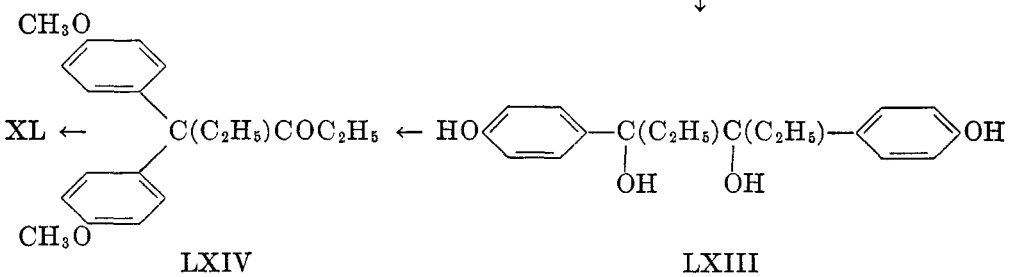
Hobday and Short (91) reduced 4-phenoxypropiophenone (LXI) electrolytically and dephenylated the resulting pinacol (LXII) to the lower melting (m.p.

94–95°C.) of the two isomeric forms of 3,4-bis(*p*-hydroxyphenyl)-3,4-hexanediol (LXIII).



LXI
p-Phenoxypropiophenone

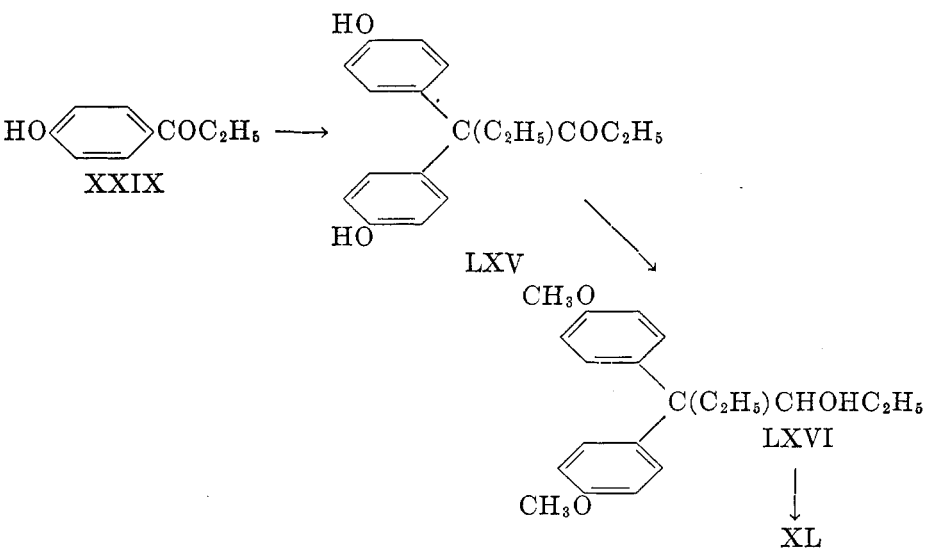
LXII



LXIV LXIII

The pinacol (LXIII) undergoes the pinacolin rearrangement to give, after methylation, 3,3-bis(*p*-anisyl)-4-hexanone (LXIV). On reduction of this compound with sodium and amyl alcohol retro-pinacolin rearrangement takes place to give the dimethyl ether (XL) of stilbestrol.

Wessely *et al.* (222) effected a similar series of reactions starting from *p*-hydroxypropiophenone (XXIX). In this case the other isomeric 3,4-bis(*p*-hydroxyphenyl)-3,4-hexanediol (LXIII), m.p. 204–206°C., was obtained as an intermediate. (Dehydration by means of a mixture of acetyl chloride and acetic anhydride gives a diene, dienestrol (XXI), to be discussed later). Potassium bisulfate, potassium persulfate, or acetic anhydride cause pinacolin rearrangement to 3,3-bis(*p*-hydroxyphenyl)-4-hexanone (LXV), also obtained by Adler *et al.* (1) by reacting LXIII with hydriodic acid and phosphorus.



XXIX

LXV

LXVI

XL

After conversion of LXV to the methyl ether (LXIV), the former authors obtained the intermediate pinacolin alcohol (LXVI), which then underwent dehydration and retro-pinacolin rearrangement to stilbestrol dimethyl ether (XL).

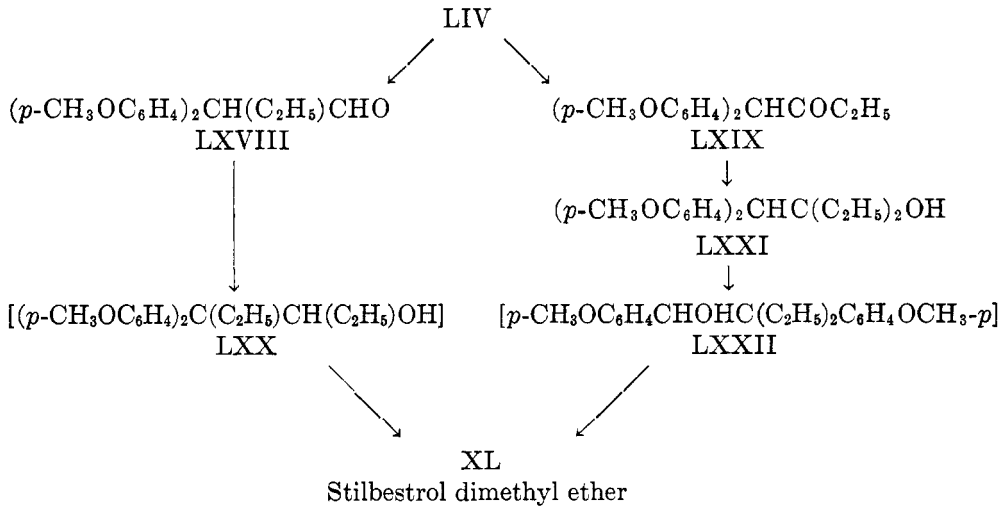
Surprisingly enough, Tendick (210a, 210b) found that pinacols of type LXIII, with free or acylated phenolic hydroxyl groups, do not undergo the pinacolin rearrangement when treated with strong mineral acids. By this method the author obtained the epoxy derivatives of type XCII, which were then reduced with sodium and alcohol to 3,4-bis(*p*-hydroxyphenyl)-3-hexanol or its phenol esters.

Returning briefly to the two isomeric forms of the pinacol (LXIII), it should be mentioned that the higher melting isomer, m.p. 204–206°C., was first obtained by Dodds and coworkers (58, 59, 60) in the course of their synthesis of dienestrol, by reduction of *p*-hydroxypropiophenone (XXIX) with aluminum amalgam in moist ether; Robinson and Resuggan (161) claimed a better yield by electrolytic reduction. According to Hobday and Short (91), either one of these two methods gives both isomeric forms of the pinacol (LXIII). Finally, the last authors obtained the higher melting form from the corresponding dimethyl ether by reaction of two moles of anisylmagnesium bromide with dipropionyl (LXVII).

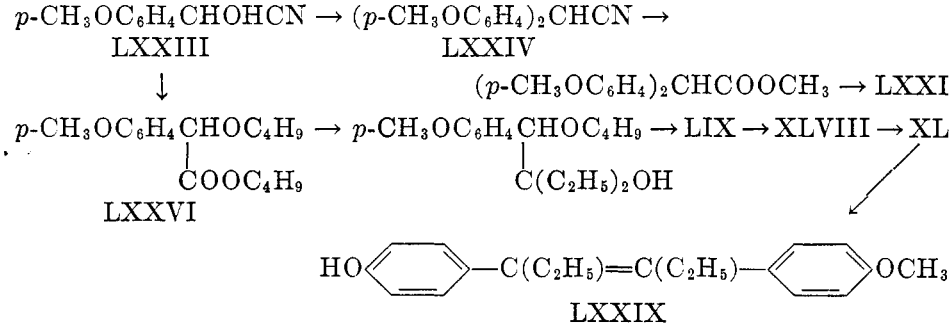
$C_2H_5COCOC_2H_5$

LXVII

Peteri (147, 148) contributed three syntheses of stilbestrol involving molecular rearrangements. The first two have as a common starting point 3,4-bis(*p*-anisyl)-3,4-butanediol (LIV), encountered earlier in another synthesis (106). Depending on the dehydrating conditions this substance may rearrange in two ways to α,α-dianisylbutyraldehyde (LXVIII) and 1,1-anisyl-2-butanone (LXIX). Both are reacted with ethylmagnesium bromide to give LXX and LXXI, and are then subjected to dehydration and a second rearrangement of the retro-pinacolin type encountered earlier.

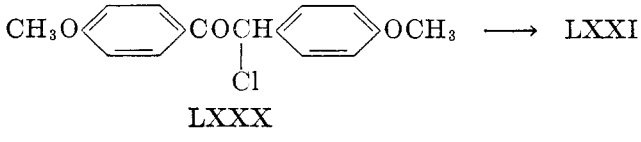


The rearrangement of 1,1-bis(*p*-anisyl)-2-ethyl-2-butanol (LXXI) over the hypothetical intermediate (LXXII) by means of phosphorus oxychloride in toluene occurs in 32 per cent yield. The intermediate (LXXI) may be prepared by a third synthesis devised by this worker. Starting from anisaldehyde cyanohydrin (LXXIII), the second anisyl group is introduced by means of sulfuric acid to give α,α-dianisylacetonitrile (LXXIV). After hydrolysis and esterification to LXXV, substitution with both ethyl groups is effected by a Grignard reaction, resulting in LXXI.



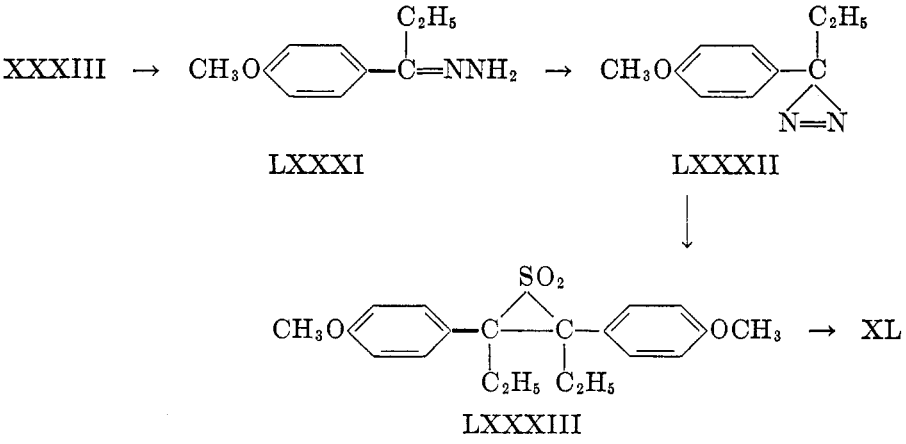
Rubin *et al.* (170) reported another synthesis involving the same starting material (LXXIII) and also a retro-pinacolin rearrangement with alkyl migration.

Anisaldehyde is converted to the cyanohydrin (LXXIII) and by reaction with butanol yields butyl α-anisyl-α-butoxyacetate (LXXVI). In the second step two ethyl groups are introduced by means of ethylmagnesium chloride, but the intermediate carbinol (LXXVII) need not be isolated and is dehydrated under rearrangement to 3-(*p*-anisyl)-4-hexanone (LIX), encountered previously in other syntheses (78, 222). In variation to the latter, Rubin *et al.* preferred to substitute with the second anisyl group by means of 4-chloroanisole and sodium, resulting in the carbinol (XLVIII) which is dehydrated, without isolation, to a mixture of stilbestrol dimethyl ether (XL) and its *cis*-isomer. The third step is completed by isomerization of the *cis*-isomer in the presence of iodine and ferric chloride, and the fourth step comprises demethylation by means of sodium or sodium hydroxide in boiling Carbitol; under these conditions the larger part is converted into stilbestrol monomethyl ether (LXXIX) desired in this instance. The over-all yield from anisaldehyde is 12 per cent for the monomethyl ether in addition to 9 per cent for stilbestrol. Foldi and Demjen (80) reacted chlorodesoxyanisoin (LXXX), also described by Dodds (56), with ethylmagnesium bromide and obtained the carbinol (LXXI), owing to change of position of an alkyl and an aryl group.

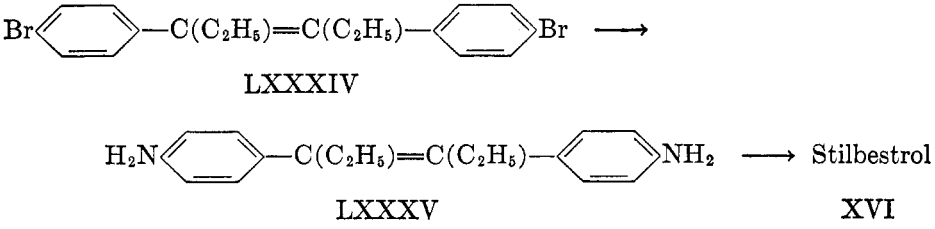


5. Syntheses involving miscellaneous rearrangements

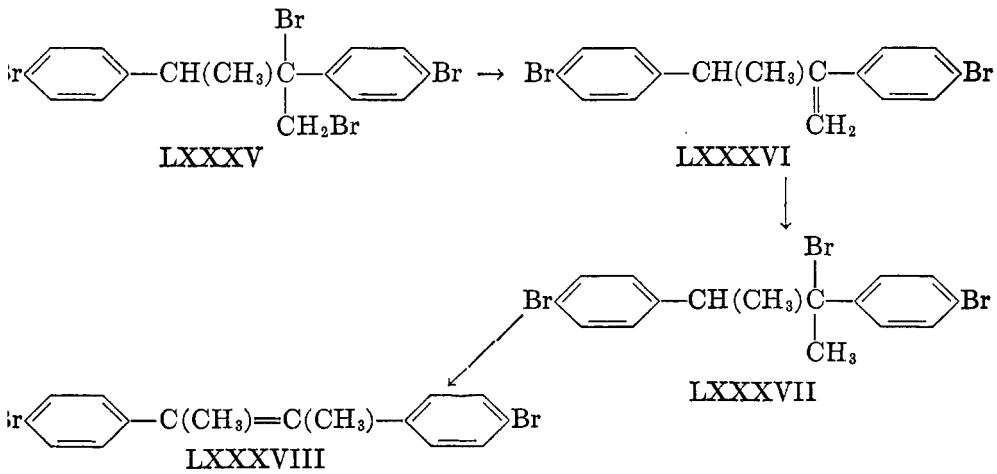
Vargha (159, 212, 213) developed an interesting synthesis with an over-all yield of 25 per cent from *p*-methoxypropiophenone (XXXIII) to stilbestrol dimethyl ether. The starting material is transformed into the hydrazone (LXXXI) and oxidized with mercuric oxide to anisylethyldiazomethane (LXXXII), which need not be isolated. It easily decomposes under partial loss of nitrogen to the ketazine (XXXV) obtained by Foldi and Fodor (81),but with sulfur dioxide in petroleum ether it mainly reacts under total loss of nitrogen to give the sulfone (LXXXIII) and by thermal decomposition of the latter, stilbestrol dimethyl ether (XL) is obtained.



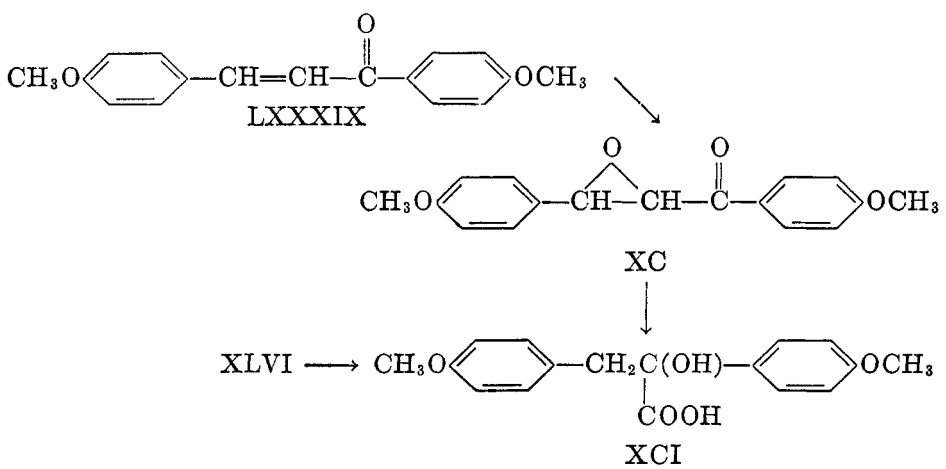
Vargha and Kovacs (213) used this method for the synthesis of the 4,4′-dibromo analog (LXXXIV) of stilbestrol; by the action of cuprous iodide and ammonium hydroxide the bromo compound was converted to the 4,4′-diamino analog (LXXXV) and by a Sandmeyer reaction to stilbestrol; the latter could not be directly obtained from the dibromo compound (LXXXIV).



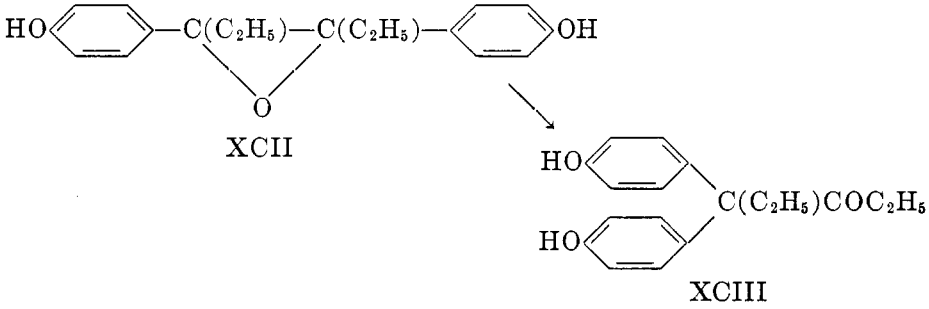
Similar bromo derivatives are accessible by still another method. Barber (9, 10) prepared 4,4′-dibromo-α,β-dimethylstilbene (LXXXVIII) by way of the compounds LXXXV to LXXXVII.



Kharasch and Kleiman (99) devised the shortest synthesis of stilbestrol with the impressive over-all yield of 22 per cent, including the final demethylation, starting from anethole hydrobromide (XXXIX). Under the influence of sodium amide in liquid ammonia two molecules couple with loss of bromine. The resulting product, m.p. 120.5°C., is isomeric but not identical with either stilbestrol dimethyl ether or its *cis*-isomer. It was mentioned before that either one of the two structures XLI and XLII has been assigned to the product. During demethylation rearrangement takes place, resulting in a mixture of stilbestrol and an unidentified oil which by repeated demethylation is also converted to stilbestrol. Rohrmann, Jones, and Shonle (168, 169) applied some previously known reactions of chalcones to a new synthesis of the important intermediate desoxyanisoin (XLVI). Anisyl *p*-methoxystyryl ketone (LXXXIX) is oxidized with hydrogen peroxide and alkali to the epoxy derivative (XC), which is rearranged with alkali to *p*-anisyl(*p*-methoxybenzyl)glycolic acid (XCI). By oxidation with red lead and simultaneous decarboxylation, desoxyanisoin (XLVI) is obtained in 50 to 70 per cent over-all yield.



A similar rearrangement had been described earlier by Wessely *et al.* (98, 222); the epoxy derivative (XCII) of stilbestrol on heating rearranges to 3,3-bis(*p*-hydroxyphenyl)-4-hexanone (XCIII).

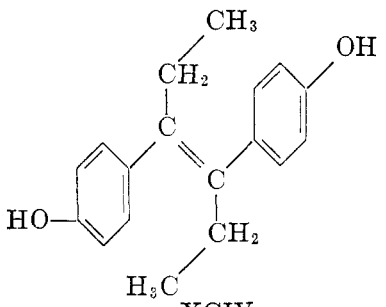


B. *Cis–trans* ISOMERISM OF STILBESTROL

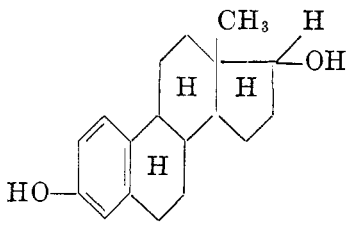
The theory requires two *cis–trans* isomers for a compound possessing the structure (XVI) of stilbestrol, and the problem of assigning the proper configuration to the two isomers has prompted much theoretical and experimental work. In the course of their synthesis of stilbestrol Dodds *et al.* (58, 59) dehydrated 3,4-dianisyl-3-hexanol (XLVIII) to obtain two isomeric forms (XL): one crystalline, m.p. 123–124°C., after demethylation yielding stilbestrol, m.p. 171°C.; the other an oil, b.p. 175–178°C. at 0.74 mm., on demethylation yielding ψ-stilbestrol, m.p. 141°C. (later 151°C.). The oily dimethyl ether is gradually transformed into the crystallized isomer, stilbestrol dimethyl ether, when exposed to sunlight and especially in the presence of iodine. For this Rubin *et al.* (170) used iodine with ferric chloride, antimony pentachloride, aluminum trichloride, or boron trifluoride while heating at 140°C. Serini and Steinruck (188) found that the rearrangement during the demethylation by means of alcoholic alkali is favored at temperatures above 200°C., in the presence of iodine at 180°C., or just by shaking at room temperature with palladium.

According to Wessely and Welleba (225) the reverse transformation could not be effected. Yet this finding was not conclusive as an argument for assigning the *cis* or *trans* configuration to stilbestrol, because under similar conditions, *cis*-α,β-dimethylstilbene also cannot be rearranged to its *trans*-isomer. Wessely (219) further noted that higher thermostability alone is no proof for the *trans* configuration, because several instances (68, 210) are known where the *cis*-form of certain ethylene derivatives proved to be the more stable.

Dodds, Robinson, and their coworkers (58, 59) reported that ψ-stilbestrol has only a fraction of the estrogenic activity of stilbestrol. These authors held that the difference in activity was strong evidence in favor of the *cis* configuration for ψ-stilbestrol, reasoning that stilbestrol, as the more active isomer, should have the *trans* configuration more closely related to estradiol. This resemblance was underlined by writing the structural formula (XCIV) for stilbestrol in a manner resembling that of estradiol (XCV).



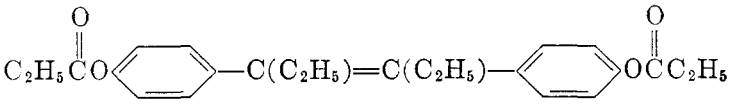
XCIV
Stilbestrol



XCV
Estradiol

For a number of years no unequivocal proof could be provided for the *trans* configuration of stilbestrol. This was mainly due to the difficulties encountered in obtaining pure ψ-stilbestrol. Consequently the conditions were unfavorable for a direct and conclusive comparison of the physicochemical characteristics of the two isomers, such as dipole measurements (219), absorption spectra, or crystallographic x-ray measurements.

Only recently reports have come forth from three different laboratories regarding the purification of ψ-stilbestrol and its dipropionate. Peteri (146) reacted stilbestrol with propionic anhydride or pyridine and, in addition to the previously known (57) stilbestrol dipropionate (XCVI), m.p. 105–106°C., obtained from the mother liquors an isomeric dipropionate, m.p. 71–72°C. Both dipropionates on hydrolysis give exclusively stilbestrol; this result may be explained by the extraordinary lability of ψ-stilbestrol.



XCVI

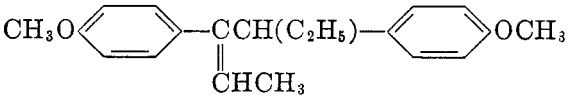
Wessely, Bauer, and Kerschbaum (220) confirmed these results. However, these workers indicated that propionylation of the purest stilbestrol does not give rise to the *cis*-isomer, while the product of mild hydrolysis of the dipropionate, m.p. 71–72°C. (79°C. for the purest preparation), on renewed propionylation gives a mixture of both isomeric propionates.

Walton and Brownlee (215) made the most thorough investigation of the propionic esters and confirmed Peteri's results. Furthermore, these authors succeeded in a further purification of a ψ-stilbestrol preparation with m.p. 141°C. by extended fractionation from benzene, resulting in stilbestrol, m.p. 171°C. (needles), and ψ-stilbestrol, m.p. 151°C. (hexagonal tablets). This preparation is believed to be pure, as evidenced by the melting-point diagram which shows that the impure preparation of Dodds *et al.* (59), m.p. 141°C., was approximately a eutectic mixture containing 60 per cent ψ-stilbestrol and 40 per cent stilbestrol. After a preliminary study, Dodds and Robinson agreed (215) with this conclusion.

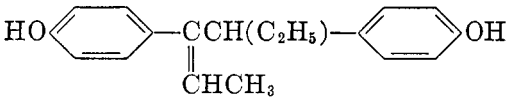
The situation is complicated by the fact that Walton and Brownlee esterified pure ψ-stilbestrol, m.p. 151°C., and obtained an oily dipropionate. This oily dipropionate on alkaline hydrolysis gives a theoretical yield of ψ-stilbestrol, and in the opinion of the authors the oil may prove to be a mixture. However, it is difficult to see why such a mixture should hydrolyze exclusively to ψ-stilbestrol, while either one of the two crystalline propionates yields exclusively stilbestrol. The interrelationship of these compounds is shown in table 3. By direct comparison, Walton and Brownlee determined the relative estrogenic activities:

Stilbestrol: ψ-stilbestrol = 14:1
Stilbestrol dipropionate: ψ-stilbestrol dipropionate = 600:1
Stilbestrol dipropionate: oily ψ-stilbestrol dipropionate = 16:1

In the following way Wessely *et al.* (220) provided good evidence for the location of the double bond in the crystalline ψ-stilbestrol dipropionate. This group of investigators had previously (222, 223) shown that dehydration of the carbinol (XLVIII) by means of potassium acid sulfate results, in addition to the dimethyl ethers of stilbestrol and ψ-stilbestrol, in a pair of two structural isomers (XCVII): the one an oil, the other crystalline, m.p. 50°C.



