THE STEROIDAL ESTROGENS

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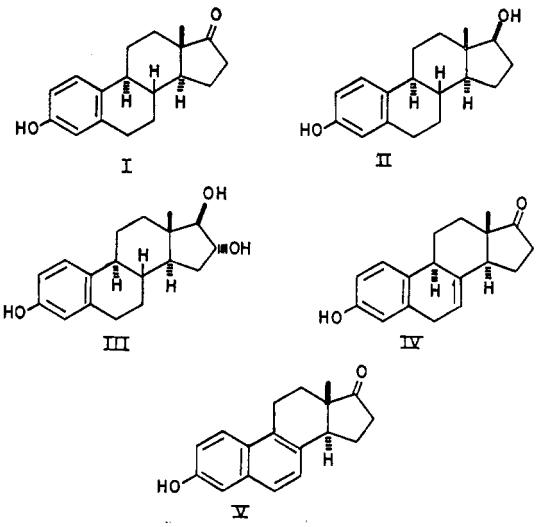
I. INTRODUCTION

Substances which are characterized by their ability to produce heat (estrus) in females of various mammalian species are called estrogens. The steroidal estrogens are without doubt the most important group of such hormones. Estrone (I),[1] estradiol (II), estriol (III), equilin (IV), and equilenin (V) represent the steroidal estrogens which have been known for the longest time. These substances were first isolated in the early 1930's in very small quantities from the urine of pregnant women and pregnant mares. This early work on the isolation and structural determination of these compounds has been discussed in some detail by Fieser and Fieser (139) and Marrian (273).

The important physiological properties (135, 184) of the steroidal estrogens created a demand for relatively large quantities of these hormones. More recently, the use of steroidal estrogens in the preparation of oral contraceptives (84, 312) and in the chemotherapy of cancer (201, 364) and circulatory diseases (271, 396) has intensified the interest in developing methods for the preparation of these hormones on a large scale.

For some time after the discovery of estrone, the main source of this substance was the urine of pregnant mammals, from which it could be isolated in very low yield. The first successful attempt at increasing the

(1) For systematic names, see section II.



I II III IV V

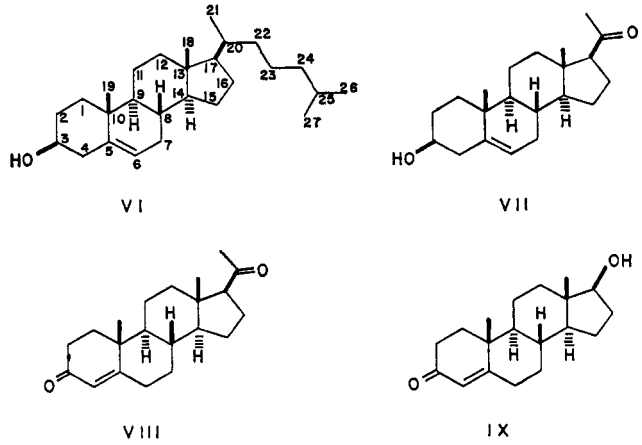
yield of estrone from natural sources involved the use of Girard's (152) reagent which formed a complex with the ketonic function of estrone. In the 1940's methods were developed to produce estrone by degradation of more easily available steroids. The efforts of several groups of workers have now made possible the total synthesis of racemic and natural estrone from a variety of simple and inexpensive starting materials by means of chemical and microbiological methods.

This review deals essentially with the biosynthesis and synthesis of steroidal estrogens. There have been many publications in the last few years on the synthesis of heterocyclic steroidal estrogen derivatives, and it seemed appropriate to include a survey of this work here. Pertinent literature references until the end of 1966 are included in this review.

II. NOMENCLATURE

The steroidal compounds discussed in this review are named according to the Definitive Rules for the Nomenclature of Steroids published by the Commission on the Nomenclature of Biological Chemistry of the International Union of Pure and Applied Chemistry (95). Compounds in which there is a methyl group attached at C-13 but not at C-10 are named as derivatives of estrane and not as derivatives of "19-norandrostane." The trivial names cholesterol (VI, cholest-5-en-3β-ol), pregnenolone (VII, 3β-hydroxypregn-5-en-20-one), progesterone (VIII, pregn-4-ene-3,20-dione), testosterone (IX, 17β-hydroxyandrost-4-en-3-one), estrone (I, 3-hydroxyestra-1,3,5(10)-trien-17-one), estradiol (II, 3,17β-dihydroxyestra-1,3,5(10)-triene), estriol (III, 3,16α,17β-trihydroxyestra-1,3,5-(10)-triene), equilin (IV, 3-hydroxyestra-1,3,5(10),-7-tetraen-17-one), and equilenin (V, 3-hydroxyestra-1,3,5(10),6,8-pentaen-17-one) are used. For the sake of simplicity these trivial names are sometimes used in naming certain derivatives. A few examples are listed below.

Trivial name	Systematic name
1-Methyl-6-dehydroestrone	3-Hydroxy-1-methylestra-1,3,5(10),6-tetraen-17-one
9-Dehydroestradiol 3-methyl ether	3-Methoxyestra-1,3,5(10),9(11)-tetraen-17β-ol
Estradiol 17-acetate	17β-Acetoxyestra-1,3,5(10)-trien-3-ol
17-Dihydroequilenin 17β-acetate	17β-Acetoxyestra-1,3,5(10),6,8-pentaen-3-ol
4-Azaestradiol 17-acetate	17β-Acetoxy-4-azaestra-1,3,5(10)-trien-3-ol
6-Oxaestrone methyl ether	3-Methoxy-6-oxaestra-1,3,5(10)-trien-17-one



VI VII VIII IX

III. OCCURRENCE

Steroidal estrogens have been isolated from mammals as well as from a large number of fish, amphibians, reptiles, and birds. In the animal body these hormones are formed by the ovaries, testes, placenta, and adrenal cortex.

Dorfman and Ungar (115) have made an exhaustive survey of all sources of steroidal estrogens. Gottfried (161) has reviewed the occurrence and biological significance of steroids in lower vertebrates, and, more recently, Velle (435) has made a survey of the literature relating to urinary estrogens in male animals.

Many nonsteroidal estrogens have been isolated from plants (47, 183). Although there has been some speculation (181) regarding the biosynthesis of steroidal estrogens from plant sources, the presence of these compounds in plants is the subject of some controversy. In 1933, Butenandt and Jacobi (69) reported the isolation of estrone (I) from an extract obtained from palm kernel residue. In the same year (378), a crystalline substance was obtained from female willow catkins which appeared to be estriol (III). The presence of estradiol (II) in the pollen of the date palm has been reported (131, 169) but the identity of the substance isolated was not rigorously established. Using tracer techniques, Jacobsohn, Frey, and Hochberg (222) were unable to confirm the presence of estrone (I) in palm kernel residue. However, Heftmann, Ko, and Bennett

(35, 182) have reported the isolation of 1.9 mg of estrone (I) from 1 kg of date seeds.

IV. BIOSYNTHESIS

The biosynthesis of cholesterol has been intensively studied, and there have been several reviews published (40, 41, 89, 325, 397) on this subject. Metabolic studies of cholesterol itself have established (116, 326, 398) that this compound plays an important role in the biogenesis of C-21 (corticoids and progestagens), C-19 (androgens), and C-18 (estrogens) steroids. The estrogens represent the final stage of degradation of cholesterol in which the tetracyclic nucleus is still intact. Chart I illustrates a general pathway for the biosynthesis of estrogens which is consistent with the available experimental data. The enzymatic mechanisms involved in many of the steps have been comprehensively reviewed by Talalay (416). In the present discussion the emphasis will be on the last few steps which precede the formation of estrogens.

A. EXPERIMENTAL APPROACH

It was only when suitable precursors labeled with radioactive atoms became available that significant correlations could be made regarding the biosynthesis of estrogens. Steroid chemists and biochemists are now able to rely on a large number of chemical (313) and bioassay (132) methods which have been developed over the years for the identification of estrogens. The physical properties (126, 134, 158, 382) of many of these compounds have been compiled and the vastly improved techniques of vapor-phase (59, 197, 198, 296) column (67, 296) and thin layer (296, 317) chromatography have made it possible to work with ex-