XCVII

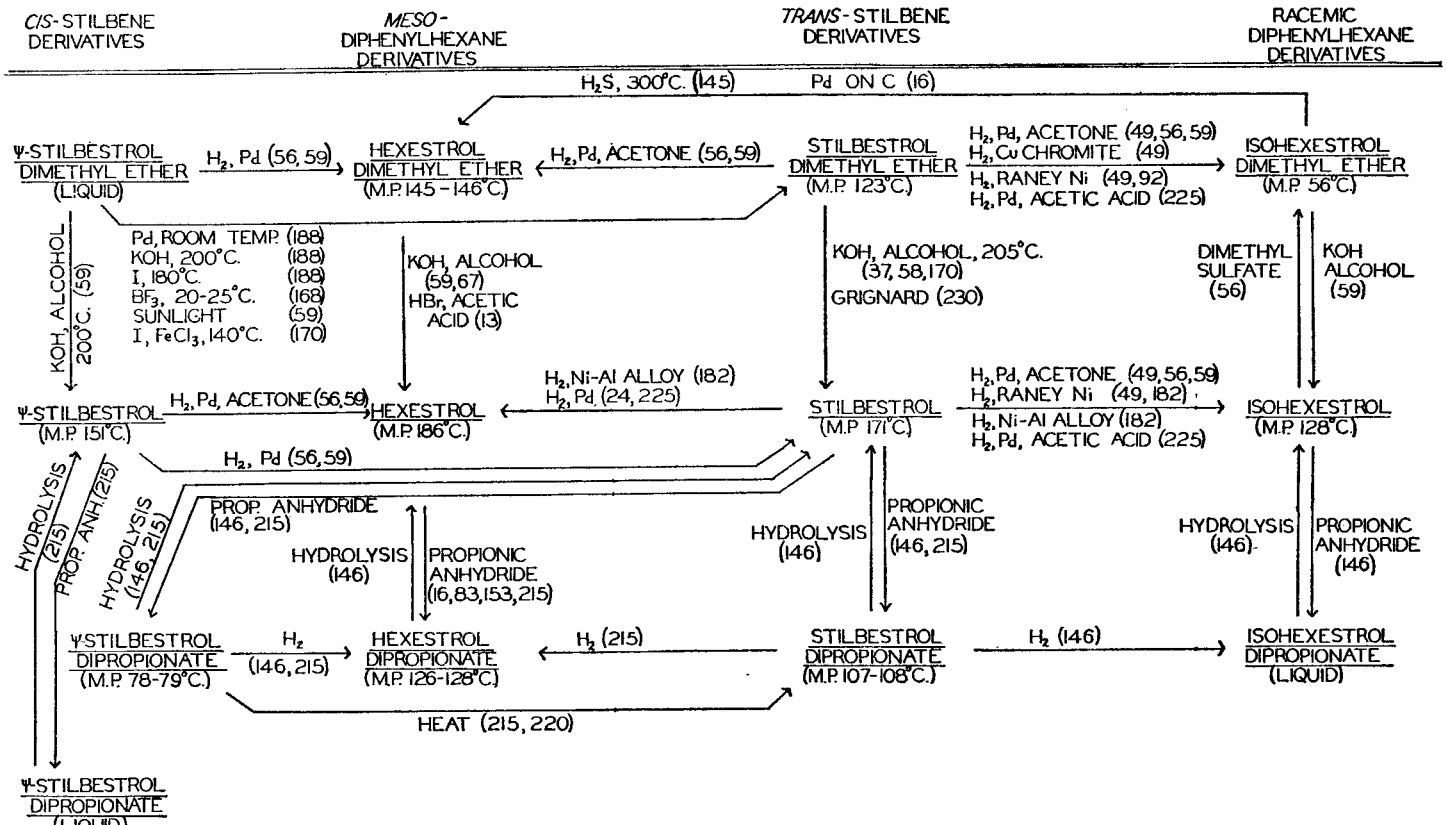


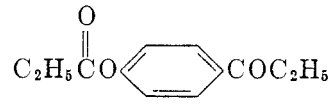
XCVIII

The structure of these new isomers was proved by ozonization to ethyldesoxyanisoin (XLVII). With iodine as a catalyst both isomers rearrange to stilbestrol dimethyl ether (XL). The two compounds are *cis–trans* isomers with the configuration not determined, both being racemic regarding the asymmetric carbon atom. The dimethyl ethers (XCVII) are demethylated to the two corresponding forms of 3,4-bis(*p*-hydroxyphenyl)-2-hexene (XCVIII), m.p. 43.5°C. and 053°C., respectively. It is worth noting that one of these is highly potent, while the other has only medium activity. A resolution of these racemates into the optical antipodes has not been reported. Wessely (220) found that both forms of 3,4-bis(*p*-hydroxyphenyl)-2-hexene give oily dipropionates not identical with the crystallized dipropionates of stilbestrol and ψ-stilbestrol. This finding refutes a statement by Jones (96) that the hexene derivative, m.p. 053°C., may be identical with ψ-stilbestrol, m.p. 151°C. It remains to be seen how the oily dipropionate obtained from ψ-stilbestrol is related to the others or if it is identical with one of the dipropionates prepared from the hexene (XCVIII).

These results make it likely that the crystalline ψ-stilbestrol dipropionate is a stilbene derivative and thus the *cis*-isomer of stilbestrol. This was further corroborated by Wessely *et al.* (37), who ozonized the crystalline ψ-stilbestrol dipropionate, and obtained *p*-propoxypropiophenone (XCIX).

TABLE 3


CIS-STILBENE DERIVATIVES
MESO-DIPHENYLHEXANE DERIVATIVES
TRANS-STILBENE DERIVATIVES
RACEMIC DIPHENYLHEXANE DERIVATIVES
H2S, 300°C. (145)
Pd ON C (16)
Ψ-STILBESTROL DIMETHYL ETHER (LIQUID)
H2, Pd (56, 59)
HEXESTROL DIMETHYL ETHER (M.P. 145-146°C.)
H2, Pd, ACETONE (56, 59)
STILBESTROL DIMETHYL ETHER (M.P. 123°C.)
H2, Pd, ACETONE (49, 56, 59)
H2, Cu CHROMITE (49)
H2, RANEY Ni (49, 92)
H2, Pd, ACETIC ACID (225)
ISOHEXESTROL DIMETHYL ETHER (M.P. 56°C.)
KOH, ALCOHOL, 200°C. (59)
Pd, ROOM TEMP. (188)
KOH, 200°C. (188)
I, 180°C. (188)
BF3, 20-25°C. (168)
SUNLIGHT (59)
I, FeCl3, 140°C. (170)
KOH, ALCOHOL (59, 67)
HBr, ACETIC ACID (13)
KOH, ALCOHOL, 205°C. (37, 58, 170)
GRIGNARD (230)
DIMETHYL SULFATE (56)
KOH ALCOHOL (59)
Ψ-STILBESTROL (M.P. 151°C.)
H2, Pd, ACETONE (56, 59)
HEXESTROL (M.P. 186°C.)
H2, Ni-Al ALLOY (182)
H2, Pd (24, 225)
STILBESTROL (M.P. 171°C.)
H2, Pd, ACETONE (49, 56, 59)
H2, RANEY Ni (49, 182)
H2, Ni-Al ALLOY (182)
H2, Pd, ACETIC ACID (225)
ISOHEXESTROL (M.P. 128°C.)
H2, Pd (56, 59)
HYDROLYSIS (215)
PROP. ANH. (215)
HYDROLYSIS (146, 215)
PROP. ANHYDRIDE (146, 215)
HYDROLYSIS (146)
PROPIONIC ANHYDRIDE (16, 83, 153, 215)
HYDROLYSIS (146)
PROPIONIC ANHYDRIDE (146, 215)
HYDROLYSIS (146)
PROPIONIC ANHYDRIDE (146)
Ψ-STILBESTROL DIPROPIONATE (M.P. 78-79°C.)
H2 (146, 215)
HEXESTROL DIPROPIONATE (M.P. 126-128°C.)
H2 (215)
STILBESTROL DIPROPIONATE (M.P. 107-108°C.)
H2 (146)
ISOHEXESTROL DIPROPIONATE (LIQUID)
HEAT (215, 220)
Ψ-STILBESTROL DIPROPIONATE (LIQUID)



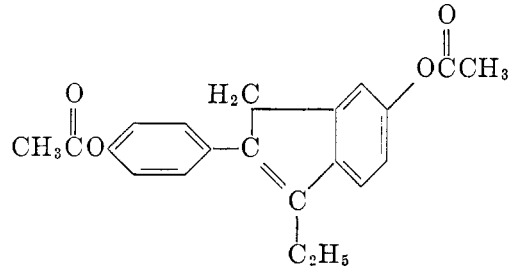
XCIX

p-Propoxypropiophenone

It was concluded that the starting material must have been an ester of the *cis*-isomer of stilbestrol, because fissure occurred in the same position as with stilbestrol, which was ozonized (222) to *p*-hydroxypropiophenone (XXIX).

Wessely and Welleba (224, 226) employed hydrogenation methods to prove the *trans* configuration of stilbestrol. The results will be discussed in a subsequent section.

The direct comparison of the ultraviolet-absorption spectra of stilbestrol and its isomer has not yet been possible, but the spectrum of stilbestrol alone is of interest. Solmssen (127) compared the spectra of the diacetate of stilbestrol and of 2-(*p*-acetoxyphenyl)-3-ethyl-6-acetoxy-2,3-indene (C).



C

This substituted phenylindene derivative has a spectrum almost identical with that of *trans*-stilbene and of the unsubstituted 2-phenylindene, according to Wiegand and Merkel (143), while stilbestrol has a quite different spectrum. It now appears that this disagreement of the spectra is due to the α,β-alkyl substitution of the stilbene double bond. The spectrum of stilbestrol was found to be very similar to that of α,β-diethylstilbene (136) and of *trans*-α,β-dimethylstilbene according to Arends (3), and in accordance with Kuwada and Sasagawa (106) it must be concluded that the *trans* configuration of stilbestrol is not in disagreement with its absorption spectrum. There is other strong evidence in favor of this configuration. Giacomello and Bianchi (86) studied the crystallographic constants of stilbestrol and its dimethyl ether. According to these authors the Patterson projection on the plane AC conforms with the *trans* structure of the molecule. Carlisle and Crowfoot (27) concluded from their study of crystallographic measurements that the general arrangement of the groups around the central double bond is that expected for the *trans* configuration in stilbestrol and stilbestrol dipropionate (m.p. 104°C.). However, the authors added, this was clearly established only in the case of the dipropionate, while in the other case a more detailed x-ray crystallographic analysis might reveal molecular symmetry not apparent from the preliminary measurements.

C. ANALYTICAL METHODS FOR STILBESTROL DETERMINATION

The commercial production of stilbestrol made it desirable to develop chemical and physical analytical procedures.

Dingemanse (45, 46, 47) utilized the fuchsin-red color developed with antimony trichloride for the colorimetric determination of stilbestrol.

According to Huf and Widmann (93) this method is suitable for pure solutions only and for samples not larger than 2.5 micrograms. These workers developed a new method where stilbestrol is coupled with diazobenzenesulfonic acid and the resulting yellow-red coloration determined colorimetrically, with linear concentration–extinction relations in the range of 50–250 micrograms per cubic centimeter.

Tubis and Bloom (211), as well as Dracass and Foster (66), developed the phenol reaction of Folin–Ciocaltu as a reliable method which was adopted by the Council of Pharmacy and Medicine for New and Nonofficial Remedies (38). The method is based on colorimetric or photometric examination of stable blue tungstic oxides due to reduction of labile phosphomolybdic phosphotungstic acids by phenolic hydroxyls. A straight-line graph was obtained for amounts of 0.2 to 0.8 mg. of stilbestrol.

Another method adopted by the Council for New and Nonofficial Remedies (38) is that of Sondern and Burson (195, 196), based on the bromometric titration of phenols and reminiscent of brominations in the stilbene series by Linnell and Shaikmahamud (112). The method requires the strict observance of specified conditions, because 6 or 8 moles of bromine are consumed, depending on the temperature; the method is suitable for amounts from 1 to 40 mg. of stilbestrol.

A qualitative assay method recommended by the Council for New and Nonofficial Remedies (38) is based on the acetylation of stilbestrol and examination of the refractive index of the crystalline diacetate under the polarizing microscope.

The conversion of stilbestrol into the diacetate and its gravimetric determination have been adopted as a quantitative method in the United States *Pharmacopoeia* (149). It may be questioned if this method matches the accuracy of some of the quantitative methods discussed earlier.

Dechene (41) proposed the application of the xanthoprotein reaction; for amounts of 0.25 to 1.75 mg. of stilbestrol the method may be used with an error of $\pm$ 1 per cent, but only when stilbestrol is the sole phenyl derivative present.

Elvidge (69, 70) used the ultraviolet-absorption spectra for the quantitative determination of stilbestrol and its derivatives. Della Croce (42) has described several qualitative color reactions for stilbestrol.

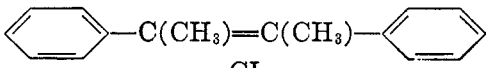
D. HYDROGENATION OF STILBESTROL

1. Hydrogenation of aliphatic double bond

The hydrogenation of stilbestrol and its derivatives reveals a rather involved relationship between members of the unsaturated and saturated series, as represented in table 3.

It is apparent that *cis* addition of hydrogen does not occur uniformly. Thus, there are many exceptions to the generally accepted conversion of derivatives of *cis*-stilbene into the *meso*-forms, and of *trans*-stilbene into the racemic forms of the hydrogenation products. It is also possible that primarily *cis* addition does take place but is followed by partial racemization of the type discussed earlier. In view of the fact that stilbestrol and its dimethyl ether have been hydrogenated to hexestrol as well as to isohexestrol, it may be questioned if it is sound to use results of hydrogenation experiments for deducing the *cis* or *trans* configuration of stilbestrol. Nevertheless, the conclusions drawn from these experiments have mostly been confirmed by various other means, discussed earlier.

Wessely and Welleba (224, 225) showed that the known *cis–trans* pair of α,β-dimethylstilbene (CI) is reduced almost exclusively by *cis* addition of hydrogen.



CI

Under identical conditions (palladium sponge, acetic acid, 18°C., atmospheric pressure) stilbestrol and its dimethyl ether were also hydrogenated with the following comparative results:

α,β-Dimethylstilbene		Stilbestrol	Stilbestrol dimethyl ether
trans (m.p. 107°C.)	*cis* (m.p. 67°C.)	↓	↓
↓	↓	88% isohexestrol (*d,l*)	97% racemic 3,4-dianisylhexane
98% racemic	99% *meso*	12% hexestrol (*meso*)	
β,γ-diphenylbutane			

Therefrom it was concluded that stilbestrol and its dimethyl ether have the *trans* configuration. However, the formation of 12 per cent of the *meso*-form indicates that not qualitative but only quantitative differences exist in the formation of hydrogenation products, throwing some doubt on the validity of this deduction.

Wessely and Welleba (226) further approached the problem of the *cis* or *trans* configuration of stilbestrol by still another method based on hydrogenation products. Various *trans*-stilbenes were found to give mixed crystals with the *meso*-forms of the corresponding hydrogenation products, while they give a eutectic mixture with the racemic forms. The *trans* configuration of stilbestrol dimethyl ether was concluded from the experimental finding that this compound gives mixed crystals with hexestrol, but gives a eutectic mixture with isohexestrol.

According to Dodds *et al.* (56, 59), stilbestrol and ψ-stilbestrol with palladized charcoal in acetone give exclusively hexestrol dimethyl ether. On the other hand, at slightly elevated temperature, the same authors obtained, from the mixture of dimethyl ethers of stilbestrol and ψ-stilbestrol, a mixture of the dimethyl ethers of hexestrol and isohexestrol. Campbell *et al.* (25) obtained hexestrol also, as well as isohexestrol, by the hydrogenation of stilbestrol.

Wessely and coworkers (98, 225) insist that stilbestrol dimethyl ether cannot be hydrogenated to hexestrol dimethyl ether, while this latter is obtained from ψ-stilbestrol dimethyl ether in quantitative yield. According to these authors the crude reaction mixture from the dehydration of 3,4-bis(*p*-anisyl)-3-hexanol (XLVIII) is a useful starting material for the preparation of hexestrol. It is obtained after removal of the larger part of stilbestrol dimethyl ether, followed by hydrogenation and demethylation of the residue.

These last results are in accord with those of Docken and Spielman (49), who hydrogenated stilbestrol to isohexestrol in quantitative yield by the use of palladium, copper chromite, or Raney nickel catalyst.

Schwenk *et al.* (182) confirmed the quantitative production of isohexestrol from stilbestrol by hydrogenation with Raney nickel. By the more protracted reduction method developed by these workers—digesting nickel aluminum alloy in alkaline solution at atmospheric pressure—stilbestrol gave a 30 per cent yield of hexestrol and a 50 per cent yield of isohexestrol.

Hoehn and Ungnade (92) hydrogenated with Raney nickel at pressures up to 5000 lb. The dimethyl ether of stilbestrol gave isohexestrol dimethyl ether as the only product. Hydrogenation of stilbestrol monomethyl ether (LXXIX) under similar conditions gave a mixture of an alkali-soluble compound which on demethylation yielded hexestrol, and an alkali-insoluble compound believed to be hexestrol monomethyl ether (XXXVIII), described earlier by Bretschneider (16).

The hydrogenation of dienestrol (XXI) to hexestrol, in almost quantitative yield, has been described by Campbell, Dodds, and Lawson (25).

Wessely and Kleedorfer (223) found that, on hydrogenation with palladium, both isomeric forms of 3,4-bis(*p*-anisyl)-2-hexene (XCVII) give a 50 to 60 per cent yield of hexestrol dimethyl ether. The same authors (98) hydrogenated the epoxy derivative (XCII) of stilbestrol to a mixture of products containing 30 per cent hexestrol dimethyl ether. Jung (97) obtained a German patent for the hydrogenation of 3,4-bis(*p*-hydroxyphenyl)-3-hexanol to hexestrol. Unfortunately no experimental details of this method are available at present.

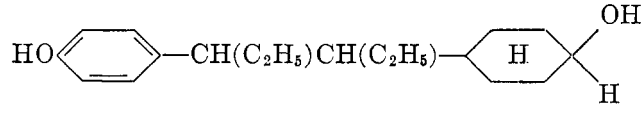
Peteri (146) hydrogenated stilbestrol dipropionate to the oily isohexestrol dipropionate, which was then hydrolyzed to isohexestrol. Correspondingly, ψ-stilbestrol dipropionate gave the crystalline hexestrol dipropionate and, after hydrolysis, hexestrol.

On the other hand, Walton and Brownlee (215) obtained hexestrol dipropionate from the crystalline dipropionates of both stilbestrol and ψ-stilbestrol. This again might be due to partial racemization of isohexestrol dipropionate or rearrangement of the unreduced stilbestrol dipropionate to ψ-stilbestrol dipropionate, because according to Wessely *et al.* (220) ψ-stilbestrol dipropionate readily isomerizes to stilbestrol dipropionate.

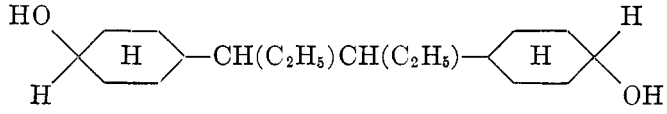
According to a Hungarian patent claim (160), hexestrol may be obtained from stilbestrol by hydrogenation of its esters in acetone, followed by saponification of the hydrogenation products.

2. Hydrogenation of aromatic rings

Ruggli and Businger (172) made an unsuccessful attempt to synthesize hexahydrostilbene derivatives containing one cyclohexyl ring and thus more closely resembling estradiol. This objective could hardly be attained by hydrogenation methods, as no catalyst is as yet available for the selective hydrogenation of an aromatic ring while leaving an ethylene bond intact. After it had been shown that the ethylene bond is not essential for the attainment of highest potency, the preservation of this bond during reduction of one aromatic ring lost part of its interest. Hoehn and Ungnade (92) obtained several hydrogenation products by partial or total reduction of the aliphatic and aromatic double bonds in stilbestrol. At 200°C. and 5000 lb. pressure three crystalline reduction products were obtained. Two of these, m.p. 145°C. and 92–94°C., respectively, have phenolic character and are believed to represent two racemic forms of 3-(*p*-hydroxyphenyl)-4-(*p*-hydroxycyclohexyl)hexane (CII).



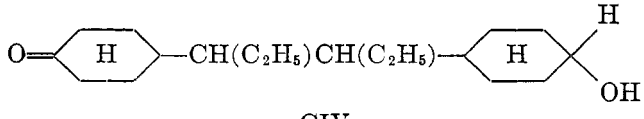
CII



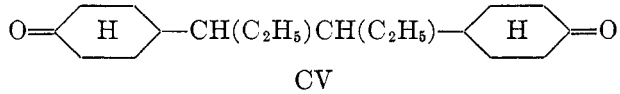
CIII

The third product, m.p. 188°C., without phenolic properties, is most likely 3,4-bis(*p*-hydroxycyclohexyl)hexane (CIII). It will be recalled that hydrogenation, under the same conditions, of the monomethyl and dimethyl ethers of stilbestrol left the aromatic rings intact, demonstrating that methylation of the phenolic hydroxyls rendered the aromatic rings more resistant to hydrogenation.

The perhydrostilbestrol, m.p. 188°C., is apparently identical with the product, m.p. 185°C., obtained earlier by Major, Christman, and Folkers (117) under similar conditions. Lane and Wallis (108) mentioned another isomeric perhydrogenation product of hexestrol, m.p. 167°C. These workers obtained from the latter, by oxidation with chromic acid, the keto alcohol (CIV) and the diketone (CV).



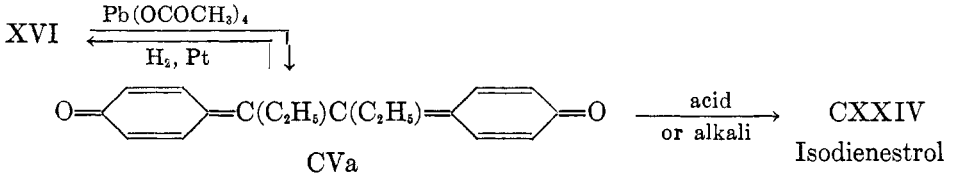
CIV



CV

Closely related is α,β-diethylstilbene quinone (CVa), prepared by Euler and Adler (75a) from stilbestrol. The quinone is active at 10 micrograms, though it

was obtained neither crystalline nor analytically pure. Hydrogenation with platinum gives again stilbestrol; and with acid or alkali the quinone rearranges to isodienestrol (CXXIV), mentioned later.



Unfortunately no reports have as yet been published regarding the potency of these various cyclohexyl derivatives (table 4). However, according to Sondern (195), the products obtained by Hoehn and Ungnade (92) were inactive. If hydrogenation of one aromatic ring together with saturation of the aliphatic double bond is sufficient to abolish the activity, there is little analogy between natural and synthetic estrogens regarding the degree of saturation.

V. Variation of Fundamental Structure

A. VARIATION OF AROMATIC RINGS

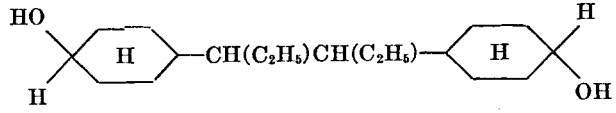
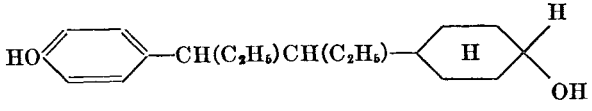
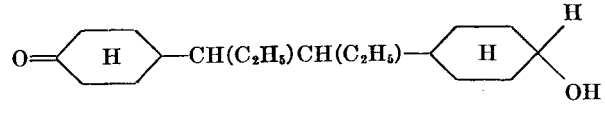
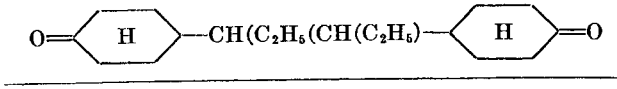
1. Acylation and alkylation of phenolic hydroxyl groups

The two phenolic hydroxyl groups present in stilbestrol and hexestrol were the subject of a systematic study of the effect of conjugation on estrogenic potency. The result is a very nearly complete series of alkyl and acyl derivatives. They are generally characterized by an activity inferior to that of the parent compound. However, the minimal effective dose is but one of the factors to be considered. Another one is the ratio of oral to parenteral activity, to be discussed later together with some metabolic conversions related to it. A third factor of importance is the prolongation of estrogenic effectiveness, as measured by the duration of the estrous cycle. According to Emery *et al.* (71) the duration of stilbestrol activity depends on the site of administration, being shortest for intraperitoneal and increasingly longer for oral, intrathoracic, subcutaneous, and intramuscular injection. Sklow (200) found that, contrary to experiments made with estrone, the action of stilbestrol could not be prolonged by administration of an adsorbate on carbon powder.

The acyl derivatives of stilbestrol have been compiled in table 5, which contains information on the prolongation of effect, expressed in days of estrus duration at a given dose level. The minimal effective dose has been reported only in a few instances, but the trend may be seen of decreasing activity with increasing size of the acyl groups. The dipropionate, m.p. 107°C., appears to combine relatively high activity with extremely prolonged effect. While in the estradiol series the maximum duration was found with the higher fatty esters and the dibenzoate was found to represent the most favorable combination of characteristics, it will be noted that stilbestrol dibenzoate possesses relatively low activity and requires very large doses for prolongation. The dicarbomethoxy derivatives possess activities equivalent to those of the dipropionate. Earlier,

TABLE 4

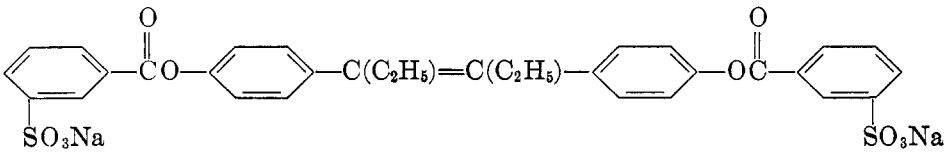
Perhydrogenation products of stilbestrol and hexestrol

FORMULA	MELTING POINT	NAME	REFERENCES
	°C. 185 188–188.5	3,4-Bis(*p*-hydroxycyclohexyl)hexane	(117) (92)
	(a) 145 (b) 92–94	3-(*p*-Hydroxyphenyl)-4-(*p*-hydroxycyclohexyl)hexane	(78)
	70 60	3-(*p*-Ketocyclohexyl)-4-(*p*-hydroxycyclohexyl)hexane Acetate Acid succinate	(108) (108) (108)
	80	3,4-Bis(*p*-ketocyclohexyl)hexane	(108)

in the discussion of the *cis–trans* isomerism of stilbestrol, it was mentioned that three isomeric dipropionates are known.

It should be borne in mind that some of the compounds summarized in the various tables may be the *cis*-forms rather than the *trans*-forms, as assumed. In a very few cases more than one form was isolated and it is not impossible that this one represents the biologically less active form.

Stilbestrol is soluble in water to the extent of 0.5 mg. per cent only (141); the sodium salt is soluble but gives alkaline solutions. Medick (122) esterified the phenolic hydroxyl groups with benzoic acid-3-sulfochloride. The reaction product (CVI) forms a water-soluble, neutral sodium salt, indicating that the carboxyl group took part in the esterification.



CVI

The activity has been reported equal to or even better than that of the equivalent quantity of stilbestrol. Similar esters of hexestrol and dienestrol were prepared. Among many other esters Miescher and Heer (125, 126, 127, 128, 129a, 193) described the water-soluble stilbestrol disulfate and some of its salts. Morren (135) reported that the potassium salt possesses 66 per cent of the oral activity of stilbestrol. Rabald and Boeller (151) obtained a reaction product, presumably a salt, of stilbestrol and hexamethylenetetramine. Preissecker (152) described a new derivative of uncertain composition, obtained by reacting choline with stilbestrol.

In the hexestrol series too, all previous reports agreed that esterification of the phenolic hydroxyl groups usually results in a loss of potency coupled with a prolongation of effect, as shown in table 6. Very recently it was reported by Prescott and Basden (153) that Brownlee found hexestrol dipropionate to be 1.5 to 3 times more potent than hexestrol when injected into rats. By mouth the dipropionate is less potent than hexestrol. Confirmation of these results by others will be awaited with great interest in view of the earlier report by Bretschneider *et al.* (16), who found hexestrol to be almost 3 times as active as the dipropionate. According to Foreman and Miller (83) the disuccinate of hexestrol approximates the activity of the parent substance.

Little needs to be added to the series of alkyl derivatives of stilbestrol shown in table 7 and those of hexestrol in table 6.

Alkylation of but one of the two hydroxyl groups in stilbestrol rapidly lowers the activity as the size of the alkoxy group increases. This is evidence for the view that alkyl derivatives possess little if any activity of their own but are dealkylated in the organism; alkyl derivatives are less active than esters, possibly because dealkylation under physiological conditions as well as *in vitro* offers more resistance than the hydrolysis of acyl groups. Alkyl derivatives

TABLE 5

Acyl derivatives of stilbestrol

FORMULA R'O—C(C$_2$H$_5$)=C(C$_2$H$_5$)—OR''		MELTING POINT	NAME	DURATION OF ESTRUS		REFERENCES
R'	R''			Rat dose subcutaneously	Time	
		°C.		*micrograms*	*days*	
H	H	171	Stilbestrol	1	4	(57, 59)
				5	4	(57, 59)
				10	5	(57, 59)
				1	2	(98, 222)
CH_3CO	CH_3CO	124	Stilbestrol diacetate	1	0	(57, 58, 59)
				1	2–3	(98, 222)
				10	21	(57)
CH_3CH_2CO	H	92–94	Stilbestrol monopropionate			(126)
CH_3CH_2CO	CH_3CH_2CO	107	Stilbestrol dipropionate			(57, 59, 126, 129, 146, 192, 215, 220, 221)
				1.25	4–5	(221, 222)
				2.5–4.5	60–80	(221)
				10	52	(57, 59)
$CH_3(CH_2)_2CO$	$CH_3(CH_2)_2CO$	98–99	Stilbestrol di-*n*-butyrate	10	10	(129, 192)
		88				(57, 59)
$(CH_3)_2CHCO$	H	109–111	Stilbestrol monoisobutyrate			(129, 192)
$(CH_3)_2CHCO$	$(CH_3)_2CHCO$	101–102	Stilbestrol diisobutyrate			(129, 192)
		86–87		10	4	(57, 59)
$CH_3(CH_2)_3CO$	$CH_3(CH_2)_3CO$	89	Stilbestrol divalerate	10	2	(57, 59)
		76.5–77.5				(129, 192)

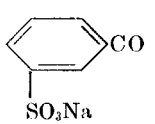
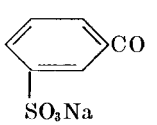
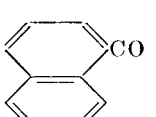
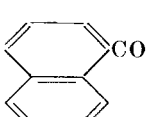
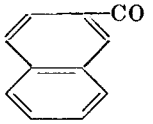
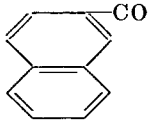
$CH_3(CH_2)_4CO$	H		Stilbestrol monocaproate			(129, 192)
$CH_3(CH_2)_4CO$	CH_3CH_2CO		Stilbestrol monocaproate monopropionate			(129, 192)
$CH_3(CH_2)_4CO$	$CH_3(CH_2)_4CO$	75–76	Stilbestrol dicaproate			(129, 192)
$CH_3(CH_2)_8CO$	$CH_3(CH_2)_8CO$	67–68	Stilbestrol dicaprate			(129, 192)
$CH_3(CH_2)_{10}CO$	H		Stilbestrol monolaurate			(129, 192)
$CH_3(CH_2)_{10}CO$	$CH_3(CH_2)_{10}CO$		Stilbestrol dilaurate			(129, 192)
$CH_3(CH_2)_{13}CO$	$CH_3(CH_2)_{13}CO$	82–84	Stilbestrol dipalmitate			(129, 192)
		77–78		50	2	(57, 59)
				100	>77	(57)
$CH_3(CH_2)_{16}CO$	$CH_3(CH_2)_{16}CO$	84–86	Stilbestrol distearate			(129, 192)
C_6H_5CO	C_6H_5CO	210–211	Stilbestrol dibenzoate	10	0	(57, 59)
				100	>77	(57, 59)
		220–222				(192)
			Stilbestrol di(3-sulfobenzoate) sodium salt			(122)
$C_6H_5CH_2CO$	$C_6H_5CH_2CO$	100	Stilbestrol di(phenyl acetate)	10	4	(57, 59)
		206–207	Stilbestrol di-α-naphthoate	100	3	(59)

TABLE 5—*Concluded*

FORMULA R'O—C(C₂H₅)=C(C₂H₅)—OR''		MELTING POINT	NAME	DURATION OF ESTRUS		REFERENCES
R'	R''			Rat dose subcutaneously	Time	
		°C.		*micrograms*	*days*	
		252–253	Stilbestrol di-β-naphthoate	100	3	(59)
CH_3OCO	CH_3OCO	142	Stilbestrol di(methyl carbonate)	1.25	4–5	(121, 222)
C_2H_5OCO	C_2H_5OCO	118	Stilbestrol di(ethyl carbonate)	1.25	4–5	(121, 222)
$(CH_3)_2CHOCO$	$(CH_3)_2CHOCO$	121	Stilbestrol di(isopropyl carbonate)			(121)
C_6H_5OCO	C_6H_5OCO		Stilbestrol di(phenyl carbonate)	1.25	4–5	(222)
PO_3H_2	PO_3H_2		Stilbestrol diphosphate			(127, 128)
			Calcium salt			(127, 128)
			Sodium salt			(127, 128)
SO_3H	SO_3H		Stilbestrol disulfate			(127, 128)
			Sodium salt			(127, 128)
			Potassium salt			(135)

are stored in the organism; Dodds *et al.* (57) found that very large doses of the little active stilbestrol dimethyl ether produced almost indefinite duration of estrus in rats: more than 126 days with 1 mg. and more than 180 days with 6.6 mg. While several esters, especially the diacetate and the dipropionate of stilbestrol and hexestrol, found clinical use, to date none of their dialkyl derivatives has acquired practical importance.

Mixed ether-esters shown in table 8– for example, the monomethyl ether monoacetate of stilbestrol prepared by Ludwig (116)—appear to combine fairly high activity with prolonged effect. Stilbestrol monoacetate monotetraacetylglucoside, prepared by Miescher *et al.* (126) and by Wessely *et al.* (221), has an activity of 2.5 to 4 micrograms, slightly higher than that of the monomethyl ether monoacetate. This confirms the view that the activity of alkyl derivatives is mostly dependent on the ease of dealkylation, with the glucosidic linkage under physiological conditions more easily hydrolyzed than the methoxyl group.

2. Position isomers and homologs with additional ring substitutes

While certain other modifications of the fundamental structures of stilbestrol and hexestrol are permissible without serious loss of potency, all but a fraction of it is lost by varying the position of the substituents of the aromatic rings. From the data assembled in tables 9 and 10, it is apparent that for maximum potency both phenolic hydroxyl groups need to be in the para-position to the aliphatic part of the molecule. Linnell and Sharma (114) demonstrated that moving one of the two hydroxyls in stilbestrol from the para- to the meta-position causes a 10,000-fold drop in activity; a further drop results from moving the second hydroxyl group into the meta-position.

The relative activities of the isomers regarding the position of the two hydroxyl groups are available in three series of estrogens: those of stilbestrol, dienestrol, and the pinacol of *p*-hydroxypropiophenone. The *p,p'*-derivative is always the most active one, while the relative activities of the *m,m'*- and of the *o,o'*-isomers do not run parallel within the three series:

Approximate relative activities (within isomeric series).

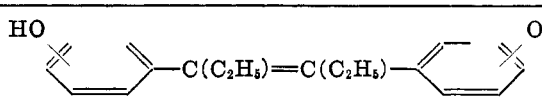
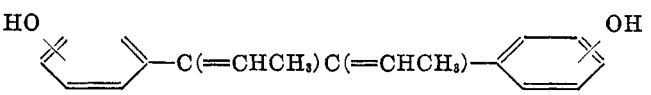
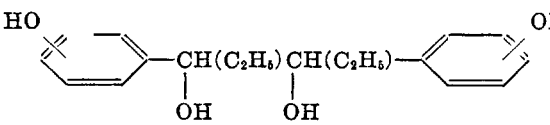
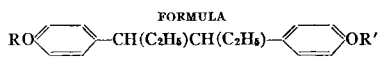
	p,p'	*m,m'*	*o,o'*
	1	1/30,000	1/3,000
	1	1/1,250	1/25,000
	1	1/1,000	Inactive

TABLE 6

Hexestrol, isohexestrol, and ethers and esters of hexestrol

FORMULA 		MELTING POINT	NAME	ESTROGENIC ACTIVITY IN RATS (*IN MICE) SUBCUTANEOUSLY (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE)			REFERENCES
R	R′			Minimum effective dose		Rat units per gram	
		°C.		*micrograms*			
H	H	185	Hexestrol	0.2		5,000,000	(24, 56)
				0.15	(75%)		(16)
		186		2			(223)
CH_3	H	120–121	Hexestrol monomethyl ether	8	(50%)		(16, 85)
		119–120					(92)
CH_3	C_2H_5CO	85–87	Hexestrol monomethyl ether monopropionate				(16, 144)
C_4H_9	H		Hexestrol monobutyl ether	50	(50%)		(85)
C_5H_{11}	H		Hexestrol monoamyl ether	150			(85)
CH_3	CH_3	145–146	Hexestrol dimethyl ether	50	(50%)		(85, 98)
C_5H_{11}	C_5H_{11}		Hexestrol diamyl ether	600	(50%)		(85)
CH_3CO	CH_3CO	139	Hexestrol diacetate	1			(98)
C_2H_5CO	H		Hexestrol monopropionate				(144)
C_2H_5CO	C_2H_5CO	126–128	Hexestrol dipropionate	0.4	(75%)		(16, 83, 153, 215)

C_3H_7CO	C_3H_7CO	106–107	Hexestrol dibutyrate	4*		(83)
$CH_3(CH_2)_4CO$	$CH_3(CH_2)_4CO$	96–97	Hexestrol dicaproate	4*		(83)
$HOOC(CH_2)_2CO$	$HOOC(CH_2)_2CO$	150–153	Hexestrol disuccinate	4*		(83)
C_6H_5CO	H	123–126	Hexestrol monobenzoate			(126)
C_6H_5CO	C_6H_5CO	236–237	Hexestrol dibenzoate	4*		(83)
CH_3OCO	CH_3OCO	145–146	Hexestrol dimethylcarbonate			(27)
$CH_3OCOCH_2CH(CHOCOCH_3)_3CH$ (O)	H	203–204	Hexestrol mono(tetraacetyl)glucoside			(126, 129a)
$CH_3OCOCH_2CH(CHOCOCH_3)_3CH$ (O)	C_6H_5CO	156	Hexestrol mono(tetraacetyl)glucoside monobenzoate			(126, 129a)
H	H	129	Isohexestrol			(58)
		130		500		(223, 225)
		80	+ Antipode	100		(225)
		80	− Antipode	1000	(40%)	(225)
C_2H_5CO	C_2H_5CO	Liquid	Isohexestrol dipropionate			(146)
CH_3OCO	CH_3OCO	95	Isohexestrol dimethyl carbonate			(27)

TABLE 7

Alkyl derivatives of stilbestrol

FORMULA RO–C(C$_2$H$_5$)=C(C$_2$H$_5$)–OR′		MELTING POINT	NAME	ESTROGENIC ACTIVITY IN RATS SUBCUTANEOUSLY (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE): MINIMUM EFFECTIVE DOSE		REFERENCES
R	R′					
		°C.		*micrograms*		
H	H	171	Stilbestrol	0.4		(56, 59)
CH_3	H	114	Stilbestrol monomethyl ether	7.5		(221)
		117		2.5	(50%)	(85, 157, 171)
		118		2.5	(50%)	(116)
		101–102				(18)
CH_3	CH_3	124	Stilbestrol dimethyl ether (*trans*)	20	(50%)	(57, 58, 157)
		Liquid	Stilbestrol dimethyl ether (*cis*)			(58, 59)
C_2H_5	H	99.5	Stilbestrol monoethyl ether	5	(50%)	(157)
C_2H_5	C_2H_5	127.5	Stilbestrol diethyl ether	50	(50%)	(157)
n-C_3H_7	H	107	Stilbestrol mono-*n*-propyl ether	17.5	(50%)	(157)
n-C_3H_7	*n*-C_3H_7	95.6	Stilbestrol di-*n*-propyl ether	250	(50%)	(157)
n-C_4H_9	H	97.5	Stilbestrol mono-*n*-butyl ether	20	(50%)	(157)
n-C_4H_9	*n*-C_4H_9	101.6	Stilbestrol di-*n*-butyl ether	250	(50%)	(157)
n-C_5H_{11}	H	82	Stilbestrol mono-*n*-amyl ether	48	(50%)	(157)
n-C_5H_{11}	*n*-C_5H_{11}	64.6	Stilbestrol di-*n*-amyl ether	600	(50%)	(157)
C_6H_{13}	H	72	Stilbestrol monohexyl ether	45	(50%)	(157)
C_6H_{13}	C_6H_{13}	74.6	Stilbestrol dihexyl ether	30,000	(50%)	(157)
C_7H_{15}	H	87	Stilbestrol monoheptyl ether	45	(50%)	(157)
C_7H_{15}	C_7H_{15}	50.4	Stilbestrol diheptyl ether	750	(50%)	(157)
C_8H_{17}	H	88.5	Stilbestrol monoöctyl ether	50	(50%)	(157)
C_8H_{17}	C_8H_{17}	72.2	Stilbestrol dioctyl ether	50,000	(50%)	(157)
C_9H_{19}	H	76	Stilbestrol monononyl ether	50	(50%)	(157)
C_9H_{19}	C_9H_{19}	57	Stilbestrol dinonyl ether	5,000	(50%)	(157)
$C_{10}H_{21}$	H	75	Stilbestrol monodecyl ether	84	(50%)	(157)
$C_{10}H_{21}$	$C_{10}H_{21}$	73	Stilbestrol didecyl ether	50,000	(50%)	(157)
$C_{11}H_{23}$	H	58.5	Stilbestrol monoundecyl ether	200	(50%)	(157)

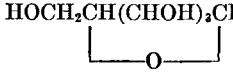
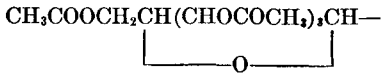
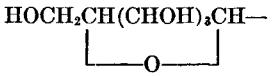
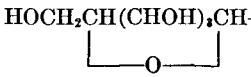
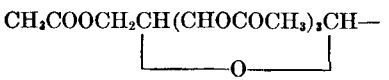
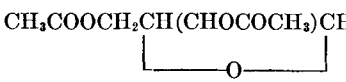
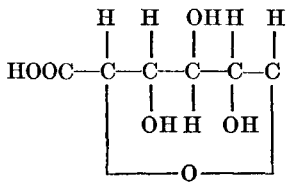
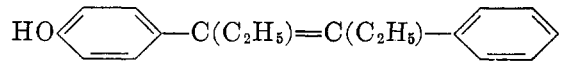
$C_{11}H_{23}$	$C_{11}H_{23}$	66	Stilbestrol diundecyl ether	40,000	(50%)	(157)
$C_{12}H_{25}$	H	83	Stilbestrol monolauryl ether	100	(50%)	(157)
$C_{12}H_{25}$	$C_{12}H_{25}$	80	Stilbestrol dilauryl ether			(157)
$C_{13}H_{27}$	H	67	Stilbestrol monotridecyl ether			(157)
$C_{13}H_{27}$	$C_{13}H_{27}$	73	Stilbestrol ditridecyl ether			(157)
$C_{14}H_{29}$	H	85	Stilbestrol monomyristyl ether			(157)
$C_{14}H_{29}$	$C_{14}H_{29}$	86	Stilbestrol dimyristyl ether			(157)
$C_{15}H_{31}$	H	73	Stilbestrol monopentadecyl ether			(157)
$C_{15}H_{31}$	$C_{15}H_{31}$	77	Stilbestrol dipentadecyl ether			(157)
$C_{16}H_{33}$	H	89	Stilbestrol monocetyl ether			(157)
$C_{16}H_{33}$	$C_{16}H_{33}$	89	Stilbestrol dicetyl ether			(157)
$C_{17}H_{35}$	H	78.5	Stilbestrol monoheptadecyl ether			(157)
$C_{17}H_{35}$	$C_{17}H_{35}$	82	Stilbestrol diheptadecyl ether			(157)
$C_{18}H_{37}$	H	94.3	Stilbestrol monoöctadecyl ether			(157)
$C_{18}H_{37}$	$C_{18}H_{37}$	94	Stilbestrol dioctadecyl ether			(157)
	H		Stilbestrol monoglucoside	3.5		(221)
	H	172 173–175	Stilbestrol mono(tetraacetyl-glucoside)	4.5		(221) (126)
		245	Stilbestrol di-β-glucoside			(126)
		221 227–230	Stilbestrol di(tetraacetyl-glucoside)	17.5		(221) (126)
		183–185	Stilbestrol di(*p*-nitrophenyl) ether			(101)
	H	175	Stilbestrol monoglycuronide			(119)

TABLE 8

Mixed ether-esters of stilbestrol

FORMULA R'O—C(C$_2$H$_5$)=C(C$_2$H$_5$)—OR''		MELTING POINT	NAME OF ETHER-ESTER	ESTROGENIC ACTIVITY IN RATS SUBCUTANEOUSLY (100 PER CENT RESPONSE, UNLESS INDICATED OTHERWISE): MINIMUM EFFECTIVE DOSE	REFERENCES
R'	R''	°C.		*micrograms*	
CH_3	CH_3CO	116	Monomethyl ether monoacetate	4.5 (50%)	(116, 170)
CH_3	CH_3CH_2CO	76–77	Monomethyl ether monopropionate		(170)
CH_3	$CH_3(CH_2)_2CO$	65	Monomethyl ether monobutyrate		(116)
CH_3	*p*-BrC_6H_4CO	132	Monomethyl ether mono(*p*-bromo)benzoate		(116)
$CH_3OCOCH(CHOCOCH_3)_3CH$—O—	C_6H_5CO		Mono(tetraacetyl-β-glucosido) monobenzoate		(126)
$CH_3OCOCH(CHOCOCH_3)_3CH$—O—	CH_3CO	152	Mono(tetraacetyl-β-glucosido) monoacetate		(126)
		148		2.5–4.0	(221)
$CH_3OCOCH(CHOCOCH_3)_3CH$—O—	CH_3CH_2CO		Mono(tetraacetyl-β-glucosido) monopropionate		(126)
$C_2H_5OCOCH(CHOCOC_2H_5)_3CH$—O—	CH_3CH_2CO	116	Mono(tetrapropionyl)glucosido monopropionate	12–16	(221)
		119			(126)

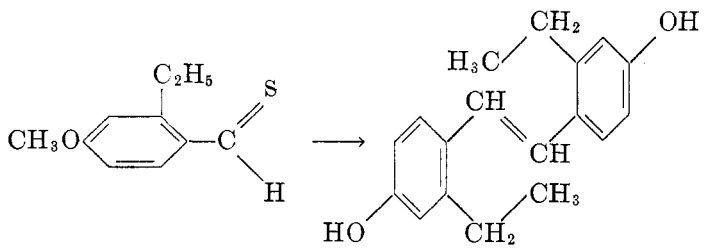
The stilbestrol analog (CVII) containing only one hydroxyl group in the para-



CVII

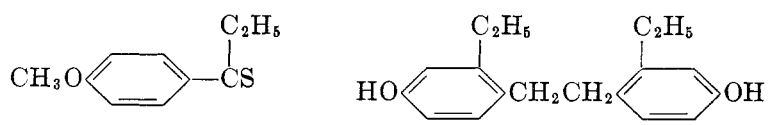
position is 1/2000 as active (59, 60) as stilbestrol; the hexestrol analog has not been assayed. Both compounds are of interest because their bactericidal activity is greater than that of dihydroxy analogs, according to Brownlee *et al.* (18) and Rubin and Wishinsky (171). The detailed discussion of their results, as well as those of Faulkner (76) and of Foley and Aycock (82), is beyond the scope of this review.

The effect of additional substituents in the rings is not consistent in the unsaturated and the saturated series. By heating 2-ethyl-4-methoxythiobenzaldehyde (CVIII) with copper powder, followed by demethylation with Grignard reagent, Linnell and Shaikmahamud (113) synthesized 2,2′-diethyl-4,4′-dihydroxystilbene (CIX).



CVIII CIX

This method was successful after various other approaches had failed, while earlier Linnell and Sharma (115) had attempted unsuccessfully to apply it to the synthesis of stilbestrol by removal of sulfur from 4-methoxythiopropiophenone (CX).



CX CXI

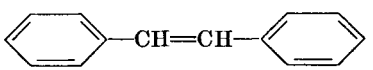
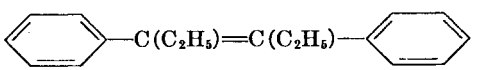
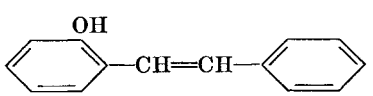
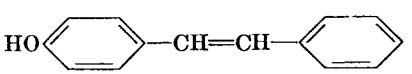
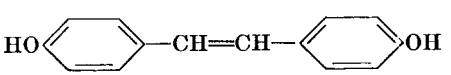
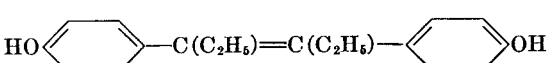
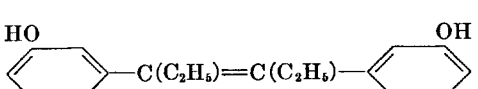
The formula of the stilbene derivative (CIX) has been written according to the authors, who interpreted its relatively low activity as evidence of the insignificance of the structural resemblance to estradiol as a requirement for high activity.

Baker (6) reported that the corresponding hexestrol analog (CXI) is inactive in doses of 100 micrograms.

Quite contrary to these results, according to Bretschneider (16) and Pallas (144), the structural isomeride (CXII) of hexestrol is practically as potent as the latter. In this case the nuclear substitution by methyl groups appears to enhance the activity, because the lower hexestrol homolog (CXIII), assayed by Dodds *et al.* (56), is less than one-half as active as hexestrol.

TABLE 9

Stilbestrol analogs with variation of aromatic substitution

FORMULA	MELTING POINT	NAME	ESTROGENIC ACTIVITY IN RATS SUBCUTANEOUSLY (* IN MICE) (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE)		REFERENCES
			Minimum effective dose	Rat units per gram	
	°C.		*micrograms*		
	124	Stilbene (*trans*)	25,000		(55, 62)
	57–8	α,β-Diethylstilbene (*trans*)	Inactive	5,000	(213) (171)
	147	2-Hydroxystilbene	Inactive		(64)
	189	4-Hydroxystilbene	10,000		(62, 64)
	284	4,4′-Dihydroxystilbene	10,000		(59, 62, 64)
	172	4,4′-Dihydroxy-α,β-diethylstilbene ("stilbestrol")	0.4	3,000,000	(56, 59)
	(a) Glass (b) Glass	3,3′-Dihydroxy-α,β-diethylstilbene Benzene-soluble form Benzene-insoluble form	 3,500* 9,000*	 (40%) (90%)	 (114) (114)

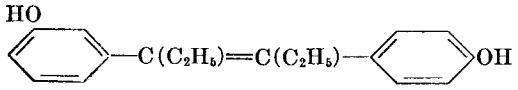
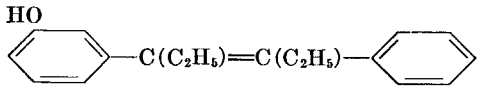
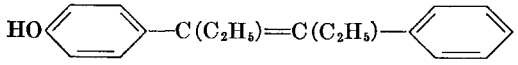
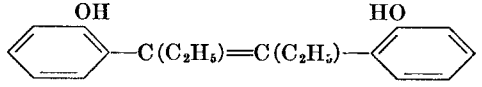
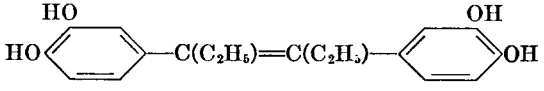
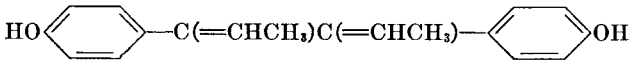
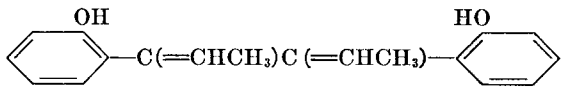
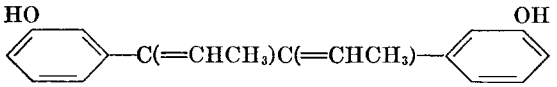
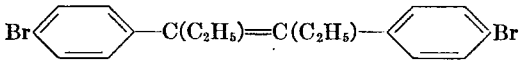
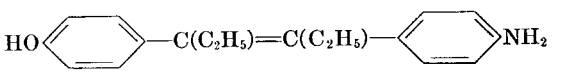
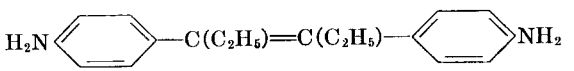
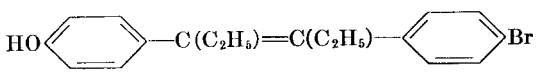
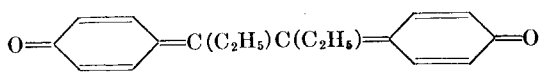
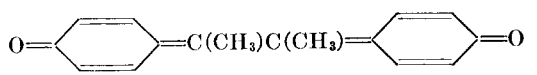
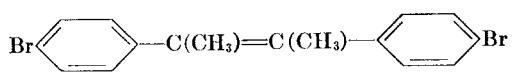
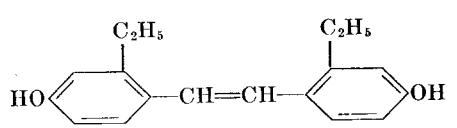
	153–154	3,4′-Dihydroxy-α,β-diethylstilbene	4,500*	(90%)	(114)
	Liquid	3-Hydroxy-α,β-diethylstilbene			(114)
	Liquid	Acetate	9,000*	(90%)	(114)
	b.p.135–140/ 0.15 mm.	4-Hydroxy-α,β-diethylstilbene	1,000		(18, 171)
	152–153	2,2′-Dihydroxy-α,β-diethylstilbene		1,000	(56)
	231–232	3,3′,4,4′-Tetrahydroxy-α,β-diethylstilbene			(13)
	227–228	3,4-Bis(*p*-hydroxyphenyl)-2,4-hexadiene ("dienestrol")	0.5	2,500,000	(54, 56, 60, 91)
	136–137	3,4-Bis(*o*-hydroxyphenyl)-2,4-hexadiene		100	(56)
	166–167	3,4-Bis(*m*-hydroxyphenyl)-2,4-hexadiene		2,000	(56)
		4,4′-Dibromo-α,β-diethylstilbene			
	125	*trans*-form		2,500	(213)
	72	*cis*-form		2,500	(213)