CHART I

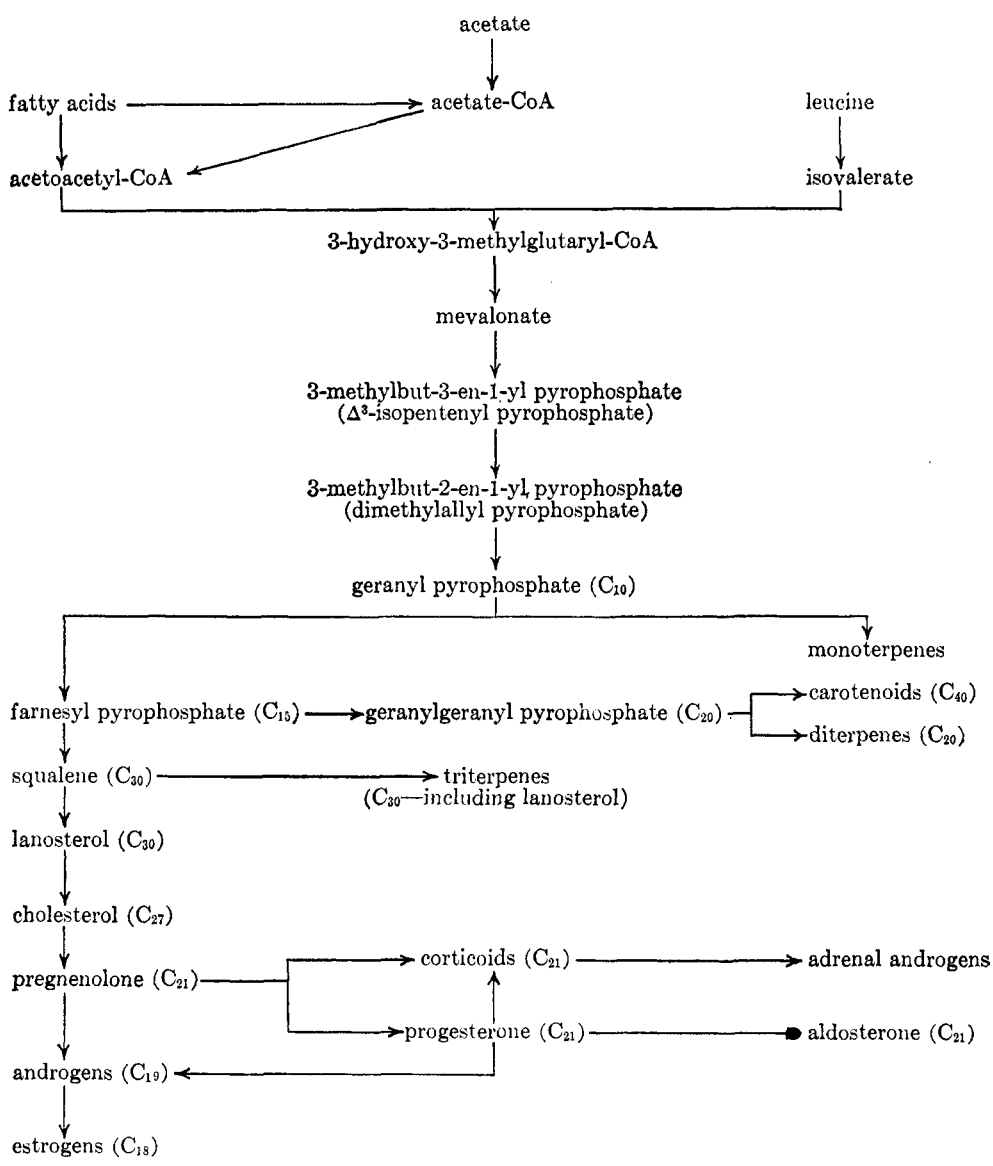


TABLE I

BIOSYNTHESIS OF ESTROGENS FROM ANDROGENS

Precursor	Product[a]	Biological system[b]	Ref
Androst-4-ene-3,17-dione-4-C^{14}	E_1, E_2	Human ovarian tissue[c]	235
Testosterone-4-C^{14}	E_2	Rat ovary	409
Androst-4-ene-3,17-dione	E_1	Rat ovary	301
Testosterone-4-C^{14}	E_1, E_2	Fetal liver, human placenta	379
3β,7α-Dihydroxyandrost-5-en-17-one and its 3-sulfate	7α-Hydroxy E_1 7α-Hydroxy E_2 7-Oxo E_2	Human ovary, placenta	403
3β,7α-Dihydroxyandrost-5-en-17-one	7α-Hydroxy E_1	Human placenta	80
3β,7β,17β-Trihydroxyandrost-5-ene	7β-Hydroxy E_1 7β-Hydroxy E_2 7-Oxo E_2	Human placenta	80[d]
Testosterone Androst-4-ene-3,17-dione 19-Hydroxyandrost-4-ene-3,17-dione	E_1, E_2	Human placenta[e]	51[f]
Androst-4-ene-3,17-dione-4-C^{14}	E_1, E_2	Human placenta[e]	454[g]
Androst-4-ene-3,17-dione 19-Hydroxyandrost-4-ene-3,17-dione 3β,19-Dihydroxyandrost-5-en-17-one 3β,19-Hydroxyandrost-5-en-17-one	E_1, E_2	Human placenta[e]	455
Androst-4-ene-3,17-dione-4-C^{14} 3β-Hydroxyandrost-5-en-17-one-4-C^{14} 3β-Hydroxyandrost-5-en-17-one-7α-H^3 sulfate	E_1, E_2	Human placenta[e]	289[h]
18-Hydroxyandrost-4-ene-3,17-dione	18-Hydroxy E_1	Human placenta[e]	217
Testosterone-19-C^{14}	HCOOH-C^{14} HCHO-C^{14}	Human placenta[e]	19[i]
17α-Methyltestosterone	17α-Methyl E_2	Human placenta[e]	6
19-Oxoandrost-4-ene-3,17-dione 19-Hydroxytestosterone Testosterone 19-Nortestosterone	E_1, E_2	Horse placenta	402[j]
3β-Hydroxyandrosta-5,7-dien-17-one Androsta-4,7-diene-3,17-dione 3β,7α-Dihydroxyandrost-5-en-17-one	Equilin, equilenin 3β-Hydroxyestra-5,7,9-trien-17-one (17β-hydroxy compounds also isolated)	Horse placenta, liver	400
3β-Hydroxyandrosta-5,7-dien-17-one	3β,17β-Dihydroxyestra-5,7,9-triene	Human placenta[k]	399
3β,7α-Dihydroxyandrost-5-en-17-one diacetate	3β-Hydroxyestra-5,7,9-trien-17-one		
Androsta-4,7-diene-3,17-dione	Equilin, equilenin	Human placenta[k]	401
3β-Hydroxyandrosta-5,7-dien-17-one	3,17β-Dihydroxyequilin		
3β,7α-Dihydroxyandrost-5-en-17-one	3,17β-Dihydroxyequilenin		
3β-Hydroxyandrost-5-en-17-one-7α-H^3 sulfate	E_1, E_2, E_3	Human placenta[k]	444
3β-Hydroxyandrost-5-en-17-one-4-C^{14} sulfate		Human, *in vivo*	
Testosterone-4-C^{14} 3β-Hydroxyandrost-5-en-17-one-4-C^{14} 3β-Hydroxyandrost-5-en-17-one-6,7-H^3 sulfate 19-Hydroxyandrost-4-ene-3,17-dione[l] 3β-Hydroxyandrost-5-en-17-one Testosterone Androst-4-ene-3,17-dione 17β-Hydroxyestr-4-en-3-one Estr-4-ene-3,17-dione 3β,17β-Dihydroxyandrost-5-ene	6α-Hydroxy E_2	Human placenta[k]	81
Androsta-1,4-diene-3,17-dione 17β-Hydroxyandrosta-1,4-dien-3-one 11β-Hydroxyandrost-4-ene-3,17-dione 17α-Hydroxyandrost-4-en-3-one 11α-Hydroxyandrost-4-ene-3,17-dione	E_1, E_2	Human placenta[k]	79
Testosterone-4-C^{14},17α-H^3	E_1, E_2	Human placenta[m]	42[n]
3β-Hydroxyandrost-5-en-17-one-4-C^{14} 3β-Hydroxyandrost-5-en-17-one-7α-H^3 Androst-4-ene-3,17-dione-4-C^{14} Androst-4-ene-3,17-dione-1,2-H^3	E_1, E_2, E_3	Human placenta[m]	43

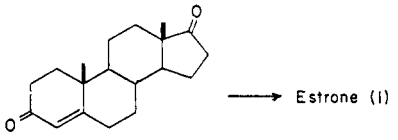
TABLE I (*Continued*)

Precursor	Product[a]	Biological system[b]	Ref
Testosterone-4-C^{14} Testosterone-1,2-H^3 Androst-4-ene-3,17-dione-4-C^{14}	E_1, E_2	Previable human fetus[k]	269[o]
Testosterone-4-C^{14} Androst-4-ene-3,17-dione-4-C^{14}	E_1, E_2 Equilenin	Human feminizing testes	367
Testosterone-4-C^{14}	E_1, E_2	Human granulosa and theca cells	345
Androst-4-ene-3,17-dione-4-C^{14}	E_1, E_2	Human granulosa–theca cell ovarian tumor	162
3β-Hydroxyandrost-4-ene-3,17-dione-4-C^{14}	E_1, E_2	Hydatidiform mole (human)	256
3β-Hydroxyandrost-5-en-17-one-7α-H^3 Testosterone-4-C^{14} Androst-4-ene-3,17-dione-4-C^{14}	E_1, E_2, E_3	*In vivo*, pregnant and nonpregnant women	33
3β-Hydroxyandrost-5-en-17-one-4-C^{14} 3β-Hydroxyandrost-5-en-17-one-7α-H^3 sulfate	E_1, E_2, E_3	*In vivo*, pregnant women	44, 45
3β-Hydroxyandrost-5-en-17-one-4-C^{14} sulfate 3β-Hydroxyandrost-5-en-17-one-7α-H^3 sulfate	E_1, E_2, E_3	*In vivo*, pregnant women (normal; hydatidiform mole)	374, 375

[a] E_1 = estrone, E_2 = estradiol, E_3 = estriol. [b] *In vitro* unless indicated otherwise. [c] Incubation with follicular stimulating hormone or with luteinizing hormone stimulated conversion of the androgen to estrogens. [d] No aromatization was observed after placental perfusion of 3β,17β-dihydroxyandrost-5-en-7-one. [e] Incubation with placental microsomes. [f] Reported that formaldehyde is the stoichiometric product of C-19 in the aromatization process. [g] Kinetic evidence is presented to show that 19-hydroxyandrost-4-ene-3,17-dione is an obligatory intermediate in the placental conversion of androst-4-ene-3,17-dione to E_1 and E_2. [h] Evidence is presented for C-19 hydroxylation in the Δ^5 precursors. [i] Labeled formic acid was found to be the major product and not formaldehyde. [j] Conversion of 19-oxoandrost-4-ene-3,17-dione, 19-hydroxytestosterone, testosterone, and 19-nortestosterone to E_1 and E_2 at relative rates of 33, 24, 20, and 6.8%, respectively, is reported. [k] Perfusion technique. [l] Androgens are listed in order of decreasing yield of estrogens after 1 hr of perfusion. [m] Perfusion *in situ*. [n] Evidence that direct conversion of testosterone to E_2 occurs in this system. [o] 3β-Hydroxyandrost-5-en-17-one-H^3 was not aromatized under these conditions.

tremely small quantities of material.

A significant contribution to the work on the biosynthesis of estrogens was made in 1958 by Ryan (341) who found that preparations of human placental microsomal fractions could convert androst-4-ene-3,17-dione (X) to estrone (I) in yields of 40 to 60%. In



X

1961, using ovarian tissue stimulated by gonadotrophins, Smith and Ryan (389) reported the following yields of labeled estrogens: 0.03% from acetate-1-C^{14}, 0.09% from cholesterol-4-C^{14} (VI), 5.6% from progesterone-4-C^{14} (VIII), and 15.3% from androst-4-ene-3,17-dione-4-C^{14} (X). These results quantitatively supported the concept that acetate, cholesterol, C-21 steroids, and C-19 steroids were necessary intermediates in the formation of estrogens. Human physiological conditions have been closely approached in more recent studies by the application of the techniques of perfusion of term placentas *in vitro* (78, 82) and of perfusion of placentas *in situ* (43, 101).

B. PRECURSORS

Using some of the techniques already mentioned, it has been possible to establish that most of the intermediates in Chart I can be converted to estrogens by a variety of tissues. A brief survey of this work will be made before discussing some of the current ideas of estrogen biosynthesis.

1. *Acetate*

a. *In Vivo*

It was reported (173) in 1956 that labeled estrone, equilin, and equilenin were isolated from the urine of pregnant mares injected with acetate-1-C^{14}, and this finding was later confirmed (352).

b. *In Vitro*

The conversion of acetate-1-C^{14} to estradiol by cell-free ovarian and testicular homogenates of the cat, the dog, and the human has been reported (314, 315). However, some of these results could not be confirmed in later studies (195). Perfusion of sow ovaries with acetate-1-C^{14} has been reported (449) to give labeled estrone and estradiol as well as labeled cholesterol. Radioactive 17α-estradiol and a small amount of estrone were among the steroids identified by the incubation of rabbit ovarian follicles (160) with acetate-1-C^{14}. When the incubations were done in the presence of follicle stimulating hormone or human chorionic gonadotrophin, the incorporation of labeled acetate into steroids was increased and the specific

activity of cholesterol was decreased. By using rat ovary preparations stimulated by endogenous gonadotrophins (parabiosis) and exogenous gonadotrophins, Rice and Segaloff (324) were able to demonstrate the formation of radioactive estradiol and estrone from acetate-1-C^{14}. As expected (199, 322, 323), progesterone and 20α-hydroxypregn-4-en-3-one were the major radioactive steroids formed by these highly stimulated ovarian preparations.

Estrone and estradiol have also been identified as radioactive products after incubations of human ovarian follicular (346, 349, 389), luteal (167), stromal (321, 353), and testicular (320) tissues with acetate-1-C^{14}. It had been reported (257, 412) that human placental tissue was capable of incorporating acetate-1-C^{14} into labeled estrogens, but these experiments (258) could not be reproduced.

To date it has not been possible to isolate labeled estrogens from acetate-1-C^{14} after incubation with the corpora lutea obtained from the cow (354), the mare (370), and the rabbit (419).

2. *Cholesterol*

a. *In Vivo*

The role of cholesterol as a precursor of estrogens had been postulated (87, 136) for some time before Werbin, Plotz, LeRoy, and Davis (448) finally established the conversion of cholesterol-4-C^{14} to urinary estrone, although in extremely low yield, in the pregnant human female. Heard and his collaborators (176, 177), however, have reported no formation of radioactive estrone when a large dose of cholesterol-4-C^{14} was administered to a pregnant mare.

b. *In Vitro*

Ryan and Smith (346) have described the conversion of acetate-1-C^{14} by human ovarian tissue to cholesterol and estrogens in amounts consistent with a possible precursor role for cholesterol. These same authors also reported (348, 349, 389) the formation of labeled estrone from cholesterol-4-C^{14} by the human ovary. A similar transformation has been described (412) using human placental slices as the incubation medium.

3. *Progestagens*

a. *In Vivo*

Davis and Plotz (99) have reported the conversion of progesterone to urinary estrone following injection of progesterone-4-C^{14} to a patient with choriocarcinoma, but no conversion was detected in the case of normal pregnant females. Labeled urinary estrogens could not be detected (374) after a single intravenous injection of C^{14}-labeled progesterone in a pregnant woman with a hydatidiform mole. Using a variety of experimental techniques it has been shown (223) that very little, if any, estrogens could be detected in the placenta, fetal tissues, and urine of pregnant women following the administration of labeled progesterone.

b. *In Vitro*

Labeled estrone and estradiol were isolated (347, 348, 389) when progesterone-4-C^{14} was incubated with human ovaries stimulated by follicular stimulating hormone. Similar results were reported by Axelrod and Goldzieher (17, 159) using normal and pathological human ovarian tissues. The incorporation of progesterone-4-C^{14} into estrone and estradiol has also been shown to occur in minced human stromal or luteal tissue as well as in bovine corpora luteal tissue (413), but in very low yield. A number of abnormal tissues are capable of utilizing progesterone or pregnenolone as a precursor (367, 368, 447) for estrogen formation. Ryan and Petro (344) have recently described a technique for the separation of human ovarian granulosa and thecal cells and have demonstrated the presence of enzymes in both cells for the conversion of pregnenolone and progesterone to estrogens.

Human term placentas, incubated with pregnenolone-4-C^{14} and 17α-hydroxyprogesterone-4-C^{14}, were unable (392) to convert these compounds into estrogens. Similar results were reported (256) when vesicles of hydatidiform moles were incubated with pregnenolone-7α-H^3.

4. *Androgens*

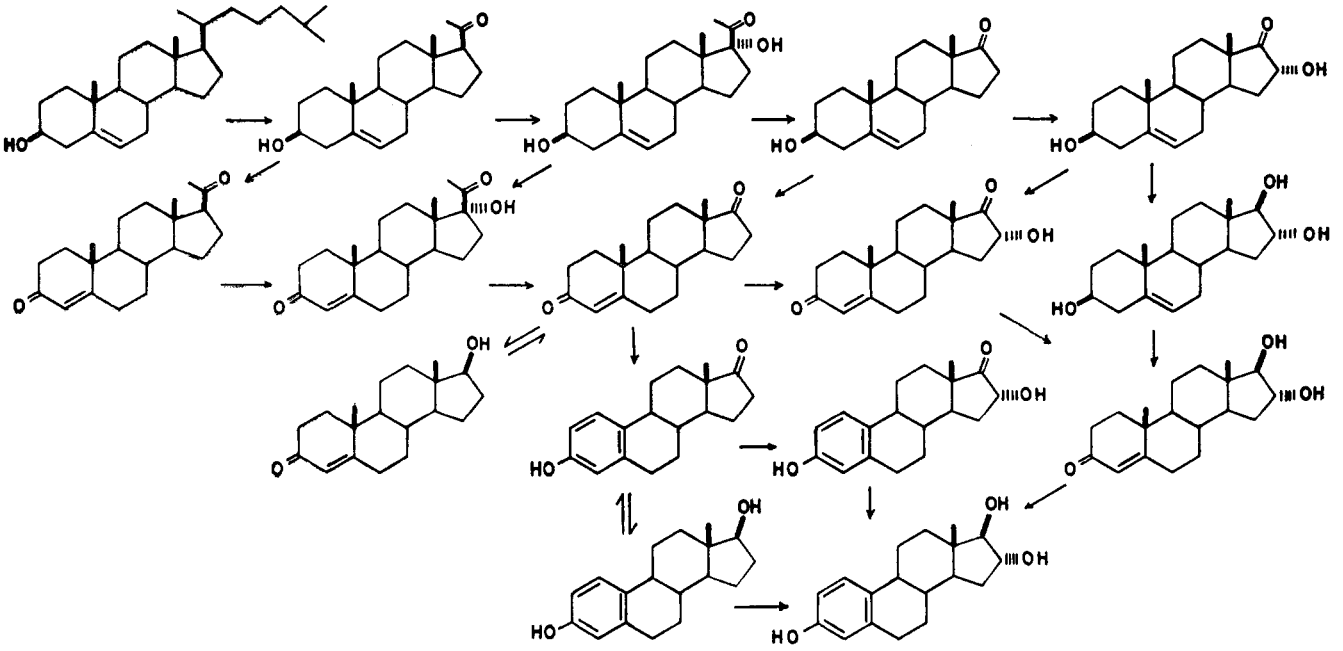
As early as 1934, Zondek (472) had postulated that androgens could possibly be the biogenetic precursors of the estrogens. Later, it was observed (407) that the administration of androst-4-ene-3,17-dione to normal and castrate male rats resulted in an increase of estrogenic substances in their urine. A similar observation was made (406) when testosterone propionate was administered to human males although it was not proven conclusively that the "female hormone" produced was, in fact, an estrogen. The role of androgens as precursors for the biosynthesis of estrogens is now firmly established, and a large number of papers have been published in the last few years describing this conversion by human and animal tissues *in vivo* and *in vitro*. Dorfman and Ungar (117) have reviewed the work in this field until 1963. Table I records some of the more recent studies involving the biosynthetic conversion of androgens to estrogens.

C. BIOSYNTHETIC PATHWAYS

1. *Estrone, Estradiol, and Estriol*

There is no doubt that many pathways exist for the biosynthesis of estrogens. In the previous section it was indicated that many postulated intermediates have been confirmed as estrogen precursors in a variety of biological systems both *in vitro* and *in vivo*. The

CHART II



scheme in Chart II shows some of the more important pathways which have been implied from experiments using radioactive tracers.

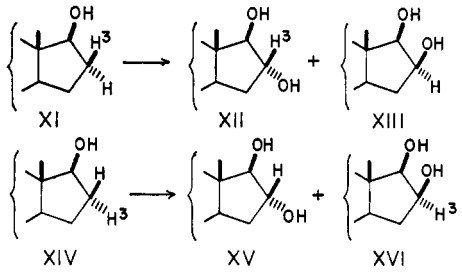
In mammals it is well established (113) that estrogens can be formed by the adrenal, the testes, the ovary, and the placenta. In man, the ovary and the placenta are the key tissues for the production of estrogens. Although there exists a vast amount of experimental data pertinent to the biosynthesis of estrogens in different tissues in a variety of species, there is no doubt that the emphasis has been, and still is, on the sequence of events in the human. Estrogens have been isolated primarily from the urine of pregnant women (16), and the three major estrogens are estrone (68, 111), estradiol (267), and estriol (110, 272). A number of other estrogens have also been identified, and in some cases their biosynthesis has been investigated to a limited extent.

The human placenta is the principal source of greatly increased amounts of estrogens produced by pregnant women. However, it is becoming increasingly apparent that the placenta must form estrogens from externally supplied C-19 steroids (33, 101, 376), and the role of the fetus in this respect has been investigated. It has been suggested that 3β-hydroxyandrost-5-en-17-one sulfate (33, 289, 374) could be an important precursor which is metabolized to estrogens by a pathway which does not involve the free steroids (*i.e.*, 3β-hydroxyandrost-5-en-17-one and androst-4-ene-3,17-dione). This view, however, is not unanimously supported (43, 44, 444).

It has been shown (143, 165) that following injection of labeled estrone or estradiol to pregnant women, the specific activity of urinary estriol is much lower than that of either estrone or estradiol. In the case of nonpregnant women there is not such an apparent difference. Similar results have been observed (224) following injection of a tracer dose of estrone-16-C^{14} into a pregnant chimpanzee. It has been suggested (45, 374, 376) that during human pregnancy considerable quantities of estriol may be produced by the fetoplacental unit, through a biosynthetic pathway which may be at least partly independent of estrone and estradiol metabolism. Ryan (343) has demonstrated the conversion of C-16 oxygenated androgens to estriol by the human placenta *in vitro* while Schwers, Eriksson, and Diczfalusy (362) have reported that the fetal liver is capable of producing C-16 oxygenated estrogens from estradiol. However, it has been shown (193) that 16α-hydroxyestrone, a normal metabolite in pregnancy (192, 255, 274) and a good exogenous precursor of urinary estriol *in vivo* in the nonpregnant human (60, 299), is probably not derived from a fetoplacental source but is most likely derived from maternal conversion of secreted estrone or estradiol. The biosynthetic pathway for the formation of estriol during pregnancy awaits further clarification.

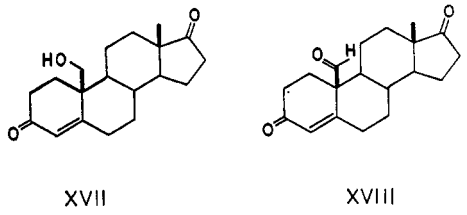
The roles of 16-oxoestradiol (255) and 16-oxoestrone (365, 380) either as precursors or oxidation products of the estriols in the human (49, 118) have been postulated, and a considerable amount of experimental evidence both *in vitro* (52, 53, 56, 57) and *in vivo* (259, 260, 261, 299, 408) has been accumulated in support of both of these ideas. Fishman, Hellman, Zumoff, and Cassouto (145), on the basis of some very elegant experimental work, have shown that 16-oxo compounds cannot be

considered as important intermediates in the biosynthesis of estriol or 3,16β,17β-trihydroxyestra-1,3,5(10)-triene (epiestriol). After administration of estradiol-16β-H^3 (XI) and estradiol-4-C^{14} or estradiol-16α-H^3 (XIV) (142) and estradiol-4-C^{14} to human subjects, the C^{14}/H^3 ratios of the urinary metabolites were determined. It was found that, when the compound with a 16β-tritium atom was used, the estriol (XII) isolated had retained its tritium while essentially all the isotope was lost from the epiestriol (XIII). When estradiol-16α-H^3 (XIV) was administered the above results were almost quantitatively reversed (XIV → XV and XVI). From this study it was also possible to conclude that hydroxylation at C-16 (adjacent to a carbonyl group) occurs with replacement of the hydrogen atom involved. This is known to be the case for enzymatic hydroxylation at other positions in the steroid nucleus which do not have enolizable hydrogen atoms (36, 96, 170, 417).



2. Aromatization of the A Ring

The importance of the C-19 steroids as intermediates in the biosynthesis of estrogens is well documented, but the manner in which these compounds are converted to estrogens remains in considerable doubt. The microsomal placental aromatization of androgens requires NADPH[2] and oxygen (341, 342), and there is



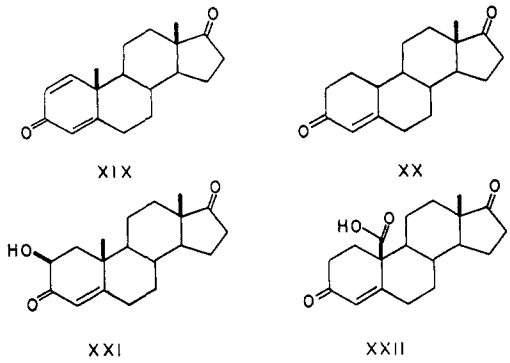
strong evidence (266, 454) that a C-19 oxygenated intermediate such as XVII (which has been isolated) or possibly XVIII (which has not been isolated) is involved. However, the aromatization process in the placenta appears to be more complex than would be predicted from a strictly chemical (129, 390) point of view. There seems to be no analogy with the mechanism involved in the microbiological aromatizations of C-19 oxygenated steroids (108, 253, 371) since in these processes the 1α-hydrogen is removed (327, 328), whereas it is the 1β-hydrogen which is involved (290) in placental aromatizations. Also, the presence of Δ^1-dehydrogenases in mammalian tissue has yet to be demonstrated.

In 1955, Meyer (279) discovered that bovine adrenal glands could hydroxylate androst-4-ene-3,17-dione at C-19, and he suggested that 19-hydroxyandrost-4-ene-3,17-dione (XVII) might be an intermediate in the biosynthesis of estrogens. It was subsequently shown (280) that the human placenta could convert this compound to estrone and estradiol. When human placental microsomes were incubated with androst-4-ene-3,17-dione-4-C^{14}, radioactive 19-hydroxyandrost-4-ene-3,17-dione (XVII) was isolated and reincubation of this substance with the same system produced labeled estrone (266). The fact that 19-hydroxyandrost-4-ene-3,17-dione (XVII) is converted to estrogens much more rapidly than is androst-4-ene-3,17-dione (172, 288) indicated that the former compound was probably an intermediate in the *in vitro* aromatization of androgens.

In 1962 results were published (194) which indicated that 19-hydroxyandrost-4-ene-3,17-dione (XVII) might not be an obligatory intermediate in the biosynthetic pathway to estrogens. Human placental microsomes were incubated with androst-4-ene-3,17-dione-4-C^{14} as well as with 19-hydroxyandrost-4-ene-3,17-dione (XVII) as a trapping agent. After 5 min of incubation it was found that there was more radioactivity in the estrogens than in the 19-hydroxyandrost-4-ene-3,17-dione (XVII). These results, in contradiction to the earlier work of Longchampt, Gual, Ehrenstein, and Dorfman (266), suggested that 19-hydroxyandrost-4-ene-3,17-dione (XVII) did not participate as an intermediate. However, in a kinetic study of this aromatization reaction, Wilcox and Engel (454) have shown that hydroxylation of the C-19 methyl group does occur and that once formed the 19-hydroxy compound is quickly aromatized. Since the aromatization was found to be complete in less than 5 min, this explains why Hollander (194) was unable to detect significant radioactivity in the 19-hydroxyandrost-4-ene-3,17-dione (XVII) used as a trapping agent after incubation for 5 min.