TABLE 9—*Continued*

FORMULA	MELTING POINT	NAME	ESTROGENIC ACTIVITY IN RATS SUBCUTANEOUSLY (* IN MICE) (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE)		REFERENCES
			Minimum effective dose	Rat units per gram	
	°C.		*micrograms*		
	155–156	4-Hydroxy-4′-amino-α,β-diethylstilbene	7.5 (50%)		(171)
	132	4,4′-Diamino-α,β-diethylstilbene (*trans*) (in oily solution)		5,000	(213)
		Hydrochloride (in aqueous solution)		25,000	(213)
	b.p.170–180/ 0.1 mm.	4-Hydroxy-4′-bromo-α,β-diethylstilbene	100 (50%)		(171)
		α,β-Diethylstilbene quinone	10		(75a)
		α,β-Dimethylstilbene quinone			(75a)
		4,4′-Dibromo-α,β-dimethylstilbene			
	125–126	*trans*-form			(9, 10)
	90–91	*cis*-form			(9, 10)
	150	2,2′-Diethyl-4,4′-dihydroxystilbene	1,000		(113)

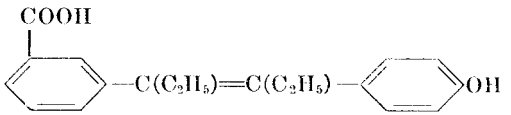
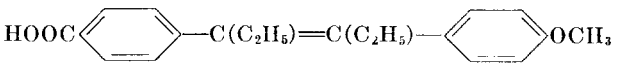
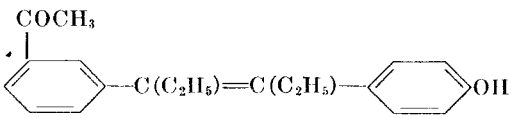
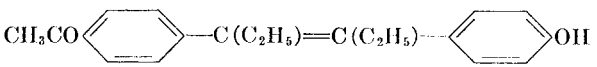
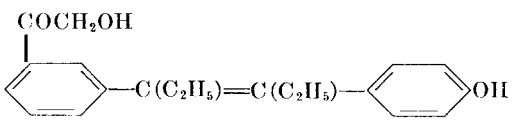
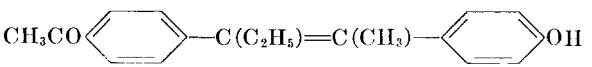
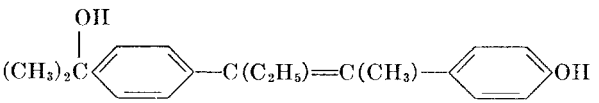
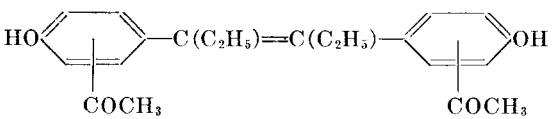
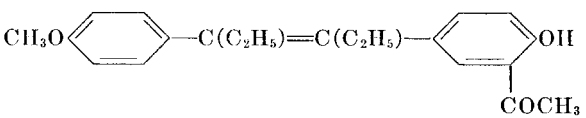
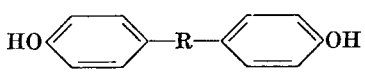
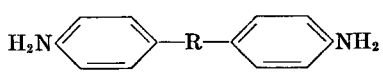
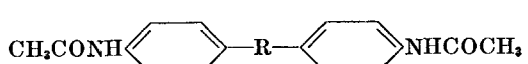
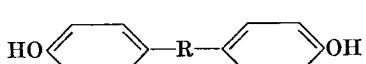
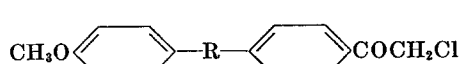
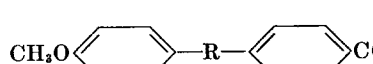
	160–161	3-Carboxy-4′-hydroxy-α,β-diethylstilbene		(111)
	167	4-Carboxy-4′-methoxy-α,β-diethylstilbene	Inactive at 1,000	(95, 171)
	80–110	3-Acetyl-4′-hydroxy-α,β-diethylstilbene		(111)
	102	4-Acetyl-4′-hydroxy-α,β-diethylstilbene	10,000	(95)
	65–67	3-(ω-Hydroxyacetyl)-4′-hydroxy-α,β-diethylstilbene	Corticosterone-like activity	(111)
	b.p.202–206/ 0.2 mm.	4-Hydroxy-4′-acetyl-α-methyl-β-ethylstilbene	10,000	(95)
		4-Hydroxy-4′-α-hydroxyisopropyl-α-methyl-β-ethylstilbene	200	(95)
	146–148	4,4′-Dihydroxydiacetyl-α,β-diethylstilbene		(218)
	Oil	4-Methoxy-4′-hydroxy-3′-acetyl-α,β-diethylstilbene		(218)

TABLE 10

Hexestrol analogs with variation of aromatic substitution

FORMULA R = [—CH(C_2H_5)CH(C_2H_5)—]	MELTING POINT	NAME	ESTROGENIC ACTIVITY IN RATS (*IN MICE) SUBCUTANEOUSLY (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE)		REFERENCES
			Minimum effective dose	Rat units per gram	
	°C.		*micrograms*		
	186	Hexestrol	0.2	5,000,000	(56)
		3,4-Bis(*p*-aminophenyl)-hexane		100	(27, 56)
	140	*meso*-form			
	132–134	*meso*-form	Inactive at 200		(6)
	63–65	Racemate	Inactive at 200		(6)
		3,4-Bis(*p*-acetylamino-phenyl)hexane			(56)
		3,4-Bis(*p*-hydroxy-*m*-nitro-phenyl)hexane			(199)
	226–228	*d,l*-form			
	113–115	*meso*-form			(199)
	139–141	3-(*p*-Anisyl)-4-(*p*-monochloroacetylphenyl)hexane	Progesterone-like activity		(18a, 218)
	135–136	3-(*p*-Anisyl)-4-(*p*-acetylphenyl)hexane	Progesterone-like activity		(18a, 218)

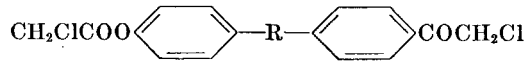
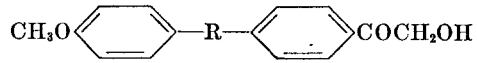
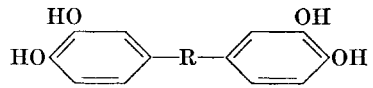
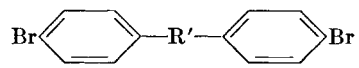
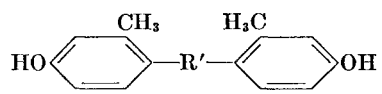
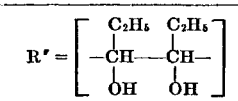
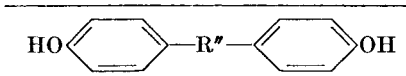
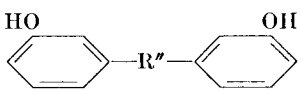
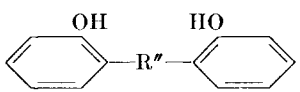
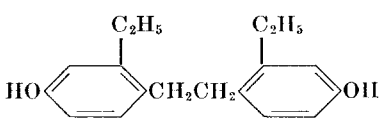
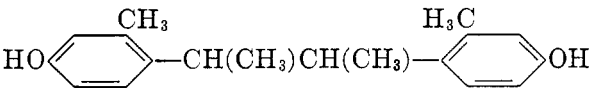
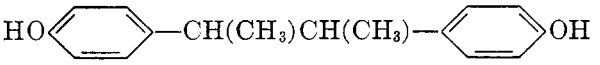
	135–136	3-(*p*-Monochloroacetylphenyl)-4-(*p*-monochloroacetoxyphenyl)hexane	Progesterone-like activity		(18a, 218)
		3-(*p*-Anisyl)-4-(*p*-glycolylphenyl)hexane	Corticosterone-like activity		(18a, 218)
		Acetate	Corticosterone-like activity		(218)
	231–232	3,4-(*m*,*p*-Dihydroxyphenyl)-hexane			(13)
R′ = [−CH(CH₃)CH(CH₃)−]					
		2,3-Bis(*p*-bromophenyl)-butane			(10)
	160–161	*meso*-form			
	b.p.166–171/ 0.3 mm.	Racemate			
	191–192	2,3-Bis(*o*-methyl-*p*-hydroxyphenyl)butane	0.3 (75%)		(16)
	164	Diacetate			(16)
	123–124	Dipropionate			(16)
					
	204–206	3,4-Bis(*p*-hydroxyphenyl)-3,4-hexanediol		100,000	(56, 58, 59, 91)
	94–95	Isomer			

TABLE 10—*Concluded*

FORMULA	MELTING POINT	NAME	ESTROGENIC ACTIVITY IN RATS (*IN MICE) SUBCUTANEOUSLY (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE)		REFERENCES
			Minimum effective dose	Rat units per gram	
	°C.		*micrograms*		
	145–146	3,4-Bis(*m*-hydroxyphenyl)-3,4-hexanediol		100	(56)
		3,4-Bis-(*o*-hydroxyphenyl)-3,4-hexanediol			
	270	α-form	Inactive		(56)
	162	β-form	Inactive		(56)
	131–133	1,2-Bis(*m*-ethyl-*p*-hydroxyphenyl)ethane	Inactive at 100		(6)



CXII



CXIII

The positive effect of methyl substitution will again be encountered in the triphenylmethane series, to be discussed later. Only brief mention needs to be made of analogs containing in the para-position aromatic substituents other than hydroxyl groups. Vargha and Kovacs (213) prepared several bromo and amino derivatives of medium activity. The dibromo analog of stilbestrol (LXXXIV) is noteworthy because the *cis*- and *trans*-isomerides do not differ in potency. One might be inclined to ascribe the activity of these compounds, moderate as it may be, to physiological conversion into the dihydroxy derivatives, but this appears doubtful in view of lower activities of the corresponding compounds in the hexestrol series.

Several analogs listed in tables 9 and 10 have been prepared with the objective of modifying the estrogenic substances in a manner corresponding to the structural differences between estradiol and the steroid hormones progesterone and corticosterone. For compounds containing the hydroxyacetyl group, feeble though definite corticosterone-like activities have been reported by Linnell and Roushdi (111) and also by Brownlee and coworkers (18a, 218), who furthermore found progesterone-like activity with synthetics carrying the acetyl group characteristic for progesterone. Similar preparations were described by Jaeger and Robinson (95); their products, listed in table 9, did not exhibit progesterone-like activity but, according to the authors, this might be due to their estrogenic properties, which are of an order sufficient to inhibit progestational activity.

Though as yet most of these results are only slightly encouraging, the material available is not extensive enough to rule out the future possibility of developing synthetics sufficiently active to replace natural hormones other than estrogenic. Nevertheless, for all practical purposes estrogenic activity remains to date the only one where the steroid structure of the natural product is not essential.

B. VARIATION OF ALIPHATIC CHAIN

1. Homologs of stilbestrol and hexestrol

By replacing the two ethyl groups with other alkyl groups a large number of homologs of stilbestrol (table 11) and hexestrol (table 2) have been prepared, most of them by Dodds and his collaborators (56, 58, 59). The majority of these compounds were accessible by means of the original synthesis starting from desoxyanisoin. Incidentally, none of the many homologs have an activity equal to that of the diethyl derivatives prepared among the very first. Either loss or gain of one single methylene group causes a reduction to one-half of the potency. The same effect is obtained by keeping the molecular weight intact but

TABLE 11

Stilbestrol homologs with varied substitution on ethylene linkage

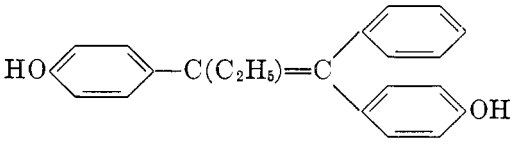
FORMULA HO—C(R′)=C(R″)—OH		MELTING POINT	NAME	ESTROGENIC ACTIVITY IN RATS (*IN MICE) SUBCUTANEOUSLY (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE)		REFERENCES
R′	R″			Minimum effective dose	Rat units per gram	
		°C.		*micrograms*		
H	H	284	4,4′-Dihydroxystilbene	10,000	140	(56, 59, 98)
CH_3	H	181–182	4,4′-Dihydroxy-α-methylstilbene	1,000 (90%)		(56)
		176–177	Diacetate		1,000	(56)
C_2H_5	H	128–129	4,4′-Dihydroxy-α-ethyl-stilbene	100 (50%)		(56, 59)
		100–102	Dibenzoate		5,000	(59)
n-C_3H_7	H	91	4,4′-Dihydroxy-α-n-propylstilbene	200		(56)
Iso-C_3H_7	H	166	4,4′-Dihydroxy-α-isopropylstilbene	500	2,000	(56)
n-C_4H_9	H	114	4,4′-Dihydroxy-α-n-butylstilbene	1,000	1,000	(37, 56)
				1,000*		(131, 132)
Iso-C_4H_9	H	128	4,4′-Dihydroxy-α-isobutylstilbene	500	2,000	(56)
n-C_5H_{11}	H	96	4,4′-Dihydroxy-α-n-amylstilbene	10,000	100	(56)
$C_{16}H_{33}$	H	b.p. 268–275/ 0.15 mm.	4,4′-Dihydroxy-α-cetylstilbene	100,000	10	(56)
			Di-β-naphthoate			(56)
		62–63	Dibenzoate			(56)
C_6H_5	H	99–100	4,4′-Dihydroxy-α-phenylstilbene	100	10,000	(56, 59)

	H	136	4,4′-Dihydroxy-α-cyclohexylstilbene	2,000	500	(56)
CH_3	CH_3	193–194	4,4′-Dihydroxy-α,β-dimethylstilbene	30	40,000	(56, 58, 59)
CH_3	C_2H_5	179–180	4,4′-Dihydroxy-α-methyl-β-ethylstilbene	1	1,000,000	(56, 59)
		175–176	Dipropionate			(55)
						(129)
CH_3	n-C_3H_7	b.p. 201–202/ 0.23 mm.	4,4′-Dihydroxy-α-methyl-β-n-propylstilbene	0.5	1,000,000	(56)
		131–132	Mixture of isomers	1*		(131, 132)
		158	*trans*-form			(56)
		202–204	*trans*-dibenzoate			(56)
		140–141	*cis*-dibenzoate			(56)
CH_3	Iso-C_3H_7	158	4,4′-Dihydroxy-α-methyl-β-isopropylstilbene	0.5*		(131, 132)
C_2H_5	C_2H_5	171	4,4′-Dihydroxy-α,β-diethylstilbene	0.4	3,000,000	(56, 58, 59)
			trans-form = "stilbestrol"			
		151	*cis*-form = ψ-stilbestrol			
		116–117	Diacetate	>1	<1,000,000	(56, 58, 59)
		78–79	Dipropionate			(146, 215)
		193–194	Dibenzoate			(59)
C_2H_5	n-C_3H_7	198–200/0.14 mm.	4,4′-Dihydroxy-α-ethyl-β-n-propylstilbene	10	300,000	(56, 59)
n-C_3H_7	n-C_3H_7	198–201/0.09 mm.	4,4′-Dihydroxy-α,β-di-n-propylstilbene	100	50,000	(56, 59)
Iso-C_3H_7	Iso-C_3H_7	202–204/0.25 mm.	4,4′-Dihydroxy-α,β-diisopropylstilbene	100	20,000	(56, 59)
			Dipropionate			(129)

TABLE 11—*Concluded*

FORMULA HO—C(R′)=C(R″)—OH		MELTING POINT	NAME	ESTROGENIC ACTIVITY IN RATS (*IN MICE) SUBCUTANEOUSLY (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE)		REFERENCES
R′	R″			Minimum effective dose	Rat units per gram	
		°C.		*micrograms*		
n-C_4H_9	n-C_4H_9	191–192/0.2 mm.	4,4′-Dihydroxy-α,β-di-n-butylstilbene	100 (40%)	5,000	(56, 59)
			Dibenzoate			(8)
C_2H_5	$C_{16}H_{33}$	90–91	4,4′-Dihydroxy-α-ethyl-β-cetylstilbene	3,000	500	(56)
C_5H_{11}	$C_{16}H_{33}$	98	4,4′-Dihydroxy-α-amyl-β-cetylstilbene	Inactive		(56)
		140–141	Di(3,5-dinitrobenzoate)			(56)
C_2H_5	C_6H_5	177–178	4,4′-Dihydroxy-α-ethyl-β-phenylstilbene	5	400,000	(56)
$C_6H_5CH_2$	$C_6H_5CH_2$		4,4′-Dihydroxy-α,β-dibenzylstilbene	Inactive		(56)
		181–182	(a)			
		160–161	(b)			
CN	CN	287	4,4′-Dihydroxy-α,β-dicyanostilbene	Weakly active (assayed otherwise)		(139)
		217	Diacetate			(139)
O ‖ OCCH$_3$	O ‖ OCCH$_3$	163–164	4,4′-Dimethoxystilbenediol diacetate	Inactive		(181)
Cl	C_2H_5	b.p. 179–184/0.1 mm.	4,4′-Dimethoxy-α-chloro-β-ethylstilbene		1,000	(56)
Cl	Cl		4,4′-Dimethoxy-α,β-dichlorostilbene		1,000	(56)

replacing one of the two ethyl groups with a methyl group and the second with a *n*-propyl group. Moore and Volwiler (131, 132) found the methyl isopropyl homolog only slightly less active than stilbestrol. A beneficial effect of branched-chain alkyl substituents, as compared with straight-chain groups, is not generally found in these or other series. If one ethyl group is replaced by a phenyl ring, the result is a tenfold drop in activity which is, however, relatively slight in view of the sharp peak of activity for the diethyl derivative in the alkyl-substituted series. The fairly high activity (5 micrograms) of 4,4′-dihydroxy-α-ethyl-β-phenylstilbene (CXIV) is of special interest because it actually represents the



CXIV

highest potency reported for the group of triphenylethylene derivatives (table 14), to be discussed separately.

Dodds *et al.* (56) demonstrated the special importance of the ethyl group; the ethyl cetyl homolog of stilbestrol is 50 times as active as the monocetyl derivatives, while the amyl cetyl homolog is inactive.

In the series of hexestrol homologs (table 2) again the question of optical isomerism needs to be considered. In the case of the dipropyl homolog Dodds *et al.* (56) described two forms and reported the crystalline isomer 200 times more active than the oily one. The same authors obtained one form of the dimethyl homolog (CXIII), m.p. 138–139°C. and fully active at 0.5 microgram, by catalytic hydrogenation and demethylation from 4,4′-dimethoxy-α,β-dimethylstilbene. Similarly Adler, Euler, and Gie (1) obtained a compound with the same melting point but found to be fully active only at the 1-mg. level. The Swedish authors obtained this isomer, believed to represent the racemate, as well as an isomer melting at 231–232°C. On account of its activity at 10 micrograms Adler *et al.* postulated that this compound represents the *meso*-form of CXIII, but the differences in activity have not yet been accounted for. The more active one of the two is about $\frac{1}{25}$ as potent as hexestrol, while about 20 times more active than the di-*n*-propyl homolog of stilbestrol. Also, the dimethyl homolog of hexestrol is no less than one-half as active as the latter, while the dimethyl homolog in the stilbestrol series is only $\frac{1}{80}$ as potent as stilbestrol. Thus the peak of activity is less sharp in the saturated than in the unsaturated series.

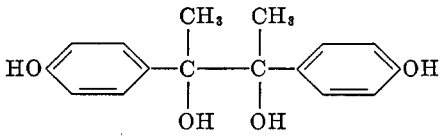
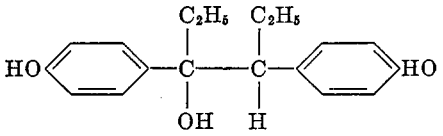
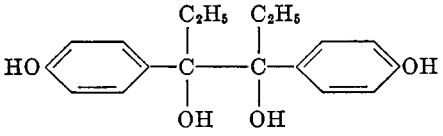
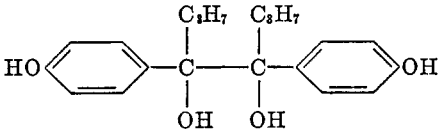
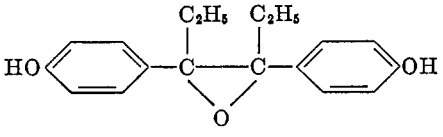
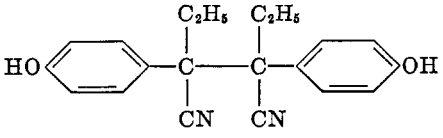
The activity of the racemic isohexestrol and of the products of resolution has been previously discussed.

2. Introduction of functional groups

Only a few stilbestrol analogs have been described carrying functional groups on the ethylene bond. Among them are mono- and di-chloro derivatives prepared by Dodds *et al.* (56) and the dicyano derivative synthesized by Niederl and Ziering (139), all of which possess but feeble activity.

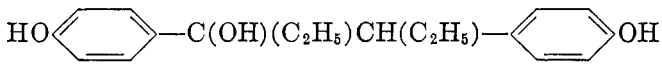
TABLE 12

Hexestrol analogs with additional functional groups

FORMULA	MELTING POINT	NAME	ESTROGENIC ACTIVITY IN RATS SUBCUTANEOUSLY (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE): MINIMUM EFFECTIVE DOSE	REFERENCES
	°C.		*micrograms*	
	96–97	2,3-Bis(*p*-hydroxyphenyl)-2,3-butanediol	100,000	(58, 59)
	232	3,4-Bis(*p*-hydroxyphenyl)-3-hexanol	50	(98, 222)
	153	*p,p'*-Diacetate	50	(98, 222)
		p,p'-Dibenzoate		(168)
	204–206	3,4-Bis(*p*-hydroxyphenyl)-3,4-hexanediol	100	(56, 58, 59, 91)
		meso-form		
	199–200	Diacetate		(58)
	94–95	Racemic form		(91)
	186–187	4,5-Bis(*p*-hydroxyphenyl)-4,5-octanediol	10,000	(58, 59)
		Diacetate		(58)
	145	4,4'-Dihydroxy-α,β-diethyl epoxystilbene	1	(98, 222)
	104	Diacetate	1	(98, 222)
	175	3,4-Bis(*p*-hydroxyphenyl)-3,4-dicyanohexane	Weakly active (tested otherwise)	(139)

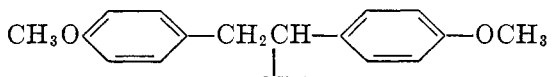
As intermediates in the stilbestrol synthesis or by addition to the double bond several saturated compounds have been obtained which may be considered functional analogs of hexestrol and have been listed in table 12. Wessely *et al.* (98, 222) obtained the highly potent epoxystilbestrol (XCII) by oxidation of stilbestrol with perbenzoic acid. The configuration of the epoxy derivative has not been established.

The dimethyl ether (XLVIII) of 3,4-bis(*p*-hydroxyphenyl)-3-hexanol (CXV) and the corresponding 3,4-hexanediol (LXIII) have been mentioned earlier as intermediates of various syntheses. Considering these compounds and their homologs as functional derivatives of hexestrol we may say that the potency is reduced 100-fold owing to replacement of the first hydrogen by a hydroxyl group, and 200-fold owing to replacement of the second one.

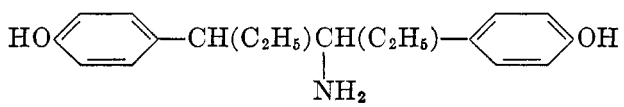


CXV

In passing, it may be mentioned that Lettré (109) suggested a possible correlation between synthetic estrogens and mitosis poisons. He synthesized α,β-bis(*p*-anisyl)ethylamine (CXVI), which is the simplest mitosis poison related to colchicine. As proposed by Lettré, Euler *et al.* (75a) attempted, so far unsuccessfully, to prepare the diethyl derivative (CXVII), which might be formed under physiological conditions by the addition of ammonia to stilbestrol.



CXVI



CXVII

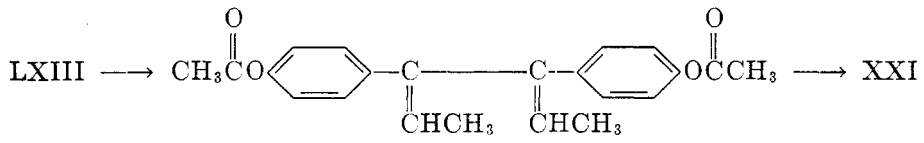
When given in large enough doses, stilbestrol itself was found to be an active mitosis poison for chicken heart fibroblasts.

3. Location and number of aliphatic double bonds

A large number of estrogens are known with the stilbene double bond shifted into a side chain or containing additional double bonds. A direct comparison between these compounds, shown in table 13, should be made with even greater reservation, on account of additional double bonds increasing the number of possible stereoisomers. Furthermore, several of these substances contain asymmetric carbon atoms, again increasing the number of possible isomers, while only in rare cases more than one isomer has been described and assayed. Among the best-studied examples regarding the effect of the configuration on the biological activity are the two forms of 3,4-bis(*p*-hydroxyphenyl)-2-hexene (XCVIII), described by Wessely *et al.* (222, 223) among the dehydration products

of 3,4-dianisyl-3-hexanol (XLVIII). Both stereoisomers are racemates regarding the asymmetric carbon atom. Similar to the relative potency of their structural isomers stilbestrol and ψ-stilbestrol, the higher melting form is apparently considerably more active; these results cannot be accepted without reservation because the ratio of activities has been reported as 30:1 (219) and as 400:1 (223), respectively. It is noteworthy that by means of iodine catalysis the lower melting form, presumably *cis*, is not converted in the usual manner into the higher melting one. In an equilibrium reaction both hexenes undergo isomerization to stilbestrol, involving a shift of the double bond. The speed with which the equilibrium is reached, as well as its position, is not significantly different for the two isomeric hexenes, in spite of the great difference between their potencies. Wessely (219) cited this as evidence that the hexenes are active on their own account and not by virtue of their conversion into stilbestrol. The problem of the "true" or "precursor" nature of synthetic estrogens will be discussed later from another point of view.