A large number of potential precursors, including androst-1,4-diene-3,17-dione (XIX) (164), estr-4-ene-3,17-dione (XX) (164, 288), 2β-hydroxyandrost-4-ene-3,17-dione (XXI) (164), and 10β-carboxyestr-4-ene-3,17-dione (XXII) (112, 288) have been found to be incorporated into estrogens by human placental microsomes less rapidly than adrost-4-ene-3,17-dione itself. Similar results have been reported (79) for some of these compounds when perfused human placentas were used as the test system. The orientation of substituents at C-11 affects the aromatization of ring A (50, 164, 342) and it has been shown that 11β-hydroxy compounds are very poor substrates. Based on studies with 17β-hydroxy-9β,10α-androst-4-en-3-one (retrotes-

(2) Reduced form of nicotinamide adenine dinucleotide.

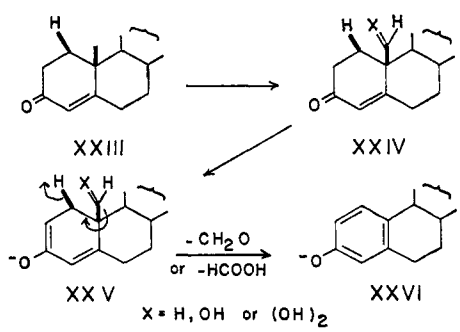


tosterone) (100) and with steroids having different configurations (443) at C-8, C-9, or C-10, it appears that the orientation of the angular methyl group at C-10 may be an important factor in the biochemical aromatization of androgens.

Since 19-oxoandrost-4-ene-3,17-dione (XVIII) is transformed by human placental microsomes more rapidly into estrone than 19-hydroxyandrost-4-ene-3-17-dione (XVII) (172, 288), it appears that the former compound is a closer intermediate to estrogens in the biosynthetic pathway. However, this compound has never been isolated from a biological system. The exact manner in which the angular methyl group at C-10 is removed in the placenta is by no means resolved.

Using two samples of androst-4-ene-3,17-dione tritiated predominantly in the 1α and 1β positions, respectively (58), the Worcester Foundation group (290) demonstrated that when these compounds were incubated with human placental microsomes the 1α-H^3 precursor retained most of its radioactive label whereas most of the tritium was lost when the 1β-H^3 compound was used as substrate. It had been reported (18) earlier that the 1α-hydrogen was lost during aromatization. However, it has since been pointed out (58) that this conclusion was based on incorrect assignment of configuration at the tritium containing carbon atom.

Morato and his collaborators (290) suggested possible mechanisms by which the angular methyl group at C-10 could be removed. The sequence XXIII → XXVI shows one of the potential pathways postulated by these workers.



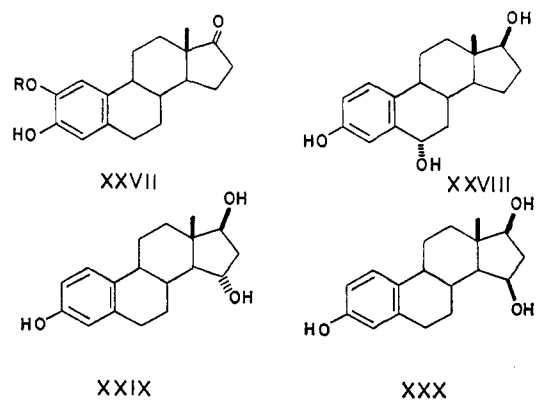
A stoichiometrical relationship between estrone and the evolved formaldehyde has been reported (51) for the placental microsomal aromatizations of androst-4-ene-3,17-dione, 19-hydroxyandrost-4-ene-3,17-dione, and testosterone. These experiments were carried out under conditions (342) which precluded the oxidation of formaldehyde. However, these results could not be confirmed (19, 114) in two other laboratories. In the more recent work (19), testosterone-19-C^{14} was incubated with placental microsomes under a variety of conditions and labeled formic acid was found to be the main product.

3. *Other Estrogens*

In recent years a number of urinary estrogens containing more than two oxygen atoms have been identified. The origin of these compounds is being investigated in many laboratories, but most of this work is still in the preliminary stage.

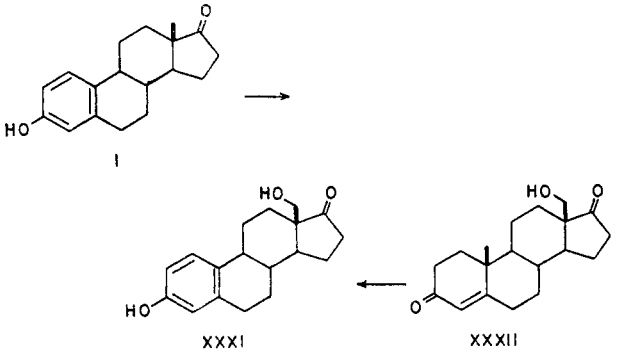
2-Methoxyestrone (XXVII, R = CH_3) (133, 250, 264) and 2-hydroxyestrone (XXVII, R = H) (141, 144, 146) both occur in human urine and have been shown to be metabolites of estrone and estradiol. Perfusion of human placentas with labeled estrone, estradiol (2, 81), or androgens (81) has led to the identification of 3,6α,17β-trihydroxyestra-1,3,5(10)-triene (XXVIII) as one of the products. Hydroxylation of estrogens at C-6 has also been found to occur when these compounds were incubated (54, 293) with liver preparations. These results confirm a biosynthetic pathway with hydroxylation at C-6 occurring after aromatization of the A ring. Whether another pathway exists which involves the aromatization of C-6 substituted androgens remains uncertain.

Both 3,15α,17β-trihydroxyestra-1,3,5(10)-triene (XXIX) (246) and 3,15β,17β-trihydroxyestra-1,3,5(10)-triene (XXX) (247) have been isolated from human pregnancy urine. On the basis of some preliminary experimental work (363), it appears likely that these compounds are metabolites of estrone and estradiol. It has also been shown that adrenal tissue is capable of hydroxylating estrone (244, 245) in the 7α or 11β positions.



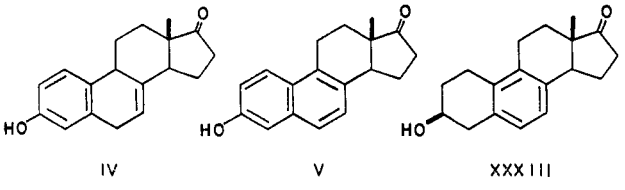
The biosynthesis of 18-hydroxyestrone (XXXI), isolated from late human pregnancy urine (265), has been

investigated and at least two pathways appear to be involved. The suggestion (265) that this compound might be formed in the human by hydroxylation of estrone (I) at C-18 was shown to be correct by the work of Knuppen, Haupt, and Breuer (248) who were able to demonstrate that this process occurred in human adrenal tissue *in vitro*. However, an alternative pathway was indicated when it was reported (147) that C-18 hydroxylation of testosterone was possible in man. More recently it has been shown that 18-hydroxyestrone is formed in high yield (217) by incubation of 18-hydroxyandrost-4-ene-3,17-dione, (XXXII) with human placental tissue. It now remains to determine the relative importance of each pathway.



4. Equilin, Equilenin, and Related Estrogens

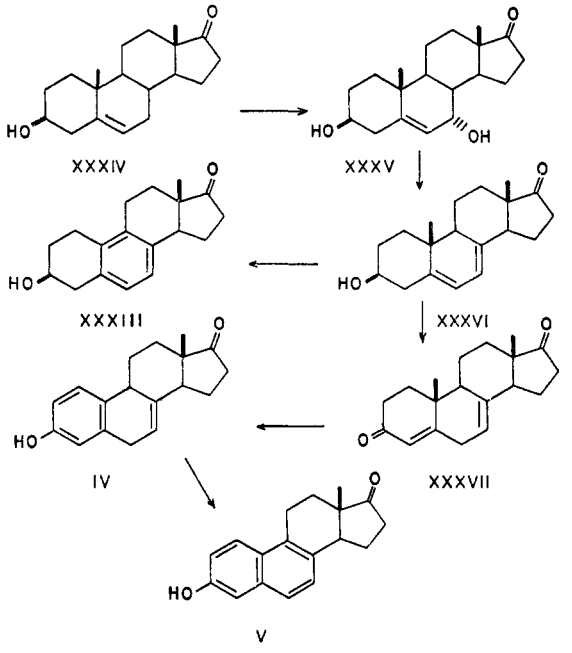
Phenolic and nonphenolic ring-B unsaturated estrogens have been isolated from equine pregnancy urine. Equilin (IV) (153), equilenin (V) (154), and 3β-hydroxyestra-5,7,9-trien-17-one (XXXIII) (155, 175) are representative of these types of estrogens. Although evidence has been obtained (350, 367) for the presence of equilenin (V) in pathological tissue in the human, these ring-B unsaturated estrogens have not yet been detected in human urine.



Experiments in the horse *in vivo* have indicated that estrone is not formed by the same biogenetic pathway as equilin (IV) or equilenin (V). It was shown (173) that after administration of acetate-1-C^{14} to the pregnant mare, the equilin (IV) and equilenin (V) isolated had only half the specific activity of the estrone produced and subsequent experiments (352) confirmed these results. Furthermore, it was found (176) that estrone is not converted to these ring-B unsaturated estrogens and that equilenin (V) is not transformed to estrone or equilin (IV) (355) in the pregnant mare. However, it has been shown (55, 287) that incubation of equilin (IV) with rat liver will result in the formation of equilenin (V). This transformation presumably occurs by a dehydrogenation process.

The biogenesis of phenolic and nonphenolic ring-B unsaturated estrogens from 3β-hydroxyandrost-5-en-17-one (XXXIV) has been investigated (400) in preparations of liver and placenta of the horse. On the basis of their experimental work, Stárka and Breuer (400) have postulated the sequence of intermediates shown in Chart III for the formation of these compounds. The high yield of 3β-hydroxyestra-5,7,9-trien-17-one (XXXIII) from 3β-hydroxyandrosta-5,7-dien-17-one (XXXVI) indicates that formation of the former compound by saturation of the A ring of equilenin (V) (174, 175) as a major pathway is unlikely.

CHART III



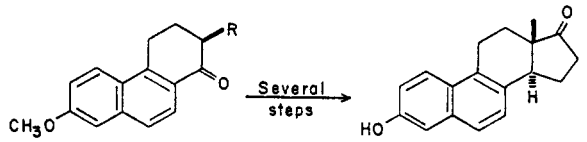
The conversion of 3β-hydroxyandrosta-5,7-dien-17-one (XXXVI) and 3β,7α-dihydroxyandrost-5-en-17-one (XXXV) to equilin (IV) and equilenin (V) (401) as well as to 3β-hydroxyestra-5,7,9-trien-17-one (XXXIII) (399) by perfusion through human placenta has recently been described. Since 3β,7α-dihydroxyandrost-5-en-17-one (XXXV) is a normal metabolite of 3β-hydroxyandrost-5-en-17-one (XXXIV) in man (359), the interesting suggestion has been made (399, 401) that ring-B unsaturated estrogens might, in fact, be present in human urine.

V. TOTAL SYNTHESES

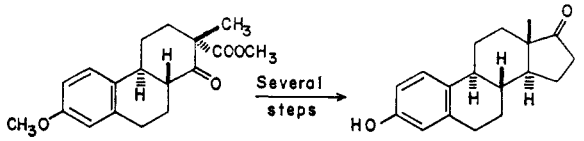
In the steroid family the estrogens have the simplest structures, and it is not surprising that these compounds were the first in this group to be prepared by total synthesis. For example, equilenin, which has only two asymmetric carbon atoms, was synthesized over 25 years ago. The interesting biological activity of the steroidal estrogens has also been a great incentive for organic chemists to investigate synthetic routes for

these compounds. Intensive work carried out in a number of laboratories in the past few years has now made it possible to prepare the natural steroidal estrogens and many of their derivatives on an industrial scale. In the following survey, only the work involving the synthesis of the natural steroidal estrogens and of their racemic mixtures will be emphasized.

The earlier syntheses for equilenin (V) involved elaboration (20, 21, 85, 230–232) of the intermediate ketone XXXVIII, a compound which was relatively easy to prepare (20, 70, 91, 92, 410, 456). Anner and Miescher (13–15) were the first to report the total synthesis of estrone (I). The key intermediate in this synthesis was Robinson's ketone (XXXIX) (22, 332, 333), but it should be pointed out that this synthesis was not stereospecific, and in fact five isomers of estrone were prepared which differed in configuration at some of the asymmetric carbon atoms. During the period 1950 to 1960 Banerjee (31), Johnson (225, 226, 228, 229), Sheehan (369), Smith (202, 203), Torgov (7), Velluz (438, 440), and Walker (93, 329), with their respective co-workers, have developed increasingly stereospecific syntheses for estrone (I). Most of this work until 1960 has been summarized by Torgov (422), and reviews on total syntheses of steroids (441) and 19-norsteroids (459) have recently been published.