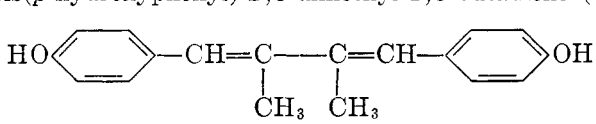
The most important preparation of this series is 3,4-bis(*p*-hydroxyphenyl)-2,4-hexadiene (XXI).



CXVIII

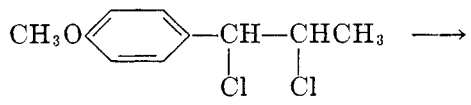
It was first prepared by Dodds, Goldberg, Lawson, and Robinson (59, 60) by way of its diacetate (CXVIII) from 3,4-bis(*p*-hydroxyphenyl)-3,4-hexanediol (LXIII) by dehydration with acetyl chloride. With the rat unit represented at 0.4 microgram this compound—also called hexadiene, hexadienestrol, or dienestrol—is one of the three most potent estrogens known.

Hobday and Short (91) undertook a careful reinvestigation of a patent claim for a novel synthesis of dienestrol by Balaban and Jones (8). It could be shown by degradative oxidation of the intermediates that the product, m.p. 192°C., claimed by Balaban and Jones to be identical with dienestrol, m.p. 227–228°C., was actually 1,4-bis(*p*-hydroxyphenyl)-2,3-dimethyl-1,3-butadiene (CXIX).

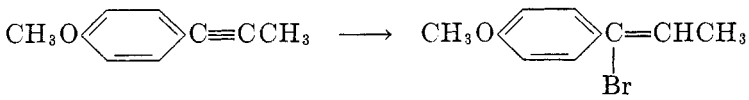


CXIX

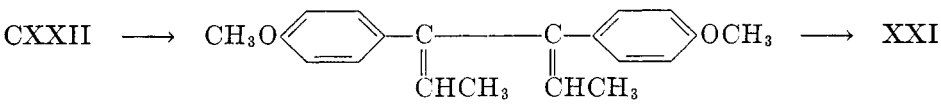
Hobday and Short developed a new synthesis of dienestrol which is analogous to that of hexestrol from anethole hydrobromide. Anethole dichloride (CXX), or the dibromide, is refluxed with pyridine and potassium methoxide to give 1-(*p*-anisyl)propyne (CXXI); the latter then adds 1 mole of hydrobromic acid resulting in 1-bromoanethole (CXXII).



CXX

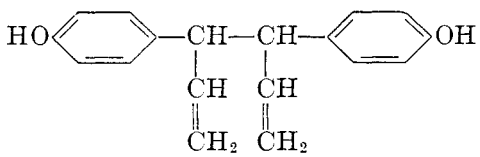


CXXI CXXII



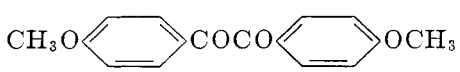
CXXIII

The next step comprised the successive action of magnesium and anhydrous cupric chloride to give the dimethyl ether (CXXIII), m.p. 130–131°C., of dienestrol. Removal of the methyl groups with Grignard reagent resulted in dienestrol, while the use of alcoholic potassium hydroxide led to a new isomeride, called isodienestrol. Remethylation of the latter gives a liquid dimethyl ether, isomeric with CXXIII. Hydrogenation of isodienestrol with palladized charcoal results in a mixture of 2 parts hexestrol (XX) and 1 part isohexestrol (XXII). Hobday and Short reasoned that this excluded the formula CXXIV for isodienestrol. Barring racemization, hydrogenation would not affect the configuration in the γ,δ-position and consequently not result in a mixture of diastereomers.



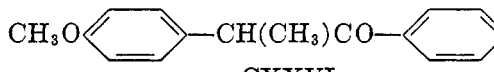
CXXIV

Yet, racemization appears all but unlikely because the hydrogenation of dienestrol, reported by Campbell *et al.* (25), and of isodienestrol dimethyl ether, reported by Hobday and Short (63), gave hexestrol derivatives as the main if not exclusive products. A more convincing argument in favor of the proposed structure for isodienestrol as one of the theoretically possible two *cis–trans* isomers of dienestrol is the finding (91) that the dimethyl ethers of both dienestrol and isodienestrol are ozonized to anisil (CXXV). Euler and Adler (75a) encountered isodienestrol as a rearrangement product of α,β-diethylstilbenequinone (CVa) and found it inactive in doses of 10 micrograms.

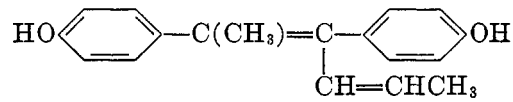


CXXV

Also, in this series the activity drops off if the aliphatic side chains are either lengthened or shortened. Still very potent is 4,4′-dihydroxy-α-methyl-β-propenylstilbene (CXXVII), prepared by Moore and Volwiler (132) and subsequently by Dodds *et al.* (56). This compound was obtained by reacting methyldesoxyanisoin (CXXVI) with allylmagnesium bromide and there is no strict proof for the position of double bonds according to formula CXXVII, though the assumption was made that under the influence of alkali during demethylation the double bond shifts into the conjugated position.



CXXVI

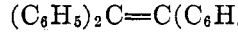


CXXVII

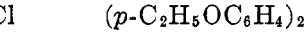
From a comparison of the ethylene derivatives listed in table 11 and the dienes in table 13 it may be concluded that introduction of an additional double bond has very little effect and that, regarding the length of the aliphatic chain, the peak of activity in both series is practically the same.

VI. Triphenylethylene Derivatives

Triphenylethylene being a phenyl-substituted stilbene, its estrogenic derivatives (table 14) may thus be considered as stilbestrol variants. Some unusual characteristics set this group apart from others. Robson and Schönberg (165) observed the notably prolonged effect of triphenylethylene, although it requires large doses. This was confirmed by Dodds, Fitzgerald, and Lawson (55), who prepared several unsubstituted di-, tri- and tetra-phenylethylenes. According to Robson, Schönberg, and Fahim (167), triphenylchloroethylene (CXXVIII) is 20 times more active than triphenylethylene and according to Segaloff (184) even 100 times. The synthesis has been described by Tadros (209a).



CXXVIII



CXXIX

The enhancing effect of halogen substitution has no parallel in other series of estrogens, and the same is true for the prolonged action of a hydrocarbon not substituted with alkoxy groups. Schönberg and his collaborators (166, 167, 181) selected α,α-bis(*p*-ethoxyphenyl)-β-phenyl-β-bromoethylene (CXXIX), also known as "D.B.E.," as the most promising synthetic of this type. The method of synthesis is the same used earlier by Koelsch (102) for the corresponding dimethyl ether. The latter was also assayed by Schönberg *et al.* (181), who reported an activity about equal to that of the diethyl ether (CXXIX). Recently Davies *et al.* (39, 40) described among others α,α,β-tri(*p*-anisyl)bromoethylene (CXXX) and, in direct comparison with D.B.E. (CXXIX), found their new estrogen more effective. This last result seems to indicate that in the

TABLE 13

Stilbestrol analogs with variation of location or number of aliphatic double bonds

FORMULA (Disregarding *cis-trans* configuration) R = 	MELTING POINT	NAME	ESTROGENIC ACTIVITY IN RATS (* IN MICE) SUBCUTANEOUSLY (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE)		REFERENCES
			Minimum effective dose	Rat units per gram	
	°C.		*micrograms*		
RCC_2H_5 ‖ RCC_2H_5	172	4,4′-Dihydroxy-α,β-diethylstilbene ("stilbestrol")	0.4	3,000,000	(56, 59)
$RCHC_2H_5$ | $RCH{=}CHCH_3$	(a) 143.5	3,4-Bis(*p*-hydroxyphenyl)-2-hexene	300		(219,222) 223)
	(b) 153	Isomer	10 2.5		(219) (222, 223)
	(a) Liquid (b) 74	Diacetate Isomer			(223) (223)
	(a) 126 (b) 184	Dibenzoate Isomer			(223) (223)
$RCCH_3$ ‖ $RCCH{=}CHCH_3$	162	4,4′-Dihydroxy-α-methyl-β-propenylstilbene	2	500,000	(56)
	158–159		1		(131, 132)
RCC_2H_5 ‖ $RCCH{=}CHCH_3$	b.p. 208–211/0.17 mm.	4,4′-Dihydroxy-α-ethyl-β-propenylstilbene	5	400,000	(56, 59)
$RCCH{=}CHCH_3$ ‖ $RCCH{=}CHCH_3$	b.p. 220–226/0.4 mm.	4,4′-Dihydroxy-α,β-dipropenylstilbene	100	20,000	(56, 59)
	164	Dibenzoate			(59)
$RCHCH_2CH{=}CH_2$ ‖ $RCHCH_2CH{=}CH_2$	Glass	4,4′-Dihydroxy-α,β-diallylstilbene			(37)
$RC{=}CH_2$ | $RC{=}CH_2$		2,3-Bis(*p*-hydroxyphenyl)-1,3-butadiene	Inactive		(60)

TABLE 13—*Continued*

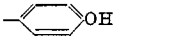
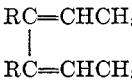
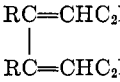
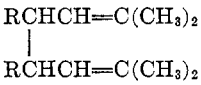
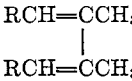
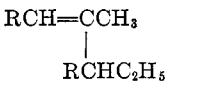
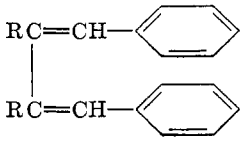
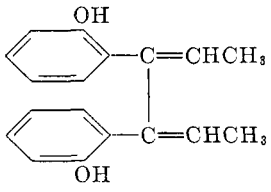
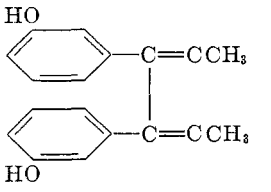
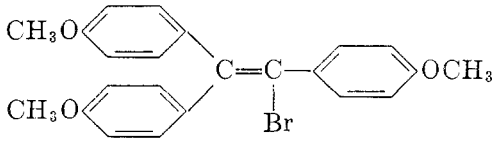
FORMULA (Disregarding *cis-trans* configuration) R = 	MELTING POINT	NAME	ESTROGENIC ACTIVITY IN RATS (* IN MICE) SUBCUTANEOUSLY (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE)		REFERENCES
			Minimum effective dose	Rat units per gram	
	°C.		*micrograms*		
	227–228	3,4-Bis(*p*-hydroxyphenyl)-2,4-hexadiene ("dienestrol")	0.5	1,000,000	(59, 60)
	142	Monomethyl ether			(91)
	224	Dibenzoate			(91)
	119–120	Diacetate			(59, 60)
	96	Dipropionate			(59)
	189	Isodienestrol	Inactive		(75a, 91)
		4,5-Bis(*p*-hydroxyphenyl)-3,5-octadiene	10		(59, 60)
		4,5-Bis(*p*-hydroxyphenyl)-1,8-dimethyl-2,7-octadiene	100		(59)
	192	1,4-Bis(*p*-hydroxyphenyl)-2,3-dimethyl-1,3-butadiene			(8, 91)
	Gum	1,3-Bis(*p*-hydroxyphenyl)-2-methyl-1-pentene ("dianol")	100		(23)
		2,3-Bis(*p*-hydroxyphenyl)-1,4-diphenyl-1,3-butadiene	Nil		(60)
		Diacetate			(60)

TABLE 13—*Concluded*

FORMULA (Disregarding *cis-trans* configuration) R = —C₆H₄—OH	MELTING POINT	NAME	ESTROGENIC ACTIVITY IN RATS (*IN MICE) SUBCUTANEOUSLY (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE)		REFERENCES
			Minimum effective dose	Rat units per gram	
	°C.		*micrograms*		
	136–137	3,4-Bis(*o*-hydroxyphenyl)-2,4-hexadiene		100	(56)
	166–167	3,4-Bis(*m*-hydroxyphenyl)-2,4-hexadiene		3,000	(56)

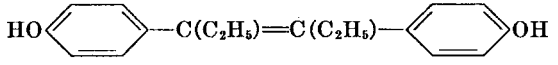
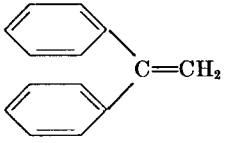
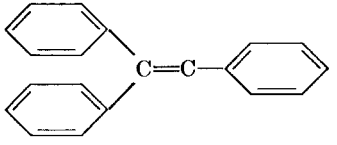
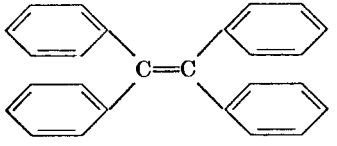


CXXX

triphenylethylene series fundamentally the same holds true as in the other series of related stilbene derivatives, i.e., maximum activity requires phenolic substitution of two rings attached to two different ethylene carbon atoms. This is not surprising in view of the finding of Dodds *et al.* (56), mentioned before, that 4,4′-dihydroxy-α-ethyl-β-phenylstilbene (CXIV) is not less than $\frac{1}{1\frac{1}{2}}$ as active as stilbestrol and thus the most active triphenylethylene derivative reported to date. On the basis of results originating from various laboratories and listed in table 14 it appears that the halogenated triphenylethylene derivatives carrying alkoxy groups are only about $\frac{1}{4}$ as active (20 micrograms) as compound CXIV, more closely related to stilbestrol. It is true that these substances possess an extremely prolonged activity subcutaneously and orally, a characteristic not shared by the ethers and esters of the stilbestrol and other series. A comparison is difficult because most of the triphenylethylene derivatives have been assayed by a special procedure devised by Robson (162). It is certainly unfortunate that no comparative data have been published regarding the activity of the dealkylation products which may, however, not be sufficiently stable, nor those of the corresponding esters.

TABLE 14

Triphenylethylene derivatives

FORMULA	NAME	ESTROGENIC ACTIVITY IN RATS (*IN MICE) SUBCUTANEOUSLY (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE)		DURATION OF ESTRUS		REFERENCES
		Minimum effective dose	Rat units per gram	Days total	Days until action halved	
		micrograms				
	Stilbestrol	0.1*			3	(166)
		50*			9	(166)
		500*			16	(166)
	α,α-Diphenylethylene	Nil				(55)
	Triphenylethylene	1,000*				(165)
		10,000*				(166)
		10,000*		>110	105	(165, 167)
	Tetraphenylethylene	Inactive				(166)

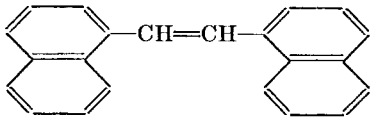
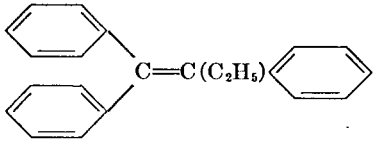
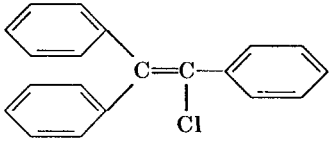
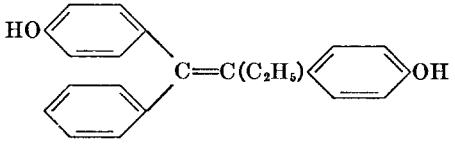
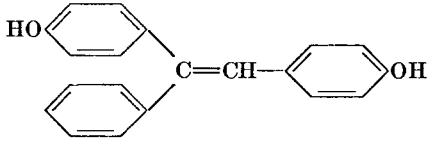
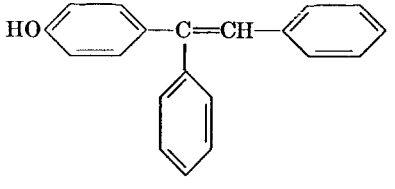
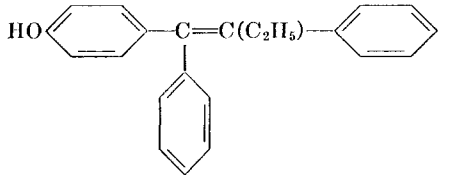
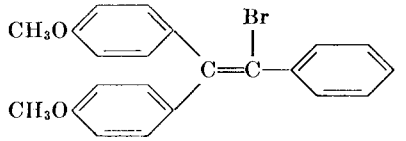
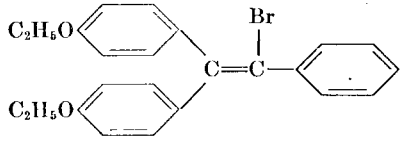
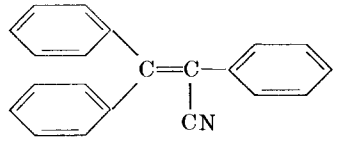
	α,β-Di(1-naphthyl-ethylene	Inactive				(166)
	α-Ethyl-β-phenylstilbene		2,500			(56)
	α,α,β-Triphenyl-β-chloroethylene	500*		>130	123	(165, 167, 209a)
		20 per 20-g. rat				(5)
	4,4′-Dihydroxy-α-ethyl-β-phenylstilbene	5	400,000		*	(56)
	4,4′-Dihydroxyphenyl-stilbene	100	10,000			(56, 59)
	α-(p-Hydroxyphenyl)-stilbene		4,000			(56)

TABLE 14—*Continued*

FORMULA	NAME	ESTROGENIC ACTIVITY IN RATS (*IN MICE) SUBCUTANEOUSLY (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE)		DURATION OF ESTRUS		REFERENCES
		Minimum effective dose	Rat units per gram	Days total	Days until action halved	
		micrograms				
	α-(*p*-Hydroxyphenyl)-β-ethylstilbene		30,000			(50)
	α,α-Di(*p*-anisyl)-β-phenyl-β-bromoethylene	20* 100*			• 9 68	(40, 181) (181)
	α,α-Bis(*p*-ethoxyphenyl)-β-phenyl-β-bromoethylene ("D.B.E.")	20* 100*			4 93	(166) (166)
	α,α,β-Triphenyl-β-cyanoethylene	1,000 per 20-g. rat				(5)

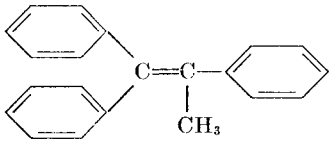
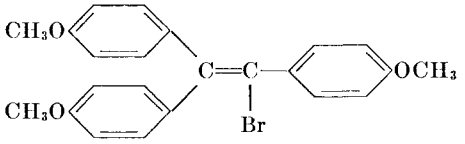
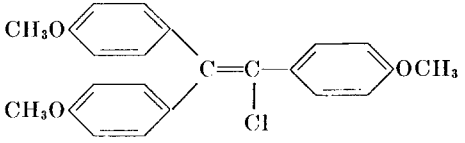
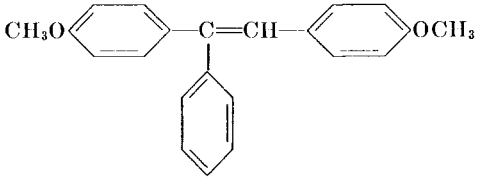
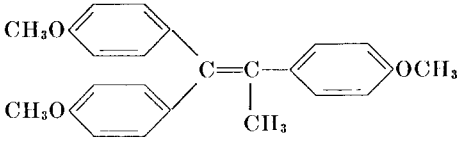
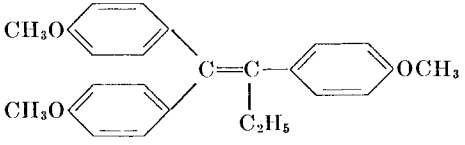
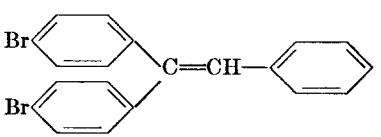
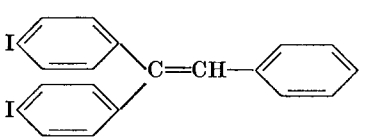
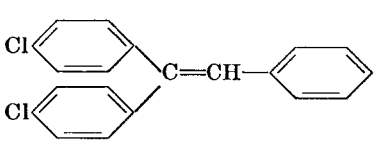
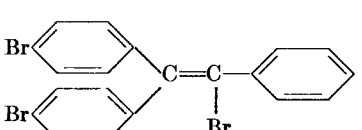
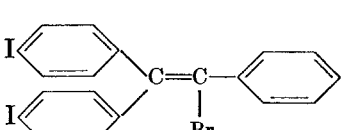
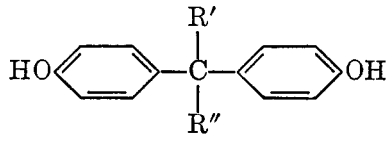
	α,α,β-Triphenyl-β-methylethylene	20 per 20-g. rat			(5)
	α,α,β-Tri(p-anisyl)-β-bromoethylene	20*		28	(40)
	α,α,β-Tri(p-anisyl)-β-chloroethylene	1,000	53		(210c)
	α,β-Di(p-anisyl)-α-phenylethylene *cis-trans* isomers				
	(a)	200* (25%)		· 2	(39)
	(b)	200* (10%)			(39)
	α,α,β-Tri(p-anisyl)-β-methylethylene	10* (45%)		6	(39)
	α,α,β-Tri(p-anisyl)-β-ethylethylene	10* (20%)		2	(39)
		50* (90%)		19	(39)

TABLE 14—*Concluded*

FORMULA	NAME	ESTROGENIC ACTIVITY IN RATS (*IN MICE) SUBCUTANEOUSLY (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE)		DURATION OF ESTRUS		REFERENCES
		Minimum effective dose	Rat units per gram	Days total	Days until action halved	
		micrograms				
	α,α-Bis(*p*-bromophenyl)-β-phenylethylene	5,000 inactive				(181)
	α,α-Bis(*p*-iodophenyl)-β-phenylethylene	5,000 inactive				(181)
	α,α-Bis(*p*-chlorophenyl)-β-phenylethylene	5,000 inactive				(181)
	α,α-Bis(*p*-bromophenyl)-β-phenyl-β-bromoethylene	5,000 inactive				(181)
	α,α-Bis(*p*-iodophenyl)-β-phenyl-β-bromoethylene	5,000 weakly active				(181)

VII. Diphenylmethane Derivatives

Prior to the development of stilbestrol and hexestrol Dodds and Lawson (61) found 4,4′-dihydroxydiphenylmethane (CXXXI) among the first simpler syn-



CXXXI: R′ = R″ = H

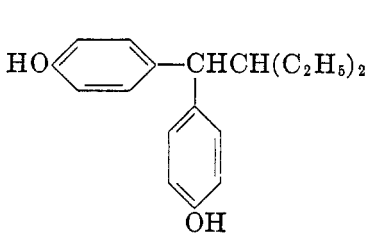
CXXXII: R′ = H; R″ = alkyl

CXXXIII: R′ = alkyl; R″ = alkyl

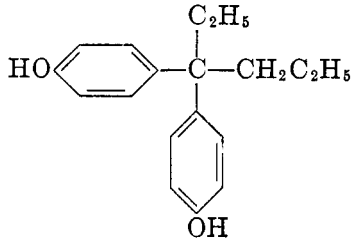
thetic estrogens not containing the phenanthrene or dibenzanthracene skeleton. These authors (64) later systematically substituted the parent compound with alkyl groups, but none of the compounds tested was active at a dose level lower than 100 mg. Thereafter the interest centered on the diphenylethane series, but more recently Campbell (22) undertook a systematic reinvestigation of the diphenylmethane series and included for assaying some compounds prepared earlier by others (44, 67, 89, 180, 231, 232). The series was finally supplemented by Reid and Wilson (158).

None of the compounds summarized in table 15 matches the potency of analogs in the stilbene or dihydrostilbene series. Nevertheless the study is of interest for two reasons. Firstly, it demonstrates the success of the systematic substitution of a given structure by various alkyl groups, resulting in a 500-fold increase of potency, and secondly, the series includes a number of structural isomers of hexestrol which offer an opportunity not available in other series for a study of the effect of the structural variation on the potency.

In the series of monosubstituted compounds (CXXXII) the activities are generally low. The peak (5 to 10 mg. dose level) is reached with R = diethylmethyl. This compound (CXXXIV) is an isomer of hexestrol (XX), the difference being the transposition of an ethyl group and one aromatic group, causing a 50,000-fold drop in activity.



CXXXIV

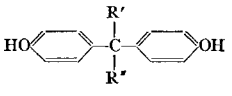


CXXXV

In the series of α,α-dialkyl-substituted diphenylmethanes (CXXXIII) a 5 to 10 times higher potency was found, with the peak for R′ = ethyl and R″ = *n*-propyl (CXXXV), again an isomer of hexestrol with transposition of one aromatic ring and one hydrogen atom.