XXXVIII V



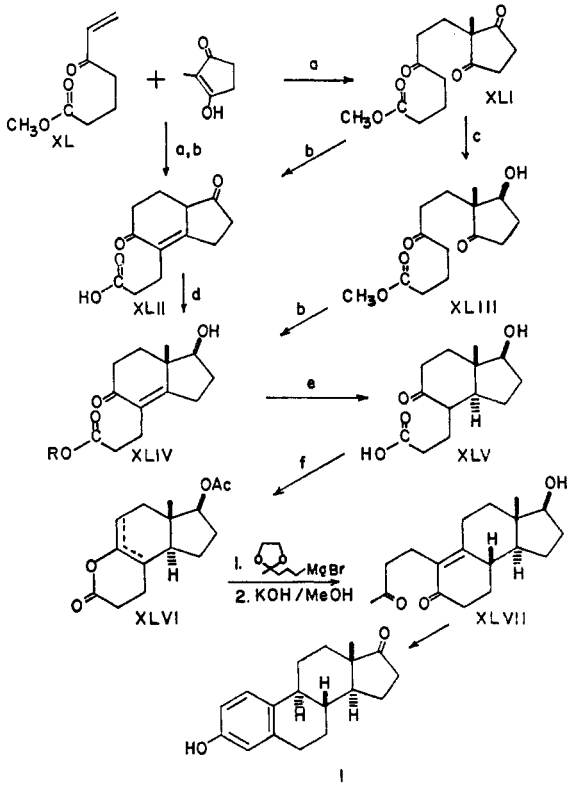
XXXIX I

A. ESTRONE

Velluz and his co-workers were one of the pioneering groups in the total synthesis of estrone on an industrial scale. Details of their earlier synthesis (438, 440) starting from 6-methoxytetralone have already been summarized (424). A later synthesis published (437) by these workers involved optical resolution of one of the intermediates to give natural estrone as the final product. The steps involved in this process, which can also be modified for the preparation of the interesting 19-norsteroids (439), are outlined in Chart IV.

In this versatile synthesis, the C and D rings were formed by heating 2-methylcyclopentane-1,3-dione (303, 304) with methyl 5-oxo-6-heptenoate (XL) in toluene containing pyridine followed by treatment with

CHART IV



[a] a = toluene–pyridine, reflux; b = 5 *N* HCl; c = *Rhizopus arrhizus;* d = ephedrine salts–optical resolution; $NaBH_4$; e = H_2–Pd in aqueous ethanol; f = $(CH_3CO)_2O$–CH_3CO_2Na.

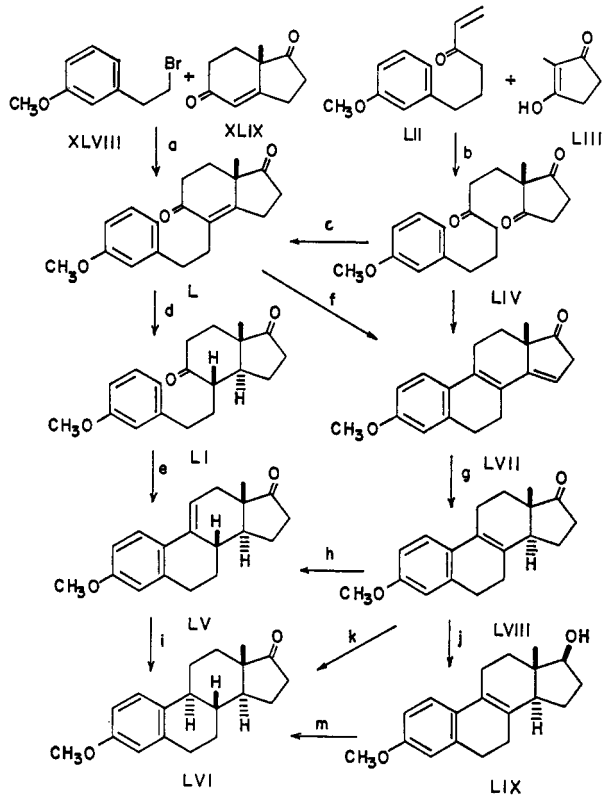
hydrochloric acid. The resulting acid XLII was then resolved into its enantiomers by fractional crystallization of the ephedrine salts. Selective hydrogenation of the double bond from the α side was achieved (30, 388) by first converting the bicyclic compound XLII to the ketol XLIV (R = H) with sodium borohydride. Subsequent hydrogenation in aqueous ethanol with palladium catalyst gave the saturated bicyclic ketol XLV. A mixture of enol lactones XLVI was obtained by treating the ketol XLV with acetic anhydride in the presence of sodium acetate. Condensation of either of the enol lactones XLVI with the Grignard reagent of 1-bromo-4,4-ethylenedioxypentane (163) followed by treatment with methanolic potassium hydroxide gave the tricyclic diketone XLVII which had been prepared earlier (440) by an alternative route. Conversion of this compound (XLVII) to estrone (I) was carried out in the manner already described by these workers (440).

Bellet, Nominé, and Mathieu have recently reported (34) the microbiological reduction of the intermediate trione XLI to the optically active cyclopentanolone (XLIII) in 70% yield. This makes possible the total synthesis of natural estrone (I) without loss of an enantiomer at a later stage (see also ref 151).

In 1963 Smith and his co-workers (120) published the details of their efficient and highly stereoselective

syntheses (202, 203, 388) of (±)-estrone methyl ether, five of its stereoisomers, (±)-equilenin methyl ether, and (±)-isoequilenin methyl ether. Chart V illustrates the synthetic routes used by these workers for the preparation of estrone methyl ether (LVI).

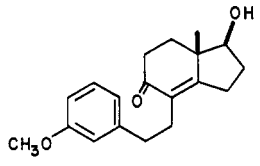
CHART V[a]



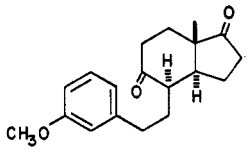
[a] a = *t*-BuOK–benzene; b = OH^-–CH_3OH; c = $(C_2H_5)_3N$, C_6H_5COOH–xylene; d = H_2/Pd–C; e = HCl–CH_3OH; f = PPA; g = H_2–Raney Ni or H_2/Pd–$CaCO_3$; h = HCl–CH_3OH; i = K–NH_3, 8 *N* CrO_3; j = $NaBH_4$–CH_3OH; k = K–NH_3, 8 *N* CrO_3; m = Na–NH_3, THF, $C_6H_5NH_2$.

Preparation of the dione L, which represents an important intermediate in this synthesis, was accomplished by two different routes. Dione L could be formed directly, although in poor yield, by alkylation of 5,6,7,8-tetrahydro-8-methylindane-1,5-dione (XLIX) (46) with 3-methoxyphenethyl bromide (XLVIII). A similar alkylation has also been reported by Crispin and Whitehurst (97). The same dione (L) could also be prepared *via* the intermediate trione LIV by Michael condensation (453) of 2-methylcyclopentane-1,3-dione (LIII) with the vinyl ketone LII. By heating the crude trione LIV in xylene containing triethylamine and benzoic acid, cyclization and subsequent dehydration (cyclodehydration) occurred, and dione L was isolated in high yield. It was also found that trione LIV could be transformed directly into the tetracyclic ketone LVII by treatment of the former with strong acids.

Catalytic hydrogenation of dione L and subsequent cyclodehydration of the crude product (LI, not isolated) by methanolic hydrochloric acid gave 3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (LV) in 40% yield. After reduction of dione L to ketol LX with sodium borohydride, the catalytic hydrogenation was found to be even more selective (30, 32, 438) and the yield of dehydroestrone methyl ether (LV) could be increased to 60%. It was assumed that the 8α-hydrogen (see LXI) was epimerized to the more stable 8β-configuration (LI) during the course of these reactions. The stereoselective reduction of 3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (LV) with potassium and liquid ammonia followed by oxidation with chromic acid gave estrone methyl ether. Using the route LIV → L → LX → LI → LV → LVI, estrone methyl ether was obtained in an over-all yield of 14% from 3-*m*-methoxyphenylpropyl bromide, the starting material for making the vinyl ketone LII.



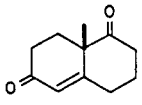
LX



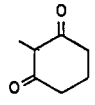
LXI

An alternative route to estrone methyl ether (LVI) involved 3-methoxyestra-1,3,5(10),8,14-pentaen-17-one (LVII) as an intermediate. This compound was obtained by acid-catalyzed cyclization of either dione L or trione LIV. Selective catalytic hydrogenation converted the pentaene LVII into 3-methoxyestra-1,3,5(10),8-tetraen-17-one (LVIII) which in turn was either directly reduced with potassium in liquid ammonia or converted to the alcohol LIX and then reduced to estrone methyl ether (LVI). With optimum conditions a yield of 18% of estrone methyl ether (LVI) starting from 3-*m*-methoxyphenylpropyl bromide (XLVIII) was reported.

The same sequence of reactions was developed for the preparation of D-homoestrone methyl ether starting from the octalindione (LXII) or 2-methylcyclohexane-1,3-dione (LXIII) instead of the indanedione (XLIX) or 2-methylcyclopentane-1,3-dione (LIII), respectively. A number of derivatives of estrone have been synthesized by further modification of the starting substances (71, 119, 121, 128, 189, 190, 386, 387), and elaboration of the intermediates (L, LV, and LVII) gave five of the stereoisomers of estrone.



LXII

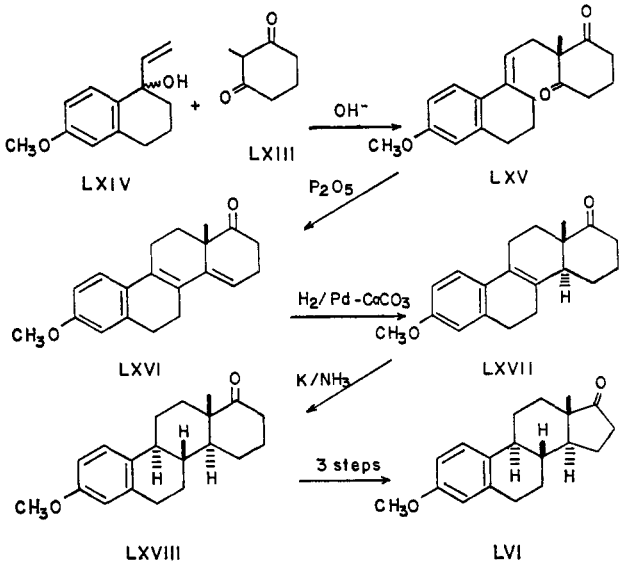


LXIII

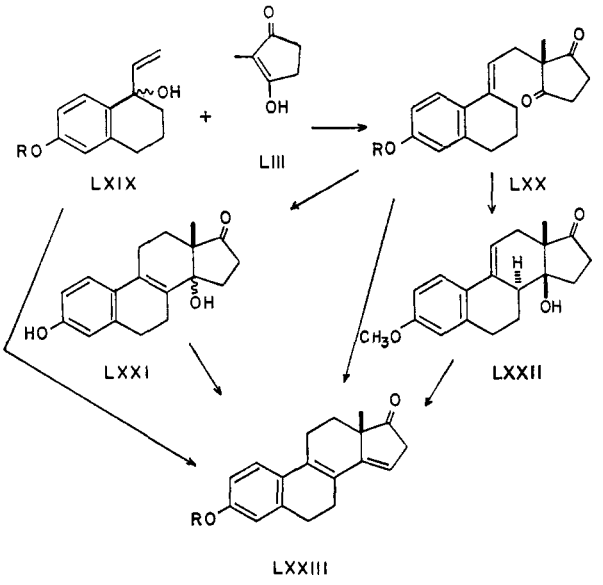
In 1959, Ananchenko and Torgov (11) reported that the vinylcarbinol LXIV, which is easily obtained by reaction of vinylmagnesium bromide with the appro-

priate tetralone (295), could be condensed with 2-methylcyclohexane-1,3-dione (LXIII) (see Chart VI) in the presence of a base to give a 50% yield of dione LXV. Cyclodehydration of this dione (LXV) with acid (7) gave the pentaene LXVI, which could then be converted to D-homoestrone methyl ether (LXVIII) by selective hydrogenation (8, 10, 120). Conversion of this compound to estrone methyl ether (LVI) was then carried out in three steps by application of Johnson's (226, 227) method for contraction of ring D.

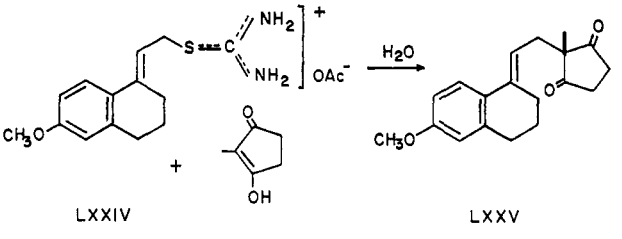
CHART VI



Soon after the publication of this work, no less than five groups independently reported (12, 98, 120, 249, 283, 284, 386, 387, 460, 465, 466, 468, 469) shortened syntheses for estrone or estrone methyl ether by using 2-methylcyclopentane-1,3-dione (LIII) (303, 304) instead of 2-methylcyclohexane-1,3-dione (LXIII) in the reaction with the vinyl alcohol (LXIX, R = H, CH_3). The dione LXX obtained could be easily cyclodehydrated to 3-methoxyestra-1,3,5(10),8,14-pentaen-17-one (LXXIII, R = CH_3), a compound which previously had been converted (120) to estrone methyl ether. It had been suggested (120) that aldol condensation was involved in the formation of the pentaene LXXIII (R = H, CH_3) from the dione LXX (R = H, CH_3), and this suggestion has now received experimental support. Zakharychev, Hora, Ananchenko, and Torgov (467) recently succeeded in isolating ketols LXXI and LXXII by varying the conditions for the acid-catalyzed cyclization of the phenolic dione LXX (R = H) and the methyl ether LXX (R = CH_3), respectively. Kuo, Taub, and Wendler (251) have reported that the vinyl alcohol LXIX (R = CH_3) and 2-methylcyclopentane-1,3-dione (LIII) in acetic acid–xylene at 120° afforded 3-methoxyestra-1,3,5(10),8,14-pentaen-17-one (LXXIII, R = CH_3) directly in 60–65% yield. Microbiological reduction (151) of the intermediate dione LXX has made it possible to prepare natural estrone methyl ether by this route.

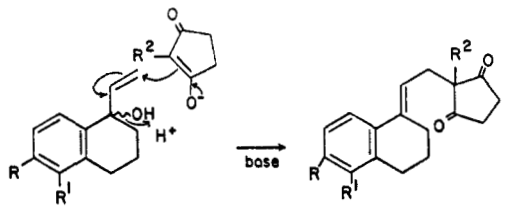


The nature of the condensation reaction leading to the formation of dione LXX (R = CH_3) has been investigated (251, 252), and it was found that the reaction is, in fact, catalyzed by acid and not base. A mechanism involving an ion-pair intermediate arising from acid–base interaction of the reactants was suggested. It was found that the vinyl alcohol LXIX (R = CH_3) in acetic acid in the presence of thiourea formed the crystalline thiuronium salt LXXIV in almost quantitative yield. This salt, on reaction with 2-methylcyclopentane-1,3-dione in aqueous solution, gave 80–85% of the desired dione LXXV.



Recently, Strike, *et al.* (411), have taken a critical look at some of the mechanisms which have been postulated (452, 465) for the formation of secosteroids (*e.g.*, LXXV). Experimentally they have found that condensation of 2-alkylcyclopentane-1,3-dione occurs easily with the vinylcarbinol LXXVI (R = OCH_3, R^1 = H) in refluxing methanol with a trace of base. However, when 1-vinyl-1-tetralol (LXXVI, R = R^1 = H) or its 5-methoxy derivative (LXXVI, R = H; R^1 = OCH_3) was used as precursor, no condensation product (LXXVII) could be isolated under the above conditions. These results have been interpreted as being consistent with an anionotropic mechanism similar to that involved with the rearrangements of 1- to 3-phenylallyl alcohols (210, 270). Such reactions

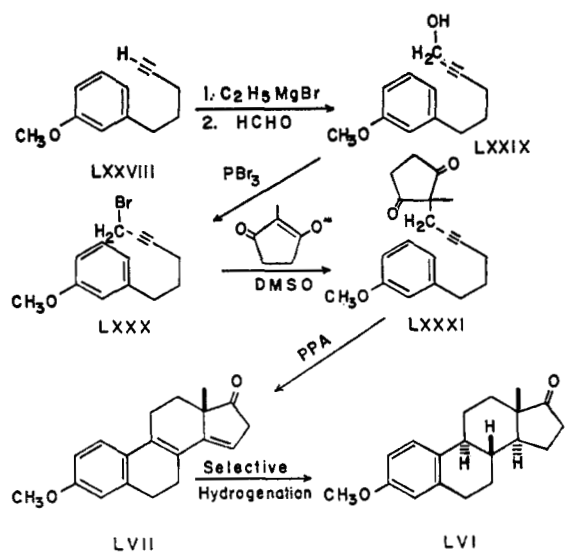
are enhanced by electron release to the carbon atom which loses the hydroxyl group, and this would explain why the 6-methoxytetralol (LXXVI, R = OCH_3; R^1 = H) reacts more readily than the 5-methoxytetralol (LXXVI, R = H; R^1 = OCH_3). A mechanism was proposed in which a proton is derived from another molecule of the acidic 2-alkylcyclopentane-1,3-dione. In the absence of base, a similar mechanism involving the enol form of the 2-alkylcyclopentane-1,3-dione instead of the enolate anion would be operative.



LXXVI LXXVII

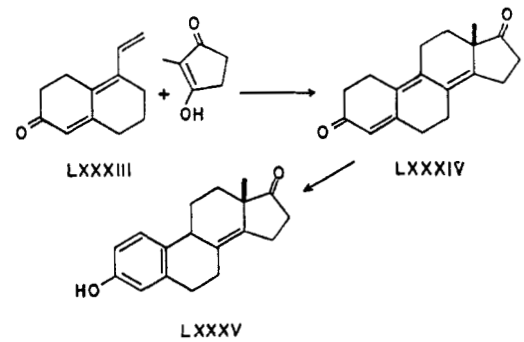
Hiraoka and Iwai (191) have reported a synthesis for estrone (see Chart VII) which, however, does not appear to be more efficient than some of the previous syntheses reported by other groups. The starting material in this case was 5-(*m*-methoxyphenyl)-1-pentyne (LXXVIII), and this compound was converted to the alcohol LXXIX by treatment with ethyl magnesium bromide followed by hydroxymethylation with formaldehyde. Bromination of the acetylenic alcohol LXXIX with phosphorus tribromide gave 1-bromo-6-(*m*-methoxyphenyl)-2-hexyne (LXXX) which could be converted to the acetylenic dione LXXXI in 67% yield by treatment with the sodium salt of 2-methylcyclopentane-1,3-dione in dimethyl sulfoxide (DMSO). Cyclization of LXXXI with polyphosphoric acid (PPA) gave the known 3-methoxyestra-1,3,5,(10),8,14-pentaen-17-one (LVII) which previously had been converted (120) to estrone methyl ether (LVI). A mechanism for the cyclization reaction was proposed (218).

CHART VII



LXXVIII LXXIX LXXX LXXXI LVII LVI

Application of a reaction first described by Gaidamovich and Torgov (148) has led to the preparation (461) of the tetracyclic compound LXXXIV. Treatment of the trienone LXXXIII with 2-methylcyclopentane-1,3-dione in the presence of diethylamine gave the tetracyclic compound LXXXIV, which was treated with isopropenyl acetate under acidic conditions. The crude product on hydrolysis gave a 30% yield of 3-hydroxyestra-1,3,5,(10),8,(14)-tetraen-17-one (LXXXV) (318).

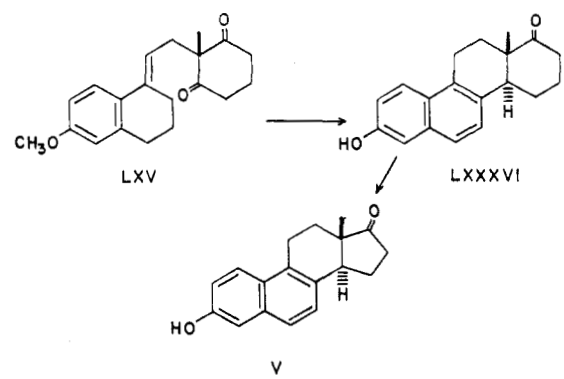


LXXXIII LXXXIV LXXXV

B. EQUILENIN

Some of the earlier work on the total synthesis of equilenin has already been discussed in the introduction to this section of the review. There now exist many synthetic routes to equilenin, and most of the recent syntheses that have been reported are essentially modifications of processes developed for the preparation of estrone.

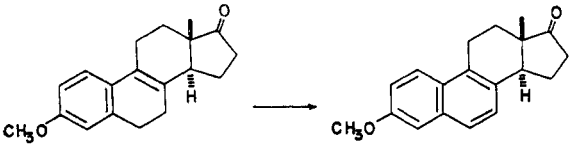
For example, by heating one of the intermediates (LXV) involved in the total synthesis of estrone (7) with pyridine hydrochloride at 180°, it was possible to isolate (9) D-homoequilenin (LXXXVI) in 55% yield. This compound LXXXVI was then converted to equilenin (V) by Johnson's (226, 227) procedure for contraction of ring D.



LXV LXXXVI V

Smith (120, 202) and his co-workers have also reported a synthesis of equilenin involving an intermediate in the synthesis of estrone. In this case selenium dioxide oxidation (30) of the tetracyclic com-

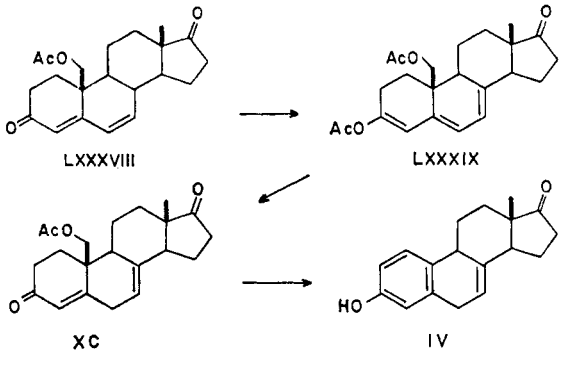
pound LVIII, obtained by total synthesis, gave equilenin methyl ether (LXXXVII). A similar conversion has also been described by Miki, Hiraga, and Asako (283, 284).



LVIII LXXXVII

C. EQUILIN

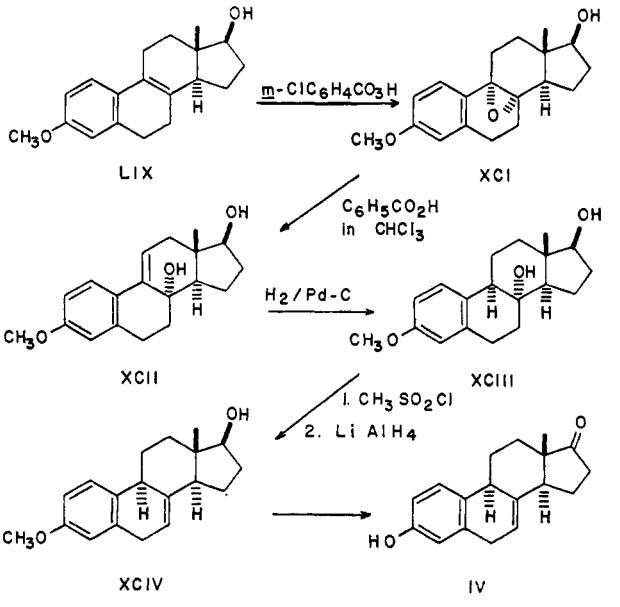
Equilin (IV), with its unconjugated double bond in the B ring, presents a considerably greater challenge from the point of view of total synthesis than does equilenin or estrone. The first synthesis of equilin was reported (470, 471) in 1958. Estrone was the starting material in this multistage process, and a microbiological dehydrogenation was involved as the last step in the synthesis. Later, a relatively simple and completely chemical synthesis of this hormone was reported (24), in which the easily accessible conjugated dienone LXXXVIII (188) was converted by enol acetylation to the diacetoxy compound LXXXIX. Selective hydrolysis of the latter with sodium bicarbonate in methanol afforded the acetoxy dienone XC, which on dehydrogenation with 2,3-dichloro-4,5-dicyanobenzoquinone (DDQ) followed by hydrolysis with methanolic sodium hydroxide gave equilin (IV).