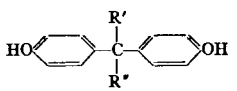
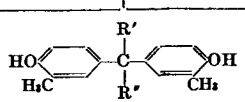
TABLE 15

Diphenylmethane derivatives

FORMULA  R′	R″	MELTING POINT	NAME	ESTROGENIC ACTIVITY IN RATS SUBCUTANEOUSLY (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE)		REFERENCES
				Minimum effective dose	Rat units per gram	
		°C.		*micrograms*		
H	H		Bis(4-hydroxyphenyl)methane	100,000		(61, 192)
					20	(21)
H	CH_3	122	1,1-Bis(4-hydroxyphenyl)ethane		20	(21, 89)
CH_3	CH_3	155	2,2-Bis(4-hydroxyphenyl)propane	100,000		(61, 64)
					36	(21, 231)
					28	(158)
H	C_2H_5	129	1,1-Bis(4-hydroxyphenyl)propane	100,000		(61)
					16	(21, 89)
CH_3	C_2H_5	124	2,2-Bis(4-hydroxyphenyl)butane	100,000		(61, 64, 67, 120)
					124	(158)
					100	(21)
H	n-C_3H_7	137	1,1-Bis(4-hydroxyphenyl)butane		40	(21, 89)
H	Iso-C_3H_7	152	1,1-Bis(4-hydroxyphenyl)-2-methylpropane		36	(21)
CH_3	n-C_3H_7	149	2,2-Bis(4-hydroxyphenyl)pentane	100,000		(61, 64, 67, 120)
					200	(21, 158)

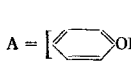
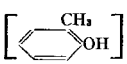
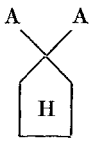
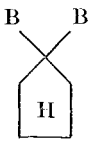
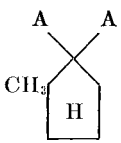
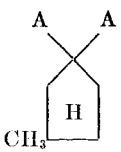
CH_3	Iso-C_3H_7	194	2,2-Bis(4-hydroxyphenyl)-3-methylbutane		50	(158)
C_2H_5	C_2H_5	204	3,3-Bis(4-hydroxyphenyl)pentane	100,000		(44, 61, 64)
					200	(158)
H	Iso-C_4H_9	145	1,1-Bis(4-hydroxyphenyl-3-methylbutane		100	(21)
CH_3	n-C_4H_9	Liquid	2,2-Bis(4-hydroxyphenyl)hexane		40	(21, 158)
CH_3	Iso-C_4H_9	153	2,2-Bis(4-hydroxyphenyl)-4-methylpentane		250	(21, 120)
					200	(158)
C_2H_5	n-C_3H_7	155	3,3-Bis(4-hydroxyphenyl)hexane		1,000	(21)
H	$(C_2H_5)_2CH$	168	1,1-Bis(4-hydroxyphenyl)-2-methylbutane	7,500	140	(21)
H	C_6H_{13}	120	1,1-Bis(4-hydroxyphenyl)heptane	100,000		(61, 64)
					40	(21)
n-C_3H_7	n-C_3H_7	154	4,4-Bis(4-hydroxyphenyl)heptane		500	(21)
					2,000	(158)
CH_3	C_5H_{11}	101	2,2-Bis(4-hydroxyphenyl)heptane		35	(158)
CH_3	C_6H_{13}	88	2,2-Bis(4-hydroxyphenyl)octane		50	(158)
n-C_3H_7	n-C_4H_9	150	4,4-Bis(4-hydroxyphenyl)octane		200	(21)
H	$(n$-$C_3H_7)_2CH$	128	1,1-Bis(4-hydroxyphenyl)-2-n-propylpentane		90	(21)

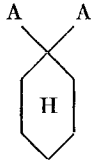
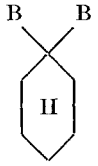
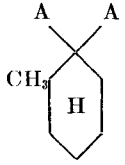
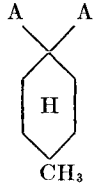
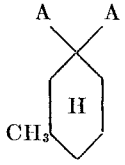
TABLE 15—*Continued*

FORMULA  R′	R″	MELTING POINT	NAME	ESTROGENIC ACTIVITY IN RATS SUBCUTANEOUSLY (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE)		REFERENCES
				Minimum effective dose	Rat units per gram	
		°C.		*micrograms*		
n-C_4H_9	n-C_4H_9	170.5	5,5-Bis(4-hydroxyphenyl)nonane		20	(21, 158)
C_5H_{11}	C_5H_{11}	148.5	6,6-Bis(4-hydroxyphenyl)undecane		10	(158)
H	C_6H_5	161	Bis(4-hydroxyphenyl)phenylmethane	100,000		(64)
CH_3	C_6H_5	188	1,1-Bis(4-hydroxyphenyl)phenylethane	100,000 (60%) Inactive		(64) (158)
CH_3	p-$CH_3OC_6H_4$	245	1,1-Bis(4-hydroxyphenyl)-p-anisylethane		55	(158)
p-HOC_6H_4	p-HOC_6H_4	282	Tetra(4-hydroxyphenyl)methane	Inactive		(64)
$C_6H_5CH_2$	$C_6H_5CH_2$	193	Bis(4-hydroxyphenyl)dibenzylmethane	Inactive		(158, 232)
 R′	R″					
H	C_2H_5	94	1,1-Bis(3-methyl-4-hydroxyphenyl)propane		8	(21, 89)

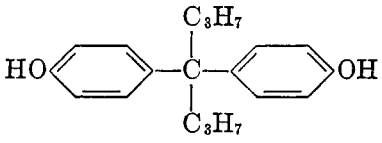
CH_3	CH_3	137–139	2,2-Bis(3-methyl-4-hydroxyphenyl)-propane	100,000	40	(21) (64)
CH_3	C_2H_5	145–147	2,2-Bis(3-methyl-4-hydroxyphenyl)-butane	100,000	40	(21, 67, 120) (64)
C_2H_5	C_2H_5	120	3,3-Bis(3-methyl-4-hydroxyphenyl)-pentane		1,000	(21)
CH_3	n-C_3H_7	128	2,2-Bis(3-methyl-4-hydroxyphenyl)-pentane		250	(21)
H	Iso-C_4H_9	124	1,1-Bis(3-methyl-4-hydroxyphenyl)-2-methylpropane		28	(21)
CH_3	n-C_4H_9	104–105	2,2-Bis(3-methyl-4-hydroxyphenyl)-hexane		40	(21)
CH_3	Iso-C_4H_9	128	2,2-Bis(3-methyl-4-hydroxyphenyl)-4-methylpentane		180	(21, 120)
C_2H_5	n-C_3H_7	90	3,3-Bis(3-methyl-4-hydroxyphenyl)-hexane		4,000	(21)
n-C_3H_7	n-C_3H_7	173	4,4-Bis(3-methyl-4-hydroxyphenyl)-heptane		5,000	(21)
n-C_3H_7	n-C_4H_9	140	4,4-Bis(3-methyl-4-hydroxyphenyl)-octane		1,000	(21)
n-C_4H_9	n-C_4H_9	128	5,5-Bis(3-methyl-4-hydroxyphenyl)-nonane		200	(21)

TABLE 15—*Concluded*

FORMULA A =  B = 	MELTING POINT	NAME	ESTROGENIC ACTIVITY IN RATS SUBCUTANEOUSLY (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE)		REFERENCES
			Minimum effective dose	Rat units per gram	
	°C.		*micrograms*		
	156	1,1-Bis(4-hydroxyphenyl)cyclopentane		15 66	(21, 120) (158)
	162	1,1-Bis(3-methyl-4-hydroxyphenyl)-cyclopentane		36	(21)
	161	1,1-Bis(4-hydroxyphenyl)-2-methylcyclopentane		100	(21)
	171	1,1-Bis(4-hydroxyphenyl)-3-methylcyclopentane		40	(21)

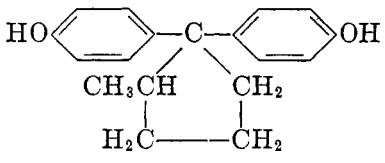
	184	1,1-Bis(4-hydroxyphenyl)cyclohexane	100,000	40	(21, 64, 120)
	191–192	1,1-Bis(3-methyl-4-hydroxyphenyl)-cyclohexane	100,000	40	(21, 64)
	235	1,1-Bis(4-hydroxyphenyl)-2-methyl-cyclohexane		25	(21)
	179	1,1-Bis(4-hydroxyphenyl)-4-methyl-cyclohexane		200	(120, 158)
		1,1-Bis(4-hydroxyphenyl)-3-methyl-cyclohexane			(120)

In both the mono- and the di-substituted series a comparison was made with homologs carrying methyl groups in the ortho-position to the two phenolic hydroxyl groups. The detrimental effect of this substitution had been reported earlier (64) for compounds of the type of CXXXI and was now confirmed by Campbell (22) in the monosubstituted series (CXXXII). Quite unexpectedly, a strong enhancing effect was found in series CXXXIII, resulting in a four- to five-fold increase over the most active homologs without nuclear methyl groups. The peak lies here with the di-*n*-propyl derivative (CXXVI), which is not an isomer of hexestrol; its potency at the 200-microgram level represents the highest one yet found in the diphenylmethane series.

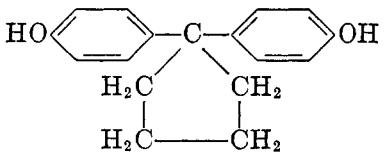


CXXXVI

Campbell remarked that the peak for the dipropyl-substituted compound (CXXXVI) recalls the maximum potency found for the equally substituted compound (III) in the 9,10-dialkylanthraquinol series. This author also included structures where the central carbon atom is part of a ring system. The activities were 50- to 200-fold lower than in the preceding series. Within the cyclic series the highest activity lies with the α-methylcyclopentane derivative (CXXXVII), which is six to seven times as active as the lower homolog (CXXXVIII).



CXXXVII



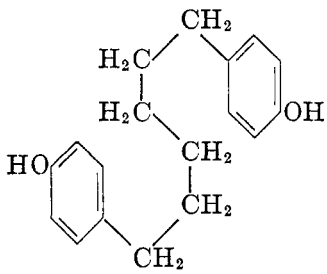
CXXXVIII

On the other hand, ortho-methylation of the cyclohexane analog of CXXXVIII, prepared by Dodds and Lawson (61), lowered the activity.

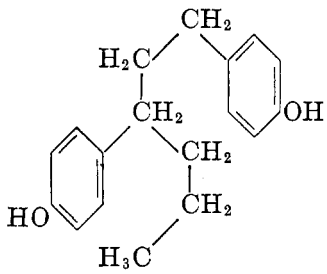
VIII. Diphenylpropane Derivatives

Numerous estrogenic compounds have been investigated with longer and branched alkane chains between the two hydroxyphenyl rings (table 16). Some of these have been reported by Dodds and coworkers (25,64) for the purpose of identifying the highly active estrogen among the demethylation products of anethole. Baker (6) endeavored to obtain substances still conforming to the estradiol pattern but with its hydronaphthalene skeleton ruptured at places other than in hexestrol. Among these compounds, written according to Baker, are 1,6-bis(*p*-hydroxyphenyl)hexane (CXXXIX), 1,3-bis(*p*-hydroxyphenyl)-

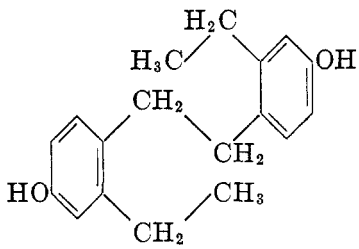
hexane (CXL), and 1,2-bis(2-ethyl-4-hydroxyphenyl)ethane (CXLI, identical with CXI); all of these are practically inactive.



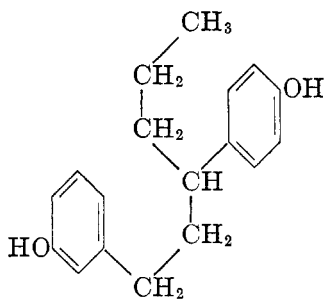
CXXXIX



CXL

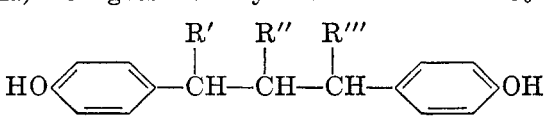


CXLI



CXLII

Blanchard, Stuart, and Tallman (12, 206, 207) at first followed similar lines and synthesized 1-(*m*-hydroxyphenyl)-3-(*p*-hydroxyphenyl)hexane (CXLII), which is moderately active. These authors then disregarded the hypothetical structural resemblance and prepared a series of di(*p*-hydroxyphenyl)propane derivatives and concluded, on the basis of their results, that this resemblance is coincidental. In the series of monosubstituted di(*p*-hydroxyphenyl)propane derivatives (CXLIII) the highest activity was found for R = C_3H_7, with the rat

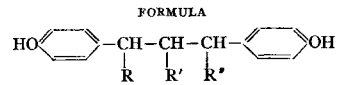


CXLIII: R″=R‴=H
CXLIV: R′=R‴=H

unit at 5 to 10 mg. When the substituent was attached to the central methylene group (CXLIV), the optimum activity for R″ = C_2H_5 was found to be of the same order as that of the unsymmetrically substituted compound (CXLIII). A decisive improvement of activity was obtained when all three aliphatic carbon atoms carried alkyl substituents. Here the optimal rat unit of 3 micrograms was found for the methyl-ethyl-ethyl substitution, resulting in 2,4-bis(*p*-hydroxyphenyl)-3-ethylhexane (CXLIX). This substance was prepared by way of the condensation product (CXLV) of anisaldehyde with *p*-methoxypropiophe-

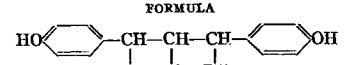
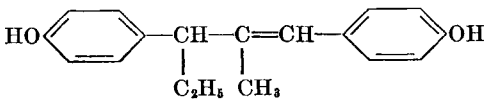
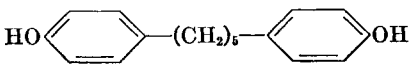
TABLE 16

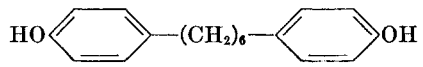
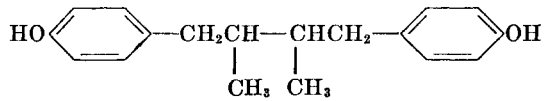
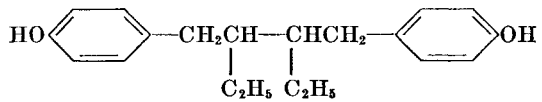
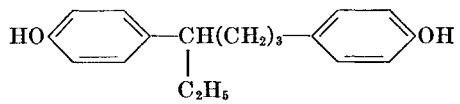
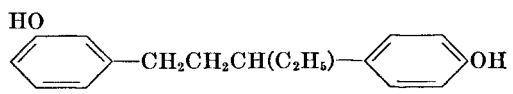
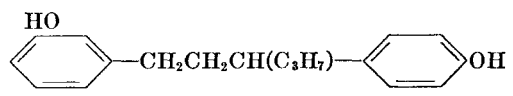
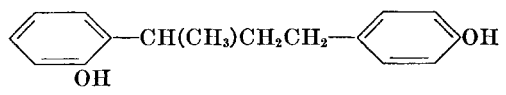
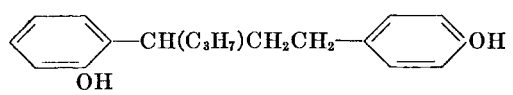
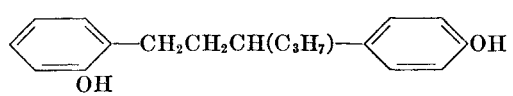
Diphenylpropane derivatives and higher homologs

FORMULA  R	R′	R″	MELTING POINT	NAME	ESTROGENIC ACTIVITY IN RATS SUBCUTANEOUSLY (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE): MINIMUM EFFECTIVE DOSE	REFERENCES
			°C.		*micrograms*	
H	H	H	104–105	1,3-Bis(*p*-hydroxyphenyl)propane	100,000 10,000	(64, 105) (207)
CH_3	H	H	Resin	1,3-Bis(*p*-hydroxyphenyl)butane	<10,000	(207)
C_2H_5	H	H	99–100	1,3-Bis(*p*-hydroxyphenyl)pentane	10,000 Inactive at 100	(207) (6)
n-C_3H_7	H	H	101	1,3-Bis(*p*-hydroxyphenyl)hexane	2,000 (70%)	(12, 207)
Iso-C_3H_7	H	H	b.p. 178–179	2-Methyl-3,5-bis(*p*-hydroxyphenyl)pentane	<10,000	(207)
n-C_4H_9	H	H	Resin	5,7-Bis(*p*-hydroxyphenyl)heptane	<10,000	(207)
n-C_6H_{11}	H	H	Resin	6,8-Bis(*p*-hydroxyphenyl)octane	<10,000	(207)
C_6H_5	H	H	105–106	1-Phenyl-1,3-bis(*p*-hydroxyphenyl)propane	<10,000	(207)
$C_6H_5CH_2$	H	H	108–110	1-Phenyl-2,4-bis(*p*-hydroxyphenyl)butane	<10,000	(207)
$CH_3OC_6H_4$	H	H	62–63	1-Anisyl-1,3-bis(*p*-hydroxyphenyl)propane	<10,000	(207)

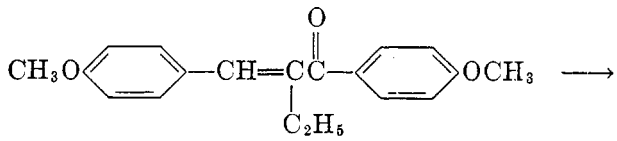
H	CH_3	H	130	1,3-Bis(*p*-hydroxyphenyl)-2-methylpropane	<10,000		(207)
H	C_2H_5	H	102	3-(*p*-Hydroxybenzyl)-4-(*p*-hydroxyphenyl)butane	<10,000		(207)
H	*n*-C_3H_7	H	118–119	4-(*p*-Hydroxybenzyl)-5-(*p*-hydroxyphenyl)pentane	5,000	(70%)	(207)
C_2H_5	H	C_2H_5		3,5-Bis(*p*-hydroxyphenyl)heptane	1,000	(70%)	(12)
H	C_2H_5	C_2H_5		3-(*p*-Hydroxyphenyl)-4-(*p*-hydroxybenzyl)hexane	15	(70%)	(12)
C_2H_5	CH_3	H	128	3,5-Bis(*p*-hydroxyphenyl)-4-methylpentane			(25)
C_2H_5	H	C_2H_5		3,5-Bis(*p*-hydroxyphenyl)heptane	1,000	(70%)	(12)
CH_3	C_2H_5	CH_3		2,4-Bis(*p*-hydroxyphenyl)-3-ethylpentane	10	(70%)	(12)
CH_3	*n*-C_3H_7	CH_3		2,4-Bis(*p*-hydroxyphenyl)-3-propylpentane	8	(70%)	(12)

TABLE 16—*Concluded*

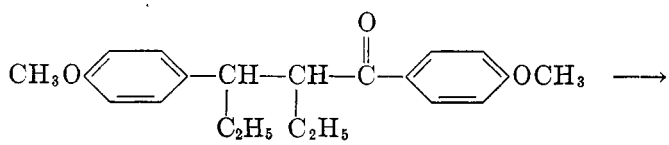
FORMULA  R	R′	R″	MELTING POINT	NAME	ESTROGENIC ACTIVITY IN RATS SUBCUTANEOUSLY (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE): MINIMUM EFFECTIVE DOSE	REFERENCES
			°C.		*micrograms*	
CH_3	C_2H_5	C_2H_5		2,4-Bis(*p*-hydroxyphenyl)-3-ethylhexane (mixture of four racemates)	3 (70%)	(12, 206)
			Resin	Racemic mixture "A-1"	10 (70%)	(12, 206)
			75	Racemic mixture "A-2"	5 (70%)	(206)
			144	Racemic mixture "B-1"	35 (70%)	(206)
			162	Racemic mixture "B-2" ("benzestrol")	0.8 (70%)	(12, 206)
			Oil	Diacetate	5	(206)
			Oil	Dipropionate	7.5	(206)
			Oil	Dibutyrate		(206)
			Oil	Divalerate		(206)
			Oil	Dilaurate	100	(206)
			Oil	Dicaprylate	40	(206)
			38	Dipalmitate	200	(206)
			118	Dibenzoate	50	(206)
CH_3	C_2H_5	C_3H_7		2,4-Bis(*p*-hydroxyphenyl)ethylheptane	15	(12)
CH_3	n-C_3H_7	C_2H_5		2,4-Bis(*p*-hydroxyphenyl)-3-propylhexane	12	(12)
				1,3-Bis(*p*-hydroxyphenyl)-2-methyl-1-pentene ("dianol")	100 1,000	(23) (25)
			Resin	1,5-Bis(*p*-hydroxyphenyl)pentane	100,000	(105)

		1,6-Bis(*p*-hydroxyphenyl)hexane	Inactive	(6, 25)
	152	1,4-Bis(*p*-hydroxybenzyl)butane	10,000	(25)
	156–157	3,4-Bis(*p*-hydroxybenzyl)hexane	Inactive at 50	(6)
	98	1,4-Bis(*p*-hydroxyphenyl)hexane	5,000	(25)
	Resin	1-(*m*-Hydroxyphenyl)-3-(*p*-hydroxyphenyl)pentane		(90)
	Resin	1-(*m*-Hydroxyphenyl)-3-(*p*-hydroxyphenyl)hexane	20,000 (70%)	(12, 90)
	Resin	1-(*p*-Hydroxyphenyl)-3-(*o*-hydroxyphenyl)butane		(90)
	Resin	1-(*p*-Hydroxyphenyl)-3-(*o*-hydroxyphenyl)hexane		(90)
	Resin	1-(*o*-Hydroxyphenyl)-3-(*p*-hydroxyphenyl)hexane		(90)

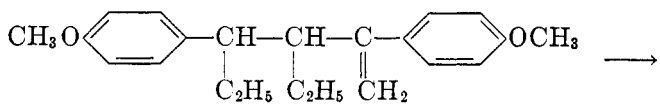
none (XXXIII). A series of Grignard reactions effects introduction of the second ethyl group to CXLVI and of the methylene group to CXLVII. Hydrogenation to CXLVIII and demethylation complete the synthesis.



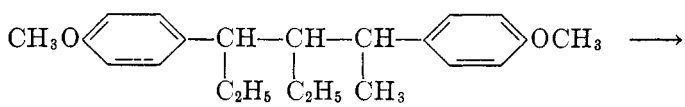
CXLV



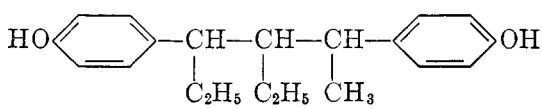
CXLVI



CXLVII



CXLVIII



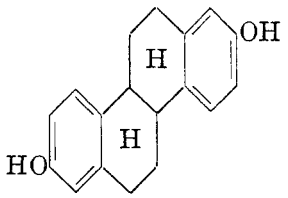
CXLIX

The end product is a resinous mixture of four theoretically possible racemates and is active at the 3-microgram level. From this complex mixture individual racemates have been isolated, though more conveniently by means of a preliminary separation of the two racemic modifications of the ketone (CXLVI). Each racemate was then carried through the remaining reactions, resulting in mixtures of only two racemic mixtures. The relative amounts of the two isomers produced in each case could be varied somewhat depending on the conditions (yet unpublished) of hydrogenation. As shown in table 16, the four racemic mixtures vary considerably in potency. The most active one was called "octofollin" or "benzestrol" and is fully active in doses of 0.8 microgram. Various esters have been prepared which again show prolonged activity but require increased dosage. The series was recently supplemented by position isomers regarding hydroxyl groups; for these substances so far only the bactericidal activity has been reported by Heinemann (90).

IX. Ring-closed Analogs

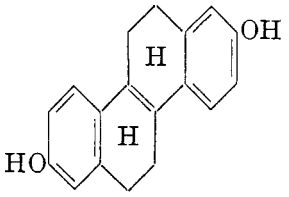
It has been shown how the development of synthetic estrogens began with condensed ring systems, whence it led to the simple hydroxystilbene derivatives. Variation of the stilbestrol structure prompted once more the investigation of condensed ring systems with the stilbestrol skeleton as part of their structure (table 17).

Stilbestrol, written in the *trans*-form, is suggestive of ring-closed analogs of three structural types: chrysene, phenylnaphthalene, and phenylindene. Compounds representing the first two were prepared in the early stage of their work by Dodds, Goldberg, Lawson, and Robinson (59) without, however, encountering highly active estrogens. *trans*-2,8-Dihydroxy-5,6,11,12,13,14-hexahydrochrysene (CL)



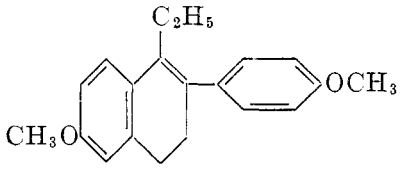
CL

is active only in doses of 1 mg. Salzer (175) synthesized the diacetate of 2,8-dihydroxy-5,6,11,12-tetrahydrochrysene (CLI). Introduction of the 11,12



CLI

double bond results in a greatly increased activity of 10 micrograms. Dodds *et al.* (59) further obtained 1-ethyl-2-(*p*-anisyl)-3,4-dihydro-6-methoxynaphthalene (CLII), but demethylation resulted in the corresponding 1,2,3,4-tetrahydro

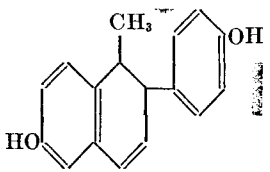
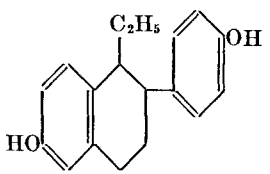
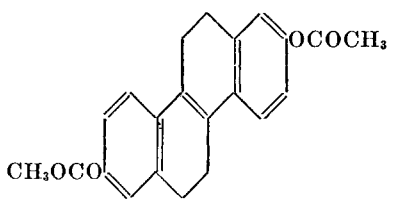
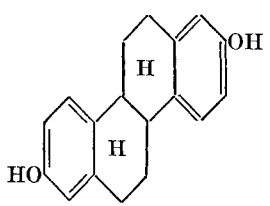


CLII

derivative, which is active only at the 10-mg. dose level. The reductive demethylation, possibly by disproportionation, recalls the formation of hexestrol by demethylation of anethole.

TABLE 17

Synthetic estrogens with condensed ring systems

FORMULA	MELTING POINT	NAME	ESTROGENIC ACTIVITY IN RATS (*IN MICE) SUBCUTANEOUSLY (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE): MINIMUM EFFECTIVE DOSE	REFERENCES
	°C.		*micrograms*	
	193	1-Methyl-2-(*p*-hydroxyphenyl)-3,4-dihydro-6-naphthol	0.3–0.5 0.2	(175) (174)
	256	1-Ethyl-2-(*p*-hydroxyphenyl)-1,2,3,4-tetrahydro-6-naphthol	10,000	(59)
		3,9-Diacetyl-5,6,11,12-tetrahydrochrysene	100	(175)
	263–264	*trans*-4,10-Dihydroxy-1,2,7,8,13,14-hexahydrochrysene	1,000	(58, 59)

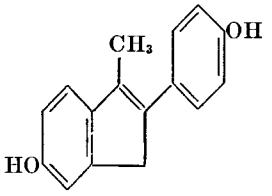
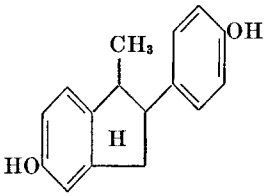
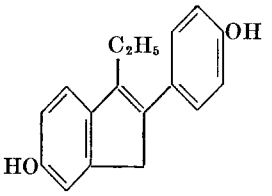
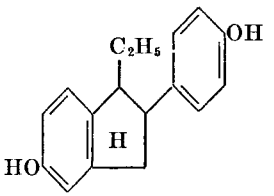
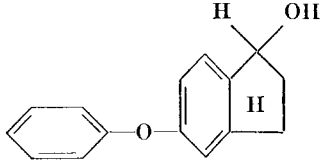
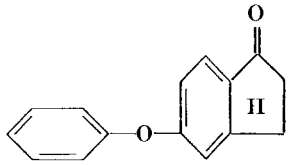
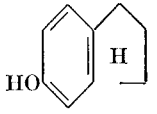
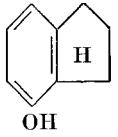
		2-(*p*-Hydroxyphenyl(-3-methyl-6-hydroxy-2,3-indene		(175)
	131	Diacetate	0.3–0.5	(175)
			0.2	(174)
	Liquid	2-(*p*-Hydroxyphenyl)-3-ethyl-6-hydroxyindane	Inactive at 200	(175)
	Liquid	Diacetate		(175)
	136	2-(*p*-Hydroxyphenyl)-3-ethyl-6-hydroxy-2,3-indene	1.2 (50%)*	(194)
	118–120	Diacetate	0.9 (50%)*	(194)
	88–89	Dipropionate	30 (50%)*	(194)
	162–163	2-(*p*-Hydroxyphenyl)-3-ethyl-6-hydroxyindane	1.8 (50%)*	(194)

TABLE 17—*Continued*

FORMULA	MELTING POINT	NAME	ESTROGENIC ACTIVITY IN RATS (*IN MICE) SUBCUTANEOUSLY (100 PER CENT RESPONSE UNLESS INDICATED OTHERWISE): MINIMUM EFFECTIVE DOSE	REFERENCES
	°C.		*micrograms*	
	111	6-Benzoxy-1-indanol	Inactive at 99	(137)
	141	6-Benzoxy-1-indanone		(137)
	55	6-Hydroxyindane	Inactive	(64)
	244–246	7-Hydroxyindane	Inactive	(64)

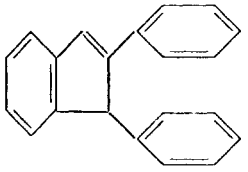
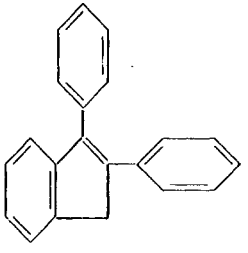
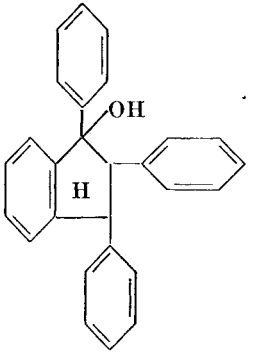
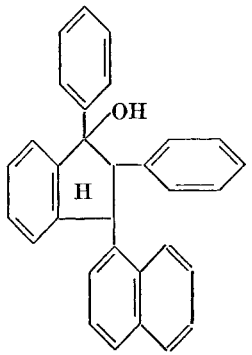
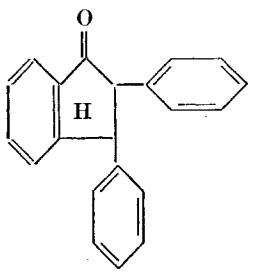
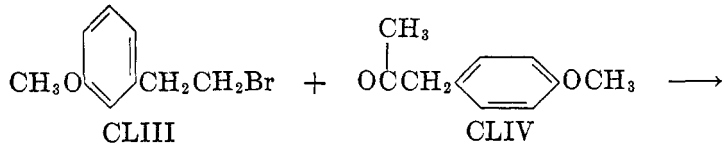
		1,2-Diphenylindene	20 mg. per 20-g. rat	(5)
		2,3-Diphenylindene	20 mg. per 20-g. rat	(5)
		1,2,3-Triphenyl-1-indanol	100,000	(130)

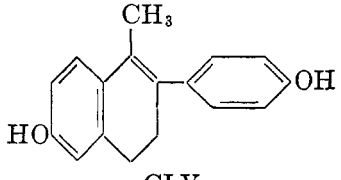
TABLE 17—*Concluded*

FORMULA	MELTING POINT	NAME	ESTROGENIC ACTIVITY IN RATS (*IN MICE) SUBCUTANEOUSLY (100 PER CENT) RESPONSE UNLESS INDICATED OTHERWISE): MINIMUM EFFECTIVE DOSE	REFERENCES
	°C.		*micrograms*	
		1-α-Naphthyl-2,3-diphenyl-1-indanol	100,000	(130)
		2,3-Diphenyl-1-indanone	100,000	(130)

Salzer (174, 175) succeeded in preparing the desired phenolic dihydro derivative of the next lower homolog (CLV) in a three-step synthesis from 2-(*m*-methoxyphenyl)ethyl bromide (CLIII) and *p*-anisylacetone (CLIV), followed by ring closure and demethylation; the resulting 1-methyl-2-(*p*-hydroxyphenyl)-

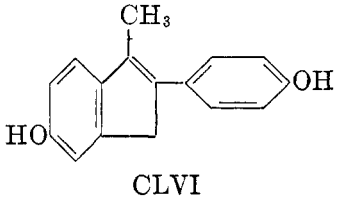


CLIII CLIV

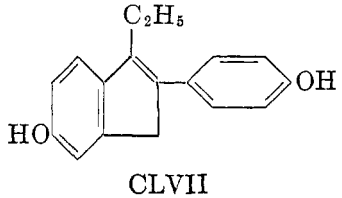


CLV

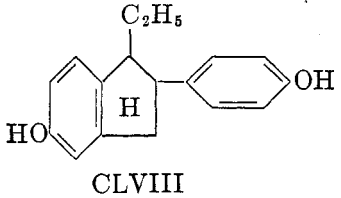
3,4-dihydro-6-hydroxynaphthalene (CLV) was reported active in the order of stilbestrol. In an analogous manner this worker condensed (*p*-anisyl)acetone with *m*-methoxybenzyl chloride followed by ring closure and demethylation, to give 2-(*p*-hydroxyphenyl)-3-methyl-6-hydroxy-2,3-indene (CLVI).



CLVI



CLVII



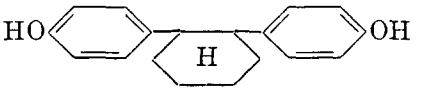
CLVIII

Its diacetate possesses the same activity as the dihydronaphthalene derivative (CLV). Salzer found that the indene-ring closure by means of sulfuric acid could not be effected when the methyl group was replaced by an ethyl group. Solmssen (194) obtained this ethyl homolog (CLVII) by a different method and found its diacetate (C) to be $\frac{1}{12}$ as active as stilbestrol. Incidentally, the 6-position of one of the hydroxyl groups has not yet been strictly proven for either the methyl or the ethyl derivative. Salzer found that catalytic reduction of the indene (CLVI) resulted in a dihydro derivative inactive in doses as high as 200

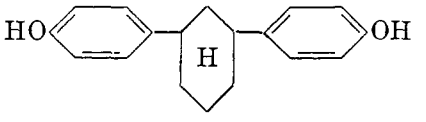
micrograms. The low activity of this indane, as well as that of the hexahydrochrysene (CL), led Salzer to conclude that disappearance of the "stilbenoid" double bond in cyclic analogs reduces the activity to 1/1000 of that of the unsaturated compound. This conclusion is certainly not justified, because the indane (CLVIII), prepared by hydrogenation of the indene (CLVII), is not less than one-half as active as the latter (194). Plentl and Bogert (150) undertook model experiments for the synthesis by a third method of similar phenylindene and phenylnaphthalene derivatives. So far these authors have described only compounds lacking the phenolic hydroxyl groups in the molecule. For feeble estrogenic activity these are possibly not essential, because Badger *et al.* (5) described some active hydrocarbons, and Monche and Monguio (130) some active indane derivatives with hydroxyl groups in the cyclopentane ring only.

Mentzer and Urbain (123) synthesized compound CLV by a modification of the methods employed by Salzer and by Dodds.

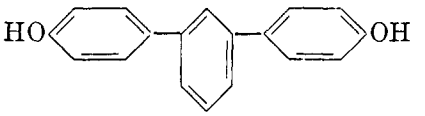
Price and Mueller (154) attempted unsuccessfully to synthesize 1,2-bis(*p*-hydroxyphenyl)cyclohexane (CLIX), which might be considered a ring-closed analog of hexestrol.



CLIX



CLX



CLXI

The Friedel–Crafts reaction between 1,2-dichlorocyclohexane and anisole proceeded with rearrangement to the 1,3-isomer (CLX), and yielded further 4,4'-dihydroxy-*m*-terphenyl (CLXI); both compounds were found to be inactive. Several cyclohexane derivatives with phenolic rings attached to the same carbon atom are listed in table 15 under cyclic diphenylmethane derivatives.

X. Relation of Synthetic Estrogens to Carcinogenic Substances

The early work of Cook and Dodds on synthetic estrogens (32, 35) originated from the interest in the problem of a possible correlation between estrogenic and carcinogenic effect. The then somewhat unexpected estrogenic activity of 5,6-cyclopenteno-1,2-dibenzanthracene and 1,2-benzopyrene appeared at first to be significant. Later it was seen that the low order of potency of these compounds is shared by many other non-carcinogenic substances. Subsequent years brought the further development of synthetic carcinogenic hydrocarbons and of phenolic estrogens as two independent lines of research which, to this date, have added little to the understanding of the influence of female sex hor-

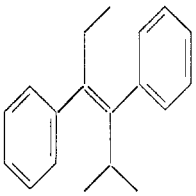
mones on the transformation of normal into cancerous tissue. Nevertheless, synthetic as well as natural estrogens are rapidly gaining in importance for the treatment of certain malignant diseases. The discussion of the rationale of this therapy is beyond the scope of this review. The earlier work has been treated by Fieser (77) and the more recent developments by Dodds (53) and by Haddow *et al.* (88).

TABLE 18

Carcinogenic effectiveness of estrogens (on injection, in mice)

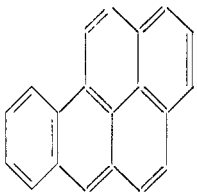
ESTROGENS	(a) ESTROGENIC DOSE (50 PER CENT RESPONSE) IN MICROGRAMS	(b) CARCINOGENIC DOSE		(c) RATIO (b):(a)
		Milligrams	Response	
Estrone	1.0	32.8	100%	32.8
Estradiol	0.3	25.0	50%	83.3
Estradiol benzoate	0.6	0.6	100%	1.0
Stilbestrol	0.3	18.2	100%	60.8
Stilbestrol monomethyl ether	2.0	9.5	50%	4.8
Stilbestrol dimethyl ether	25.0	116.5	50%	4.6

Dodds, Lawson, and Williams (65) selected α-ethyl-β-*sec*-butylstilbene (CLXII) as a stilbene derivative closely resembling 3,4-benzopyrene (CLXIII) and dimethylchrysene (CLXIV).



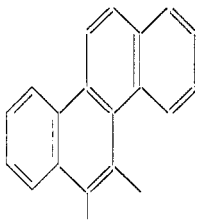
CLXII

α-Ethyl-β-*sec*-butylstilbene



CLXIII

3,4-Benzopyrene



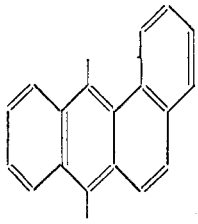
CLXIV

Dimethylchrysene

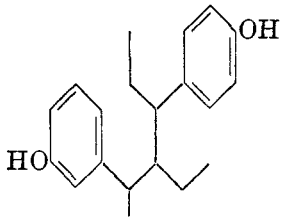
When painted on mice, this stilbene derivative proved to be carcinogenic, while no positive results were obtained with diphenylhexane, diphenylhexadiene, diethylstilbene, stilbestrol, hexestrol, and 4,4′-dihydroxystilbene.

Employing another technique, Geschickter and Byrnes (85) produced mammary cancer in mice with stilbestrol and some derivatives. Their data, reproduced in table 18, are of particular interest because they include parallel experiments with some natural estrogens. Similar results had been obtained earlier by Shimkin and Grady (189), and it appears that there may be a quantitative, but no qualitative, difference between synthetic and natural estrogens in their relation to the production of cancer. Martin (118) called attention to the similarity of 9,10-dimethyl-1,2-dibenzanthracene (CLXV), one of the most

active carcinogenic hydrocarbons known, and benzestrol (CXLIX) when the latter is written as shown in CLXVI.



CLXV

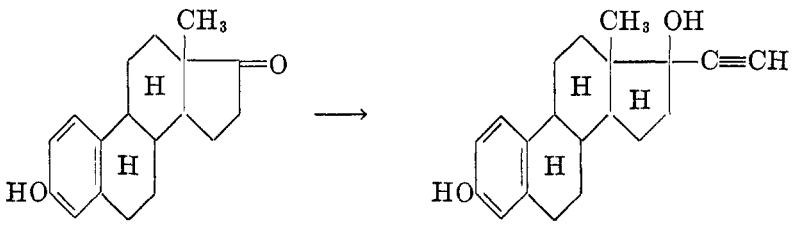


CLXVI

However, the postulated carcinogenic effectiveness of benzestrol has not been corroborated by experimental evidence (206).

XI. Metabolic Conversions and Efficacy By Various Routes

Whereas the subcutaneous activity provides the most convenient yardstick for comparing various estrogens, the comparative efficacy by different routes is of physiological interest. Moreover, the high oral activity of synthetics is important from a practical point of view. For the benefit of the subsequent discussion it is proposed to include ethinylestradiol (CLXVIII) among the synthetic estrogens.



CLXVII CLXVIII

Inhoffen *et al.* (94) prepared this compound by the action of potassium acetylide on estrone (CLXVII), and reported its especially high oral activity. Today it is recognized as probably the most active estrogen known. As a synthetic conversion product of a natural estrogen it represents an intermediate type, but for reasons apparent in the course of the following discussion it is more appropriate to classify it with the synthetic estrogens.

The oral efficacy of synthetics is relatively and absolutely superior to that of the natural hormones. Zondek and Sulman (234) advanced the theory that this is due to differences in the resistance of the products to metabolic degradation. After rats had been injected with estrogenically equivalent amounts of estrogens, stilbestrol was recovered in 25 per cent from the body and in equal amounts from the excreta; the esters of natural estrogens behaved similarly, while only 1 to 2 per cent of the administered estrone was found in the body and none in the excreta. Silberstein and coworkers (191) had previously shown *in vitro* that estrone is inactivated by liver tissue as well as by blood of dogs. Consequently it was generally accepted that the process of estrone inactivation took place in the liver, possibly involving an enzyme, and that the stability of stil-

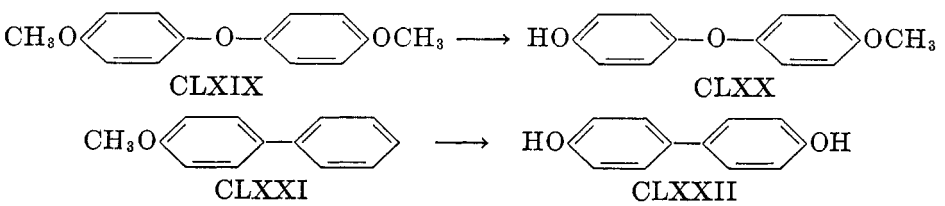
bestrol within the organism was due to the inability of the liver to inactivate the synthetic compound. Later this interpretation had to be modified when more experimental evidence became available. Dingemanse and Tyslowitz (48) found an appreciably higher urinary excretion of estrone than reported previously. Zondek *et al.* (235) investigated the *in vitro* inactivation of stilbestrol and reported that rat liver pulp inactivates it also, though less readily than the natural estrogen. According to these workers the susceptibility to inactivation is the same if the two types of estrogens are compared on the basis of their estrogenic activity. Chamelin and Funk (233), applying this finding, reported that the mortality of rats due to excessive doses of stilbestrol could be significantly lowered by the concurrent administration of liver extract.

The hypothesis of enzymatic inactivation was elaborated by Westerfeld (227), reasoning that estrogens, like other phenols, might be metabolized by oxidation to *o*- or *p*-dihydrophenols and subsequently to the corresponding quinones. The enzyme tyrosinase effects such oxidations and, applying it to estrogens, Westerfeld showed that estrone, estradiol, and stilbestrol are inactivated *in vitro*, the latter in amounts exceeding 75 per cent. This author recognized that these results are inconclusive without the isolation of the postulated inactivation products and, in fact, no such products have been encountered among the excretion products isolated by others (119, 205). Moreover, tyrosinase has not been encountered in mammalian tissue and thus the above experiments do not elucidate the mechanism of inactivation *in vivo*.

The fate of estrogens after parenteral administration has been the subject of further investigations. Stroud (203) made a quantitative study of the recoveries of various estrogens from the urine of rabbits. For the first time the excretion products of synthetics were isolated in crystalline form and in amounts corresponding to the total estrogenic activity of the urine. One half of the total recovered stilbestrol was present as conjugate, the other half free.

Mazur and Shorr (119) identified the conjugate as the glucuronide, with stilbestrol combined in glucosidic linkage. Up to 30 per cent of the administered amount was recovered as crystalline conjugate, and the authors concluded that "its magnitude indicates the significance of this conjugating mechanism for the intermediary metabolism of stilbestrol."

Stroud (205) contributed experimental evidence for the dealkylation of estrogenic phenol ethers in the organism of female rabbits. Thus 4,4′-dimethoxydiphenyl ether (CLXIX) was physiologically converted into the monohydroxymonomethoxy derivative (CLXX) and 4-methoxydiphenyl (CLXXI) into 4-hydroxy- and 4,4′-dihydroxy-diphenyls (CLXXII). Only the last compound is estrogenically active. This was the first observed instance of the biological production of an active substance from inactive material. The same worker



(202) extended the investigation of excretion products to other active and inactive phenols previously assayed by Dodds *et al.* (59, 64).

In all cases (shown in table 19) phenolic products were formed, resulting in activation rather than inactivation of the parent compounds. However, only the stilbenes, active on their own account, gave diphenols of significant activity. Stroud noted that the yield of recovered phenols seemed to be inversely proportional to the estrogenic activity of the parent compound and of the phenol produced. The metabolic conversion product of diphenylhexadiene (CLXXIX) was obtained in minute amounts only, but its identity with dienestrol (XXI) has been made very probable.

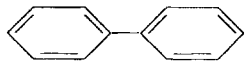
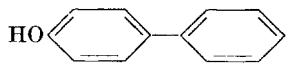
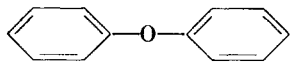
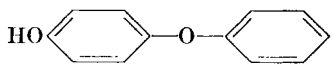
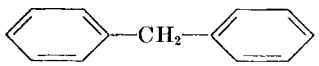
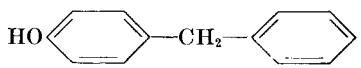
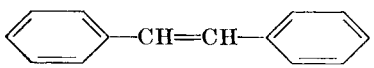
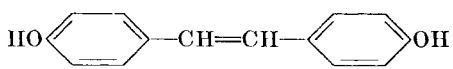
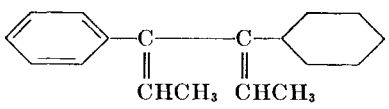
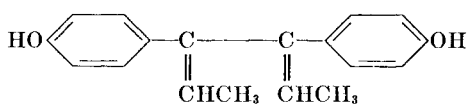
This evidence for physiological transformation into *p*-hydroxy derivatives may explain the lower activity of the ortho- and meta-substituted estrogens, as shown in table 9. Compounds with one hydroxyl group in the para-position, or even without any, may be biologically activated by conversion into *p,p'*-substituted substances. On the other hand, in compounds with hydroxyl groups in the ortho- or meta-position no additional phenolic groups in the para-position need to be introduced for conjugation and elimination from the organism.

The problem of the true or precursor nature of various compounds has been the subject of an interesting treatise by Emmens (75), who derived the classification into two groups of "true" estrogens and of "pro-estrogens," based on the striking difference in the subcutaneous and intravaginal potency as shown by Freud (84). Emmens reasoned that in the case of intravaginal application only the "true" estrogen would act directly on the vagina and cause cornification of the mucosa, while "pro-estrogens" would be absorbed from the vagina into the circulation as from injection elsewhere, converted into an active metabolite, and returned to the vagina in no greater dose or concentration than available after subcutaneous injection.

Previously, Robson and Adler (163) and also Morell and Hart (201) had shown that estrogens may act locally on the vaginal mucosa without appreciable absorption into the general circulation. The former authors constructed in mice a separate vaginal pocket from the lower vagina; the administration of 0.2 microgram of stilbestrol into one part of the vagina produced there complete cornification while leaving the other, separated part unaffected. Similar results were obtained with natural estrogens and their esters.

Emmens then determined the ratio (S/L) of the systemic to the local dose for a large number of synthetic and natural estrogens, and this led to the classification into two clearly differentiated groups: "true estrogens" with S/L in no case less than 50 and "pro-estrogens" with S/L in no case more than 2. Among the compounds listed as "true estrogens" are estrone, estradiol, estriol, ethinylestradiol, stilbestrol, ψ-stilbestrol, hexestrol, isohexestrol, dienestrol, and esters of natural and of synthetic compounds. The group of "pro-estrogens" includes only synthetic compounds of low activity like 4-hydroxydiphenyl (CLXXIV), 4,4'-dihydroxydiphenyl (IX), 4-hydroxydiphenyl ether (CLXXVI), stilbene (X), 4-hydroxystilbene, 4,4'-dihydroxystilbene (XI), 4-hydroxy-α,β-diethylstilbene (CVII), dihydroxyhexahydrochrysene (CL), and 9,10-di-*n*-propyl-9,10-

TABLE 19

PARENT COMPOUND	PHENOLIC METABOLIC PRODUCT	TOTAL RECOVERY†
		per cent
 CLXXIII (inactive)*	 CLXXIV (inactive)	25.4
 CLXXV (inactive)	 CLXXVI (100 mg.)	22.8
 CLXXVII (inactive)	 CLXXVIII (inactive)	14.7
 X (25 mg.)	 XI (5 mg.)	2.9
 CLXXIX (10 mg.)	 XXI (0.4 microgram)	

* "Inactive" infers inactivity in rats at 100-mg. dose level.

† Total recovery includes "free" and "combined" phenols.

dihydroxy-1,2,5,6-dibenzanthracene (III). Emmens classified triphenylchloroethylene (CXXVIII) among the true estrogens, but Robson *et al.* (189) reported that the closely related α,α-bis(*p*-ethoxyphenyl)-β-bromo-β-phenylethylene (CXXIX) is a pro-estrogen by Emmens definition, and the same result was obtained by Thompson and Werner (210c) for β-tri(*p*-anisyl)-β-chloroethylene.

Emmens remarked that there is no rigid proof regarding the soundness of his theory, but he cited the sharp differentiation of S/L values close to unity and those above 50 as an argument in favor of it. On the other hand, the S/L values within the group of "true" estrogens vary from 50 to 3000, raising some doubt as to the weight of Emmens' argument. Obviously S/L will be greatly affected by relatively minor changes of either systemic or local efficacy, both depending on factors distinct from estrogenic activity, like the rate of absorption or the stability under local conditions. For example, Muhlbock (242) demonstrated that the increased action on intravaginal application was further increased by administration in 50 per cent aqueous glycerine.

As mentioned before, the group of "true" estrogens includes the various esters of natural as well as of synthetic compounds. Emmens remarked that the S/L ratio is raised for the esters owing to an increase of the subcutaneous dose, while the intravaginal dose, on a molar basis, is little different from that of the parent compounds. This is explained by the assumption of a high degree of efficiency of the vaginal mucosa for ester hydrolysis. Emmens postulated that "physiological doses of substances which are active locally are fixed or utilized in the tissues, and do not escape in appreciable amounts into the circulation, whereas pro-estrogens are not immediately utilized or fixed, but pass into the circulation and undergo metabolic changes to estrogens." The same author (74) later confirmed experimentally that "true estrogens" administered into one part of the separated vagina, even in amounts exceeding the locally effective dose, do not stimulate the second part, while "pro-estrogens" stimulated both parts when introduced into one of them. These findings add weight to the arguments in favor of the classification into "true" and precursor estrogens, and it is significant that on purely biological grounds, the highly active synthetic estrogens are classified together with the natural hormones.

Segaloff (217) undertook further investigations of the mechanism of estrogen inactivation in the living organism. In rats various estrogens were injected into the spleen transplanted to a subcutaneous position without portal drainage to the liver, and into the spleen *in situ*. The ratio of the minimal effective dose for *in situ* injection and the dose for injection into the transplanted spleen is interpreted as a measure for the degree of inactivation taking place in the liver. For stilbestrol and hexestrol the ratio is about 20, which indicates that these compounds are inactivated, but to a lesser extent than estrone and estradiol, as shown previously by the same author. Esterification protects stilbestrol to a certain extent (ratio 3.5), but complete protection (ratio 1) is only achieved by alkylation. Benzestrol (CXLIX) is subcutaneously active at a higher threshold than stilbestrol, but it is inactivated to a lesser degree (ratio 10). That the mechanism of

TABLE 20

Comparative oral activities

(a) Minimum effective dose in micrograms (100 per cent response unless indicated otherwise); (b) oral dose as multiple of subcutaneous dose

STILBESTROL		HEXESTROL		DIENESTROL		ESTRONE		ESTRADIOL		ETHINYLESTRADIOL		REFERENCE
(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	
Rats												
3 (50%)	7.5	3		3	7.5							(91)
5		3										(59)
5	4.5					70	20					(221)
2.75 (50%)	1.6					225 (50%)	75	175 (50%)	97			(197)
5	4											(156)
1.35	10											(104)
0.3	3–6					4	0.8	4	16			(183)
Mice												
0.35 (50%)	5					9 (50%)	105	7.5 (50%)	500			(197)
0.38 (50%)	4.75											(127)
0.4 (50%)	4			0.1 (50%)	1	1 (50%)	10	1.1 (50%)	45	1.2 (50%)	60	(73, 166)
0.5 (50%)	5					25	35					(72, 104)

benzestrol inactivation may be different is indicated by the practically identical ratio for its diacetate. Ethinylestradiol (CLXVIII) has the high ratio 42, while the subcutaneous threshold dose of 0.18 microgram (for 50 per cent response) is low compared with 0.33 for stilbestrol or hexestrol. Segaloff concluded that the high oral activity of ethinylestradiol is due not to its greater resistance to hepatic inactivation but indeed to its greater potency. The triphenylethylene derivatives and the substituted dibenzanthracene (III) believed to be "pro-estrogens" show an entirely different ratio. Their activity is enhanced by passage through the liver, where chemical changes take place resulting in the formation of more active compounds.

This last study demonstrates that high oral efficacy may be the composite result of various factors, among them the susceptibility to hepatic degradation and the structural conditions favorable for the biological conversion into more active compounds. Probably most important are specific structural requirements like the phenolic hydroxyls and the six-carbon chain of stilbestrol and its analogs, or the ethinyl group in ethinylestradiol.

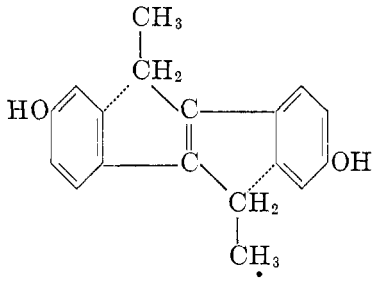
In order to give a rough estimate of comparative oral activities, though by no means a complete evaluation, those of some of the more prominent compounds have been summarized in table 20. Considerable disagreement between the figures from various origins and a marked species difference will be noted. The duration of estrogenic effect after subcutaneous administration has been discussed earlier; the situation is quite different regarding oral administration. Kreitmair and Sieckmann (104) and Emmens (72) agreed that prolongation of effect due to esterification of stilbestrol and hexestrol does not occur on oral application. Both, parent substances and their esters, give only a short lasting effect and very large amounts of certain esters, especially the dipropionate, are required to achieve moderate prolongation. Undoubtedly, the main factor involved in the prolonged effect of these compounds is the delayed resorption from the site of injection, while in the case of oral administration hydrolysis might occur in the gastric tract or the larger amount of administered estrogens may be excreted without resorption taking place. The situation is different with estrogens of the triphenylethylene series. Robson and Schönberg (166, 167) and Davies *et al.* (39) showed that the prolonged effect of these compounds and the regulation of duration by proper dosage is obtained also on oral administration.

The investigations discussed above do not yet give a complete picture of the mechanism of estrus production and biological inactivation, apparently both being related to each other. Nevertheless, the study of synthetics and their difference in behavior from the natural estrogens has made a start towards the understanding of the chemical reactions taking place in the course of hormonal action.