LXXXVIII LXXXIX XC IV

Recently Stein, Buzby, and Smith (405) have reported an elegant total synthesis of optically active equilin (see Chart VIII). The estratetraene (LIX) (284) prepared by chemical resolution of the corresponding racemate (120), on treatment with *m*-chloroperbenzoic acid, gave a mixture of the epoxide XCI and the diol XCII. This mixture was converted to pure diol XCII with benzoic acid in chloroform. Catalytic hydrogenation of XCII gave the diol XCIII which was converted to the tetraene alcohol XCIV by treatment with methanesulfonyl chloride followed by reduction with lithium aluminum hydride. XCIV was then converted to equilin (IV) in a routine manner. The over-all yield for this synthesis starting from the estratetraene LIX was reported as 16%.

CHART VIII



LIX XCI XCII XCIII XCIV IV

VI. AROMATIZATION OF A AND B RINGS

The primary reason for developing methods of aromatization of the A ring of steroids was essentially a practical one—that of finding efficient partial syntheses of estrogens. Almost as soon as the steroidal estrogenic hormones were isolated from natural sources (early 1930's) the potential clinical use of these compounds was realized, and when their structures were elucidated in the late 1930's attempts were made to prepare them from other, more abundant, steroids (*e.g.*, cholesterol).

By 1950 reasonably efficient methods for the preparation of estrogenic hormones from androgens had been developed, but androgens were not readily available since they were obtained mainly from cholesterol, and at that time an efficient method of removing the side chain of cholesterol had not been found.

In recent years greatly improved total syntheses of estrogens have been developed, and it is now possible to prepare estrogens economically from nonsteroidal compounds. Another advance in recent years has been the use of microbiological reactions in the preparation of steroidal estrogens. For example, cleavage of the side chain of cholesterol is now accomplished in good yield by means of a microbiological reaction.

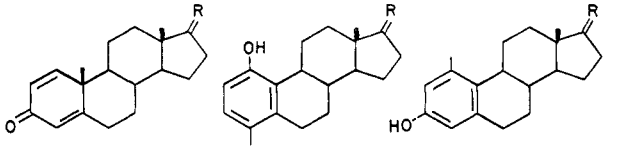
Considering the advances in the total synthesis of estrogens and in the application of microbiological reactions to the preparation of these compounds, it is unlikely that any new chemical method of aromatizing the A ring of a steroid will find commerical use. Although these aromatizations may not be of great industrial importance, many different aromatizations have been studied (366) during the past 30 years, and much interesting work remains to be done on these

reactions since in most cases their mechanisms have not been examined.

A. CHEMICAL AROMATIZATIONS

1. *Dienone–Phenol Rearrangement*

The dienone–phenol rearrangement has been used in the preparation of aromatic A-ring steroids for a long time (138), but it is only recently that the mechanism of this reaction has been demonstrated (73). By varying substituents on the substrate, reaction conditions, or acid catalysts, steroidal 1,4-dien-3-ones (XCV) rearrange to phenols of type XCVI (*para*) or XCVI (*meta*).

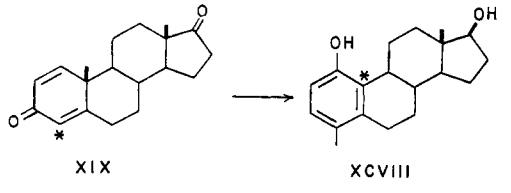


XCV XCVI XCVII

Since the *para*-type phenols are devoid of estrogenic activity, the rearrangement leading to these compounds will be discussed only briefly.

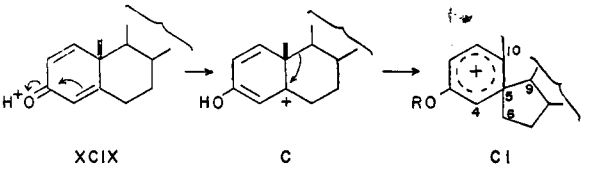
a. Rearrangement to *p*-Phenols

In the search for a synthetic method of preparation of estrogens, Inhoffen and Huang-Minlon (212) treated cholesta-1,4-dien-3-one (XCV, R = C_8H_{17} (β), H (α)) with acetic anhydride and sulfuric acid and obtained, after saponification, a phenol regarded as the *m*-phenol XCVII (R = C_8H_{17} (β), H (α)). In 1950 it was suggested that this compound was probably the *p*-phenol XCVI (R = C_8H_{17} (β), H (α)) (464). This suggestion later received confirmation (123, 463). Caspi, Grover, and Shimizu (73, 76) found that treatment of androsta-1,4-diene-3,17-dione-4-C^{14} (XIX) with zinc chloride and acetic acid–acetic anhydride (123) gave, after lithium aluminum hydride reduction, 4-methylestra-1,3,5(10)-triene-1,17β-diol-10-C^{14} (XCVIII). Degradation of the *p*-phenol XCVIII located the labeled carbon atom at



XIX XCVIII

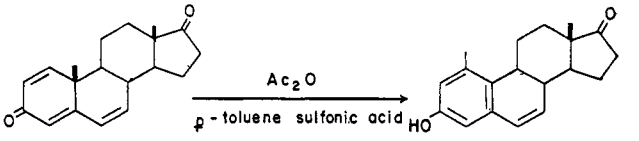
C-10. This evidence indicates that the reaction is initiated by an attack on the carbonyl group (see XCIX) forming cation C. Rupture of the C-9–C-10 bond then occurs, followed by formation of spiro intermediate CI; migration of the C-5–C-9 bond to C-4 gives the *p*-phenol (*cf.* XCVIII).



XCIX C CI

b. Rearrangement to *m*-Phenols

The presence of an additional double bond in the 6,7 position alters the course of the rearrangement. When androsta-1,4,6-triene-3,17-dione (CII) was treated with acetic anhydride and *p*-toluenesulfonic acid, 1-methyl-6-dehydroestrone (CIII) was isolated after saponification (105).

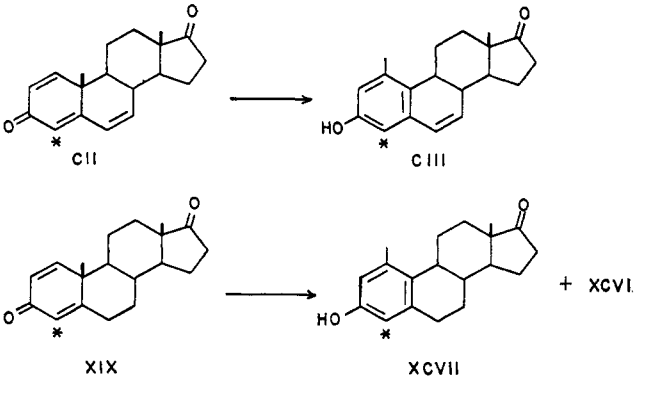


CII CIII

Various substituents on the trienone do not alter the course of the rearrangement. The reaction has been carried out on trienones with 2- and 4-chloro substituents (243), with 2,4-dibromo substituents (213), with a 2-methyl substituent (215), and with different side chains (102, 334, 351). The *meta*-type phenols were formed in all cases.

m-Phenols are also formed in the aqueous acid-catalyzed rearrangement of steroidal 1,4-dien-3-ones (66, 122). For example, treatment of androsta-1,4-diene-3,17-dione (XCV, R = O) with concentrated aqueous hydrochloric or hydrobromic acid gave a 55% yield of 1-methylestrone (XCVII, R = O). A 10% yield of the *p*-phenol, 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one (XCVI, R = O), was also obtained (122).

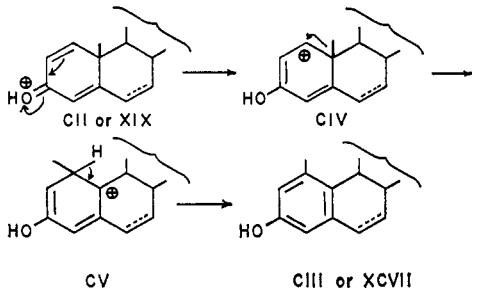
Formation of *m*-phenols was found to proceed *via* migration of the C-19 methyl group to C-1. Rearrangement of androsta-1,4,6-triene-3,17-dione-4-C^{14} (CII) with acetic anhydride and *p*-toluenesulfonic acid gave 1-methyl-6-dehydroestrone-4-C^{14} (CIII); rearrangement of androsta-1,4-diene-3,17-dione-4-C^{14} (XIX) with aqueous acetic–hydrochloric acid gave a mixture of 1-methylestrone-4-C^{14} (XCVII) and the *p*-phenol XCVI (R = O).



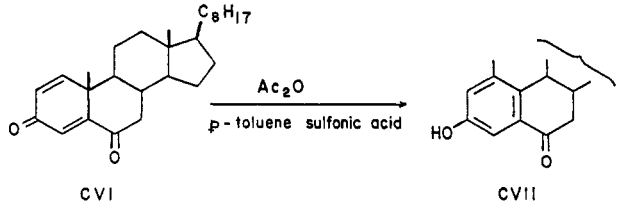
CII CIII

XIX XCVII

Caspi, Grover, and Shimizu (73, 74, 76) located the tracer atoms in both *m*-phenols CIII and XCVII at C-4. It was concluded that protonation induced formation of the cation CIV and subsequent migration of the C-10 methyl group to C-1 (CV) gave the *m*-phenol CIII or XCVII.



Any functional group which tends to stabilize the positive charge at C-1 (see CIV) will result in the formation of a *meta*-type phenol. Thus with 1,4,6-trienones, the complete conjugation of the three double bonds in the intermediate cation CIV is responsible for the location of the positive charge at C-1. A 6-oxo group has a similar conjugative effect; it was observed that cholesta-1,4-diene-3,6-dione (CVI) on treatment with acetic anhydride and *p*-toluenesulfonic acid rearranged to 3-hydroxyl-1-methyl-19-norcholesta-1,3,5(10)-trien-6-one (CVII) (66).



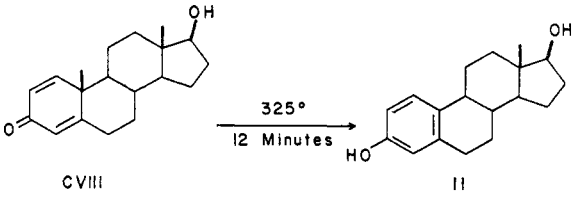
With an 11-oxo group the proximity of the negative end of the dipole of the oxo group to C-1 helps stabilize the cation. Moreover, the electron-withdrawing effect of the carbonyl probably prevents cleavage of the 9,10 bond. Dienone–phenol rearrangement of 1,4-diene-3, 11-diones in the progesterone and androstane series gave the *meta*-type phenols (25, 130). The presence of a 4-methyl group blocks the route to a *p*-phenol so with these compounds a *meta*-type phenol is formed (393).

A 10-acetoxy function also directs the reaction to the *m*-phenol (156). No explanation has yet been offered for the predominance of *m*-phenols in aqueous acid-catalyzed rearrangements.

2. *Aromatization of A Ring Involving Expulsion of C-19 Groups*

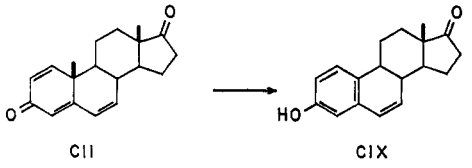
a. Pyrolytic Aromatizations

Pyrolytic aromatization was the first method used in the synthesis of estrone and estradiol. In 1941 Inhoffen and Zühlsdorff (214) reported the synthesis of estradiol (II) from cholesterol through a long series of reactions culminating in the pyrolytic aromatization of 17β-hydroxyandrosta-1,4-dien-3-one (CVIII). Estradiol (II) was isolated in 5% yield after the dienone CVIII had been heated in an evacuated tube at 325° for 12 min.



In a later publication (211) the yield was reported to have been increased to 20% when the pyrolysis was done in dihydronaphthalene in a sealed tube at 380°. However, in repeating the experiment, the maximum yield obtained by Wilds and Djerassi was 10% (457). In an improved method estrone was prepared in 15–20% yield by heating androsta-1,4-diene-3,17-dione in mineral oil at 535° (186).