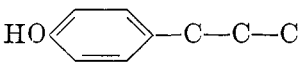
XII. Appendix

There have been several attempts to generalize the requirements of chemical structure for a high degree of estrogenic potency.

Campbell (19) called attention to the "possibility of ring-closure of certain synthetics to give compounds containing cyclopentane rings with incidental methyl groups," as shown in formula CLXXX.



CLXXX



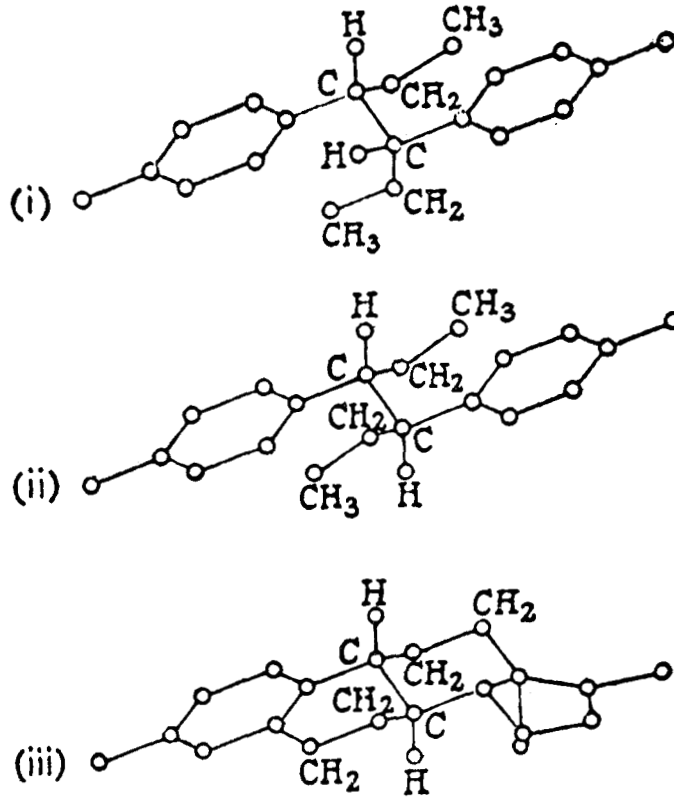
CLXXXI

Linnell and Sharma (114) postulated that the skeleton shown in CLXXXI is essential for estrogenic potency of the highest order. These generalizations in no way explain the lesser activity of isomers identical except for the spatial arrangement. Dodds *et al.* (56) underlined the importance of this spatial arrangement and added that "the disposition of the hydroxyl groups in a molecule of suitable shape may be of greater importance than a close relation to the formula of estradiol as written in one plane." There are too many deviations from the planar structural resemblance to estradiol for this to be convincing. On the other hand, this proved a useful working hypothesis, stimulating much research, though at times it has been abandoned in favor of more empirical approaches. While the structural resemblance between natural and synthetic compounds must not be taken literally, there is also good evidence that the various types of structure, divergent as they may seem, have a great deal in common and that the hormonal activity of the highly potent synthetics is by no means accidental.

Giacomello and Bianchi (86) measured the size of the molecular skeleton of stilbestrol and estrone and found complete agreement, both molecules being 8.55 Å. long and 3.88 Å. wide. No comparative measurements of the molecular size of the less active isomer have as yet been reported.

Carlisle and Crowfoot (27) found a certain similarity between the crystallography of estrone and that of hexestrol (*meso*-form) and of isohexestrol (*dl*-form of 4,4′-dihydroxy-α,β-diethyldibenzyl). Quoting these authors:

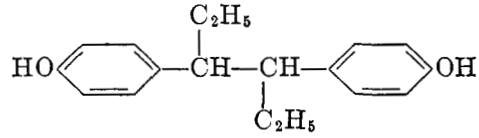
"These similarities probably express little more than the fact that the configurations of the molecules of both diethyldibenzyl series are of an extended form, perhaps that illustrated in the figure [CLXXXII] or of the variety found in dibenzyl itself. This being so, it is an interesting fact that the stereochemical arrangement of the atoms in the *meso*-series" of the diethyl derivative above, "which is biologically the most active series, is very closely related to the stereochemical form deduced for the natural sex hormones. The fact that the *meso*-compounds have a centre of symmetry in the crystals proves that the disposition of the atoms about the central carbon–carbon bond is of the *trans*-type considered characteristic of the junction between rings B and C of the sterol sex-hormone series."



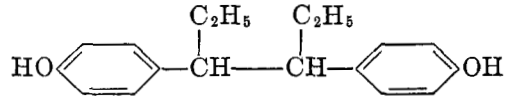
CLXXXII

Diagram (from Carlisle and Crowfoot (27)) to illustrate the relation of the stereochemical forms of the isomers of 4,4′-dihydroxy-α,β-diethyldibenzyl to that probably present in estrone. Possible atomic arrangement in (i) *d*- or *l*-4,4′-dihydroxy-α,β-diethyldibenzyl; (ii) *meso*-4,4′-dihydroxy-α,β-diethyldibenzyl; (iii) estrone.

This interpretation disposes of an apparent discrepancy between the correlation of activity and configuration in the hexestrol and in the stilbestrol series. The planar projection formulas of hexestrol and isohexestrol might seem to indicate that the racemic form (CLXXXIII) rather than the *meso*-form (CLXXXIV) would correspond to the *trans*-configurational formula (XCIV) of stilbestrol.



CLXXXIII



CLXXXIV

According to Carlisle and Crowfoot both hexestrol and isohexestrol have spatial formulas closely resembling those of estrones, the only difference being the spatial arrangement of one hydrogen atom and one ethyl group, respectively. The hundredfold difference in estrogenic activity demonstrates the importance of this group in its spatial relation to the rest of the molecule.

Regarding the relation between chemical structure and estrogenic potency, some general conclusions may be drawn, though it is recognized that their value is limited in view of the danger of attaching undue weight to the relative potency of various compounds.

The most striking fact is the almost rigid specificity of estrogenic potency regarding the presence and position of the two hydroxyl groups, combined with a considerable lack of specificity regarding the central structure linking the aromatic rings. By analogy with the natural estrogens it might be expected that one of the two hydroxyl groups need not be phenolic, but on the basis of limited evidence available to date, it appears that aromatic hydrogenation with the effect of changing one phenolic group into an alcoholic one causes inactivation. In the stilbene series, additional substituents in the aromatic rings or a shift of the hydroxyl groups from the para-position cause a sharp drop in activity; the hexestrol series appears somewhat less sensitive to variation. The central structure need not be aliphatic, though it is preferably so for highest potency. The peak of activity is usually found for derivatives with a six-carbon-atom chain or, stated more generally, for structures comprising a total of five to seven carbon atoms, or a chain or ring containing two to three carbon atoms, substituted by aliphatic groups containing two to five carbon atoms. The degree of saturation of the central structure is of less importance than the spatial arrangement, as stilbestrol and the two most active synthetics related to it contain one, two, or no aliphatic double bonds. It is difficult to attempt the interpretation of the relative importance of the phenolic hydroxyl groups and the two ethyl groups in stilbestrol and hexestrol, and the combined effect appears to be an important factor. The aliphatic substituents are definitely less specific than the hydroxyl groups. On the other hand, proper substitution of the central structure may be more specific in terms of biological conversion; while it is feasible that a weakly potent compound like α,β-diethylstilbene is hydroxylated in the organism to give highly active metabolic products, there is no evidence for the assumption that the equally feeble 4,4′-dihydroxystilbene (XI) may be rendered more active by biological substitution with the appropriate alkyl groups.

Grateful acknowledgment for valuable criticism of the manuscript is made to Drs. J. Lee and N. Ercoli of these laboratories.

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Supplement[1] *(added January 2, 1946)*

III. Hexestrol

A. Discovery

As discussed earlier, the reductive demethylation of anethole (XIII) by means of alcoholic potassium hydroxide led to the discovery of hexestrol. Another example of the reducing properties of alcoholic potassium hydroxide has been reported by Rubin (255).

B. Syntheses (methods other than hydrogenation)

Kharasch, McBay, and Urry (247) devised an ingenious new synthesis of hexestrol dimethyl ether (XXVII). These workers found that diacetyl peroxide may be decomposed to produce free methyl radicals which remove hydrogen atoms from the solvent, resulting in the production of methane and leaving more complicated free radicals, with the tendency for dimerization. When *p*-methoxy-*n*-propylbenzene is used as the solvent, approximately equal amounts of the dimethyl ethers of hexestrol and isohexestrol are formed. On the basis of recovered starting material, the yield was 16 per cent for hexestrol dimethyl ether; in addition, isohexestrol dimethyl ether was obtained in equal yield. By means of the conversion methods discussed earlier, the overall yield of hexestrol dimethyl ether may be substantially increased.

C. Optical isomerism

Peak and Short (239) obtained a patent for the isomerization of the dimethyl ether of isohexestrol into that of hexestrol by heating to 300–350°C. in the presence of either hydrogen sulfide or palladium on carbon.

IV. Stilbestrol

A. Syntheses

4. Syntheses involving retro-pinacolin rearrangements

Adler and Lundin (237) reinvestigated the chemistry of 3,4-bis(*p*-hydroxyphenyl)-3,4-hexanediol (LXIII) and succeeded in separating into two components the pinacol (m.p. 204–206°C.) obtained by Dodds *et al.* (58, 59, 60) from *p*-hydroxypropiophenone. The one melting at 217–219°C. was called "α-pinacol," and the other, melting at 212–214°C., "β-pinacol." Earlier, Hobday and Short (91) had described a compound called "iso-pinacol," m.p. 94–95°C., which they believed to be the optical isomer of Dodds's pinacol because both gave dienestrol (XXI) on dehydration with acetyl chloride. According to Adler and Lundin the α- and β-forms actually represent the optical isomers with structure LXIII, while "iso-pinacol" is an isomer of yet undetermined structure. Their indirect evidence is based on the analogous behavior of the α- and β-forms

[1] The headings and subheadings of the supplement correspond to those used in the main part of the paper.

in their transformation into the pinacolin (LXV) and into dienestrol (XXI). "α-Pinacolin" is active in 100 micrograms and by analogy with the potencies of hexestrol and isohexestrol, it is assumed to represent the *meso*-form, while the "β-pinacolin" (inactive in 1000 micrograms) would represent the racemic form.

C. ANALYTICAL METHODS FOR STILBESTROL DETERMINATION

A new colorimetric method suitable for the quantitative determination of 0.5–2.0 mg. of stilbestrol, hexestrol, and dienestrol has been described by Malpress (249). The procedure makes use of the yellow color developed after nitration in acetic acid solution, followed by neutralization. The isolation of a crystalline dinitro derivative of hexestrol suggests the same nitration mechanism for stilbestrol and dienestrol.

D. HYDROGENATION OF STILBESTROL

2. Hydrogenation of aromatic rings

Hoehn and Ungnade (242) described some derivatives of the hydrogenation products obtained earlier (92) from stilbestrol with Raney nickel under 4000–5000 lb. pressure. Ungnade and Ludutsky (258) extended this work and succeeded in isolating the two complete series with three perhydro-diols, each of the general formula CIII, and the two perhydro-diketones of the general formula CV. Experimental evidence has been presented for the assignment of the *cis–trans* configuration of the hydroaromatic substituents in the *meso* and in the racemic series. The optical configurations of the two series were derived from their relationship to hexestrol (*meso*-form) and isohexestrol (racemic), respectively (table 21).

In an earlier series of Swiss patents (256, 257, 258, 259, 260, 261), perhydrodiols have been described with characteristics substantially the same as listed in table 21.

While isohexestrol may be considered the normal hydrogenation product of stilbestrol, several instances of hexestrol as the hydrogenation product have been cited earlier; to these may be added the Raney nickel hydrogenation of stilbestrol in the presence of its sodium salt (268).

V. Variation of Fundamental Structure

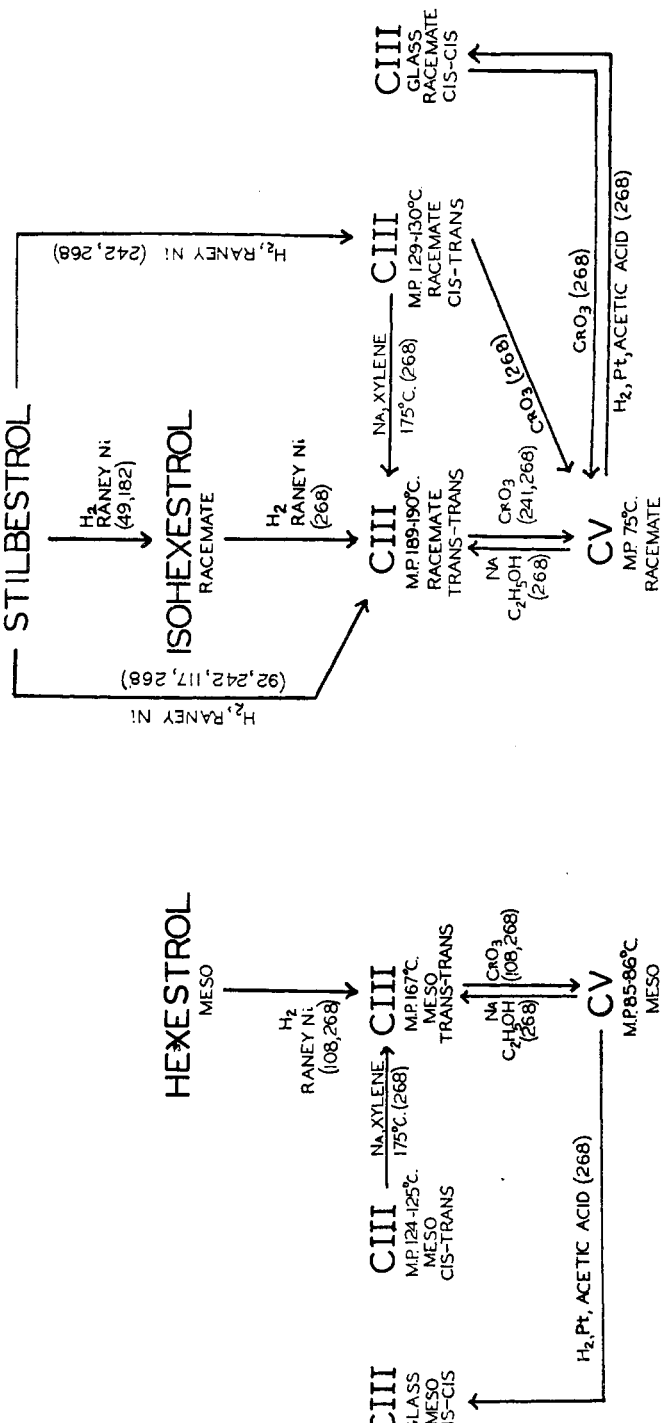
A. VARIATION OF RING SUBSTITUENTS

1. Acylation and alkylation of phenolic hydroxyl groups

Miescher and Meystre (250) found that stilbestrol monosulfate (or phosphate) is advantageously prepared from the monobenzoate, which is transformed into the monobenzoate monosulfate. On heating with sodium carbonate only the organic ester group is hydrolyzed. Reid (252) obtained a patent for the preparation of stilbestrol monoalkyl ethers; the duration of estrus as a function of the dosage is claimed to be a characteristic property of the mono ethers. A similar patent was granted to Schmelkes (262) for hexestrol monomethyl ether.

TABLE 21

Perhydrogenation products[1]



[1] The symbols CIII and CV in this table refer to the general structure only.

2. Position isomers and homologs with additional ring substituents

Another effort has been made to obtain, by suitable modification of the stilbestrol molecule, compounds with hormonal activity other than estrogenic. Ross (253) prepared non-phenolic analogs of stilbestrol, hexestrol, and diphenylethane with acetyl groups in place of the para-hydroxyl groups of the estrogens. No information has yet been given regarding the desired luteoid activity of these compounds. Walker (269) undertook earlier to prepare ω-hydroxy methyl ketones having the same side chain as the corticosteroids. Ross (254) made a similar, though unsuccessful, attempt. However, this worker succeeded in synthesizing di(ω-acetoxyacetylphenyl) ether, bis(ω-acetoxyacetyl)diphenyl, and 2,7-bis(ω-acetoxyacetyl)fluorene; all of these showed no marked effect on prolonging the life of adrenalectomized rats.

B. VARIATION OF ALIPHATIC CHAIN

3. Location and number of aliphatic double bonds

Patents for a novel synthesis of dienestrol (XXI) from stilbestrol diacetate (LII) have been granted to Turnbull (266, 267). Bromination of LII in carbon disulfide results in 4,4′-diacetoxy-α,β-dibromostilbene. Subsequent treatment with potassium iodide in alcohol gives a mixture of stilbestrol diacetate (LII) and a product which gives dienestrol on hydrolysis. Dienestrol diacetate (CXVIII) is obtained from the dibromide on refluxing with pyridine. Bromination of hexestrol dimethyl ether (XL) gave 3,4-bis(*p*-anisyl)-3,4-dibromohexane; debromination of the latter was always accompanied by reduction to the starting material (XL).

VI. Triphenylethylene Derivatives

Schönberg and Tadros (263) obtained a patent for the preparation of di(*p*-ethoxyphenyl)benzylcarbinol, presumably as an intermediate in the synthesis of α,α-bis(*p*-ethoxyphenyl)-β-phenyl-β-bromoethylene ("D.B.E.") (CXXIX).

Basford (238) described mixed ethyl methyl ethers related to CXXIX and CXXX.

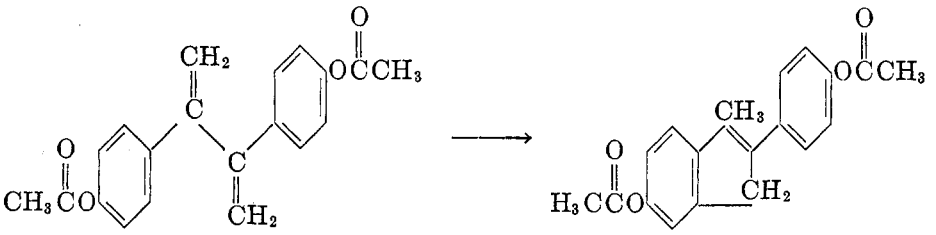
VIII. Diphenylpropane Derivatives

Stuart *et al.* (265) reported additional dialkyl substitution products of the aliphatic chain in 1,3-bis(*p*-hydroxyphenyl)propane. In the series of 1,3-dialkylpropane derivatives the highest activity of 200 micrograms lies with the methyl propyl compound. Higher activities were found in the 1,2-dialkyl series, with the optimum of 30 micrograms for one of the two racemic 1-ethyl-2-*n*-propyl derivatives.

IX. Ring-closed Analogs

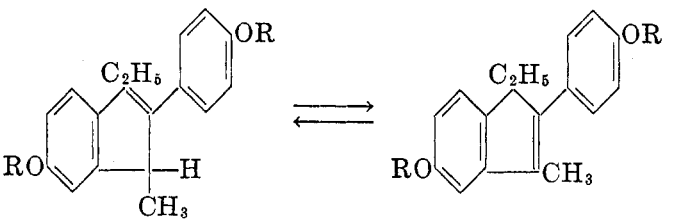
Adler and Hagglund (236) investigated the cyclization of dienestrol, isodienestrol, and its lower homolog, 2,3-bis(*p*-hydroxyphenyl)-1,3-butadiene, as

well as of their diacetates. Cyclization with boron trifluoride did not lead to the tetracyclic succindane derivatives expected by these workers, but to 2-phenylindenes. The structure of the cyclization products appears to be firmly established, because in the case of CLXXXV the reaction product (m.p. 133–134°C.) is 2-(*p*-acetoxyphenyl)-3-methyl-6-acetoxy-2,3-indene (CLXXXVI), i.e., the diacetate of CLVI synthesized by Salzer (174, 175) by another route.



CLXXXV CLXXXVI

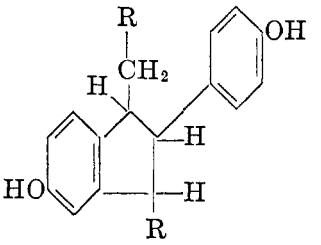
Adler and Hagglund found CLXXXVI inactive in doses of 100 micrograms (in rats, 50 per cent response), while Salzer reported an activity of 0.2–0.3 microgram. This discrepancy is no reason to doubt the identity of the two reaction products, because the inactivity of CLXXXVI at the 60-microgram level (in rats, 50 per cent response) has been confirmed by this reviewer (264) with a preparation synthesized by another method (194). Moreover, the ultraviolet-absorption spectrum of CLXXXVI, as reported by the Swedish workers, conforms closely to the spectrum (194) of the next higher homolog (CLVII). The cyclization of dienestrol (XXI) and of its stereoisomer isodienestrol led to the same reaction product (CLXXXVII), 1-methyl-2-(*p*-hydroxyphenyl)-3-ethyl-6-hydroxy-2,3-indene, m.p. 175°C.



CLXXXVII	R = H	XCC
CLXXXVIII	R = $COCH_3$	XCCI
CLXXXIX	R = COC_2H_5	XCCII

Similar ring closures were carried out with the diacetate (CXVIII) and the dipropionate of dienestrol, resulting in the diacetoxyindene (CLXXXVIII) and the dipropoxyindene (CLXXXIX). Adler and Hagglund observed that in the presence of pyridine or other bases these 2,3-indenes are converted into isomeric esters, most likely having the structure of the 1,2-dienes (XCI and XCCII). This conversion is reversible. The phenolic 2,3-indene (CLXXXVII) could not be converted under the same conditions, but hydrolysis of the esters XCCI and XCCII gave the corresponding phenolic 1,2-indene

(XCC), m.p. 128–129°C. Whether the 2,3-indene structure has been assigned correctly to the higher melting isomer or should be assigned to the lower melting form can not yet be decided definitely; both compounds have practically identical absorption spectra. The interrelationship of the two isomers is undoubtedly correct, because on hydrogenation both absorb one mole of hydrogen and give the same indane derivative (XCCIV).



XCCIII R = H
XCCIV R = CH_3

Similarly, the indene CLXXXVI was hydrogenated to the indane XCCIII. These indanes are stable, while the indenes are quite generally stable only in the form of their esters (174, 175, 194, 236). Both indanes (XCCIII and XCCIV) are inactive in doses smaller than 100 micrograms, while both 1-methyl-2-(*p*-hydroxyphenyl)-3-ethyl-6-hydroxyindenes (CLXXXVII and XCC) show the remarkably high potency of 1 microgram (in rats, 100 per cent response). The diacetate CLXXXVIII has the same activity, while the diacetate XCCI and the dipropionate XCCII are slightly less active.

Finally, the fact that Adler and Hagglund, starting from the symmetrical diene LXXXV, obtained the same indene derivative (CLXXXVI) as Salzer (174, 175) and Solmssen (194, 264) by two different routes, provides the structure proof regarding the 6-position of one of the hydroxyl groups in CLVI, CLVII, and CLVIII.

XI. Metabolic Conversion and Efficacy by Various Routes

Lipschutz and Quintana (248, 251) studied the inactivation of estrogens in the form of intrasplenic or intrahepatic pellets. These workers confirmed the observation that inactivation of synthetics takes place but to a lesser degree than with natural estrogens. Engel and Rosenberg (240) also corroborated the enzymatic inactivation of stilbestrol *in vitro*. While Zondek *et al.* (235) had found stilbestrol more resistant against the inactivating liver enzyme than estrone, these workers observed aqueous acid liver extracts to inactivate both types of estrogens equally well *in vitro*. Alkaline liver extracts inactivated stilbestrol but failed to inactivate estrone. Werthessen *et al.* (270, 271) called attention to the fact that the potency established for a substance when assayed by evaluation of the vaginal response is not necessarily the same when estimated by other methods. These workers investigated the effect of various natural and synthetic estrogens as inhibitors or stimulants of egg growth in the ovariec-

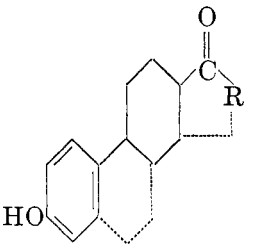
tomized rabbit, after progesterone administration; they also studied the effect on the uterine mucosa. A similar though inconclusive study had been undertaken by Fønss-Bech (241). The detailed discussion of their results is beyond the scope of this review. Nevertheless, some of the conclusions reached by Werthessen *et al.* are of great interest regarding the effect of alkylating the phenolic hydroxyl groups in synthetic estrogens. Under the conditions of the experiment stilbestrol was found to have an inhibitory effect on egg growth similar to that observed for estrone (CLXVII) but quite opposite to the effect of estradiol (XCV); stilbestrol monomethyl ether has qualitatively the same effect as stilbestrol. Quantitatively, however, the monomethyl ether was found to be four times as potent an inhibitor as the parent substance. As mentioned earlier, the ratio of potencies when assayed by the conventional evaluation of vaginal response is quite the reverse, i.e., 4:1 in favor of stilbestrol (85). The monomethyl ether further differs also qualitatively from stilbestrol in that it fails to inhibit the response of the uterine mucosa to progesterone stimulation. Werthessen and coworkers also demonstrated the potency of the monomethyl ether in stimulating the uterus on a short-time assay (6 hr.), thereby disproving the possible explanation of the differences between stilbestrol and its monomethyl ether by the prolonged effect of the latter. The authors concluded that the pharmacology of the two compounds is not the same. If this be true in general, one may have to revise the earlier picture of the alkyl derivatives acting only after physiological demethylation to the dihydroxy derivatives. That the latter process is not without significance was corroborated by the finding of Shorr and Mazur (as quoted by Werthessen and Gargill (270)) that the excretion product of the monomethyl ether is stilbestrol, presumably in the form of the glucuronide.

Contrary to the results obtained by Sondern *et al.* (198), Jaap and Thayer (244) found that stilbestrol dimethyl ether was much more active than stilbestrol, its diethyl ether, or its dipropionate, when tested orally in the domestic fowl After extending this investigation to other estrogens and to other species, Jaap (243) concluded that so far no consistent relation may be established between the oral activity and the state of the various estrogens regarding methylation of the phenolic hydroxyl groups.

Zima *et al.* (272) investigated the mode and duration of activity of stilbestrol and its esters in humans. The former was excreted completely within 24 hr., while the retention time of the esters in the organism depended on their rate of hydrolysis. These workers concluded that there is no basic difference between the parent substance and its esters regarding the mode of resorption or action.

XII. Appendix

It is worth noting an unsuccessful attempt to prepare synthetic estrogens resembling the natural estrogens in a manner different from that of stilbestrol. Johnson and Offenhauer (246) synthesized 4-(*p*-hydroxyphenyl)hexahydroacetophenone (XCCV) and the two higher homologs (XCCVI and XCCVII).



R = CH_3 XCCV
R = C_2H_5 XCCVI
R = n-C_3H_7 XCCVII

In spite of the resemblance, as indicated by the dotted lines, all compounds showed no estrogenic activity (245).

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