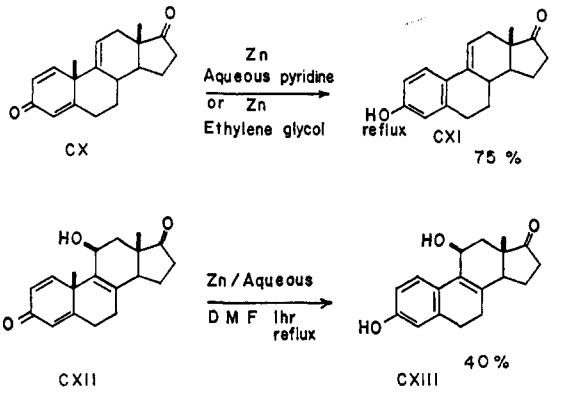
Pyrolytic aromatization of androsta-1,4,6-triene-3,17-dione (CII) gave 6-dehydroestrone (CIX) in up to 52% yield (103, 238). Hydrogenation of 6-dehydroestrone (CIX) over palladium gives estrone in excellent yield (103, 238).



There are many examples of pyrolytic aromatizations in the literature, and this reaction has been used in the commercial synthesis of estrone and estradiol. These pyrolytic reactions probably proceed by a free-radical mechanism (404). The pyrolysis of a 3-oxo-1,4-diene therefore could first involve the loss of the C-10 methyl radical, leaving the steroid radical which could then abstract a hydrogen atom from the solvent or from another steroid molecule to give the phenol (268).

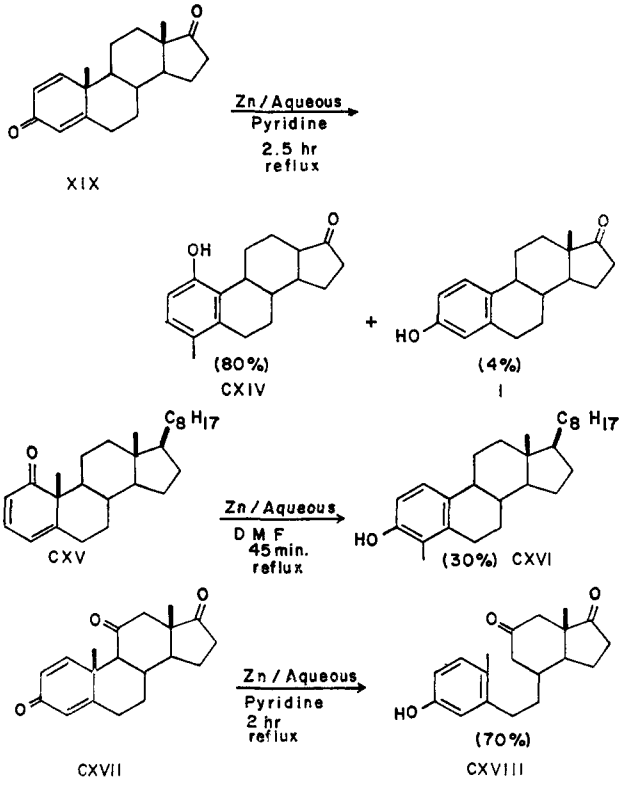
b. Expulsions Using Zinc

The action of zinc in slightly aqueous pyridine or ethylene glycol on androsta-1,4,9(11)-triene-3,17-dione (CX) has been reported to give 9-dehydroestrone (CXI) in 75% yield (431). This is a much higher yield than any reported for pyrolytic aromatizations, and it was thought that this reaction would provide a better route to estrogens. However, the more readily available androsta-1,4,6-triene-3,17-dione (CII) when treated with zinc in pyridine or ethylene glycol yields only 15–20% of 6-dehydroestrone (CIX) (430), and 11β-hydroxyandrosta-1,4,8-triene-3,17-dione (CXII) gives a 40% yield of 3,11β-dihydroxyestra-1,3,5(10),-8-tetraen-17-one (CXIII) (428). Methane is evolved during the course of these reactions.



CX CXI CXII CXIII

With 1,4-dien-3-ones the major product is the same as that formed in the dienone–phenol rearrangement of these compounds. For example, androsta-1,4-diene-3,17-dione (XIX) on treatment with zinc in pyridine yields 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one (CXIV, 80%) and estrone (I, 4%) (430). Recently a dienone–phenol type rearrangement was observed when the linearly conjugated dienone, cholesta-2,4-dien-1-one (CXV) was treated with zinc in dimethylformamide. A 30% yield of 19-nor-4-methylcholesta-1,3,5(10)-trien-3-ol (CXVI) was isolated (219).



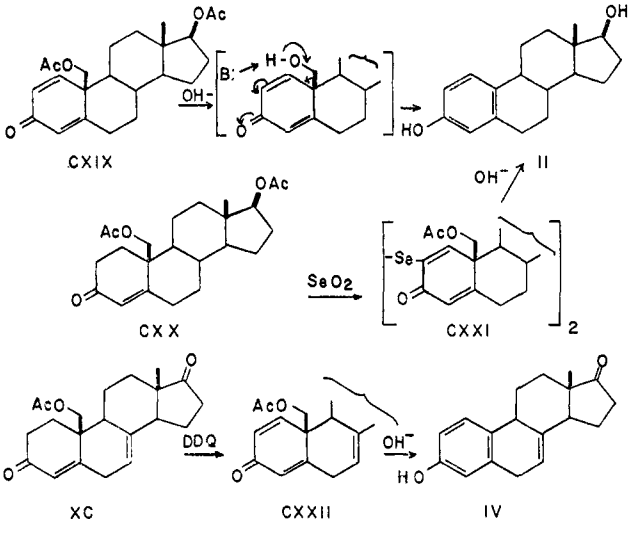
XIX CXIV I CXV CXVI CXVII CXVIII

The presence of an 11-oxo group in a 1,4-dien-3-one causes cleavage of the C-9–C-10 bond. For example, androsta-1,4-diene-3,11,17-trione (CXVII) when treated with zinc in pyridine gave a 70% yield of 3-hydroxy-9,-10-secoandrosta-1,3,5(10)-triene-11,17-dione (CXVIII) (430).

In the reactions where a dienone–phenol rearrangement takes place, it has been suggested that the zinc is acting in the ionic form as a Lewis acid. In the reductive aromatizations where bond breakage (C-9–C-10 or C-10–C-19) occurs, the zinc has been assumed to be acting as a metal, the reaction being initiated by chemisorption of the zinc on the oxo group. Since water is essential for these reactions, it is thought to be acting as a proton source (292).

c. Reverse Aldol Reaction

This reaction was first applied to the progesterone series (426) and has only been used in a few instances for the preparation of estrogens. Treatment of 17β,19-diacetoxyandrosta-1,4-dien-3-one (CXIX) with alkali resulted in the formation of estradiol (II) (129). Estrone was similarly prepared from the benzoate of 19-hydroxyandrosta-1,4-diene-3,17-dione (166, 298). The reverse aldol reaction has recently been used in a synthesis of estradiol (72). Treatment of 17β,19-diacetoxyandrost-4-en-3-one (CXX) with selenium dioxide introduces a 1,2 double bond forming the selenium compound CXXI, which on saponification gives estradiol (II) in 80–85% yield.



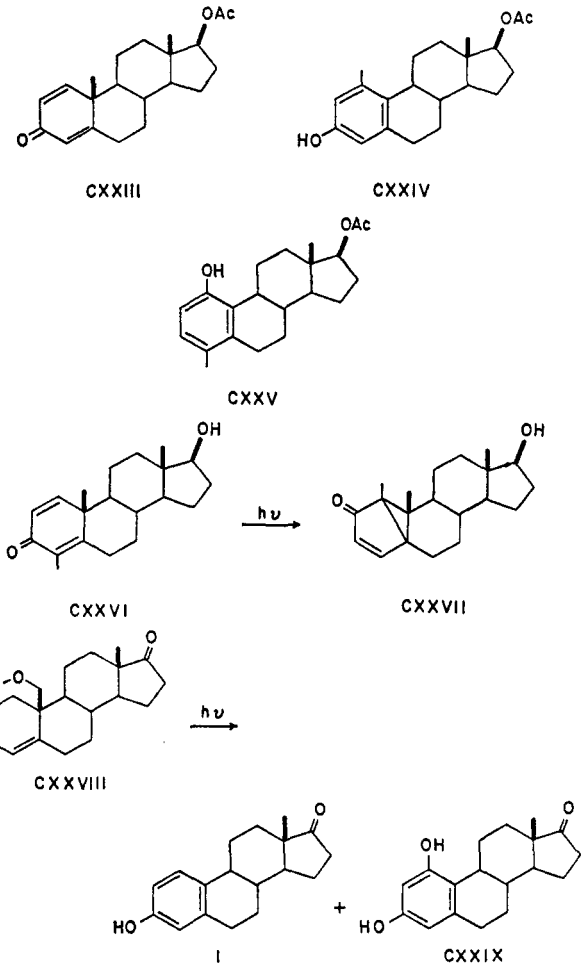
CXIX CXX CXXI XC CXXII IV

A similar reaction was used in the preparation of equilin. A 1,2 double bond was introduced into 19-acetoxyandrosta-4,7-diene-3,17-dione (XC) by treating it with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). Hydrolysis of the resulting compound CXXII with sodium methoxide gave equilin (IV) (24).

d. Photochemical Reactions

Ultraviolet irradiation of 17β-acetoxyandrosta-1,4-dien-3-one (CXXIII) in dioxane is reported to give a mixture of ketonic and phenolic compounds (86, 127, 340). Two of the phenolic compounds were identified, one as 3,17β-dihydroxy-1-methylestra-1,3,5(10)-triene 17-acetate (CXXIV), and the other as 1,17β-dihydroxy-

4-methylestra-1,3,5(10)-triene 17-acetate (CXXV). When the reaction was performed in methanol the major product was the 1-methylphenol (CXXIV) (340).

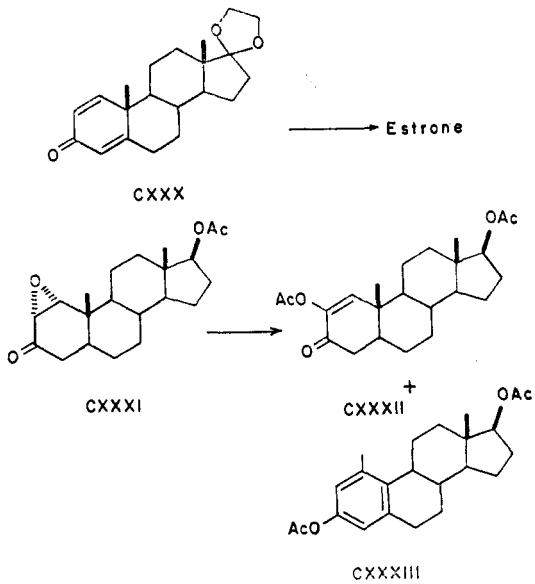


The presence of a methyl substituent at C-4 profoundly affects the course of the photochemical isomerization of cross-conjugated steroidal dienones. Ultraviolet irradiation of 17β-hydroxy-4-methylandrosta-1,4-dien-3-one (CXXVI) gives only the lumiproduct CXXVII (446). Insufficient work has been done on these reactions to discuss the mechanism, but various possibilities have been considered by Chapman (83).

A recent publication describes the formation of estrone in a photochemical reaction. Ultraviolet irradiation of 19-hydroxyandrost-4-ene-3,17-dione nitrite (CXXVIII) gave a mixture of three compounds, two of which were identified. One, obtained in 2% yield, was shown to be estrone (I) and the other, obtained in 5% yield, was identified as 1-hydroxyestrone (CXXIX) (216).

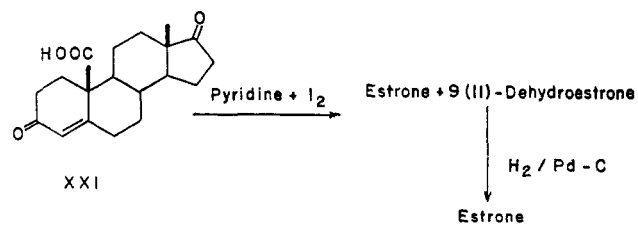
e. Miscellaneous Reactions

Estrone has been prepared in 75% yield from the 17-ethylene ketal of androsta-1,4-diene-3,17-dione (CXXX). Treatment of the ketal CXXX with an excess of the radical anion derived from lithium metal and biphenyl in boiling tetrahydrofuran solution effects the aromatization of the A ring with expulsion of the angular methyl group as methyllithium. After hydrolysis estrone was obtained in 55% yield. The over-all yield of estrone was increased to 75% by the addition to the reaction mixture of a suitably acidic hydrocarbon (*e.g.*, diphenylmethane, methylnaphthalene) which intercepts the by-product methyllithium and prevents its addition to the carbonyl group of the ketal CXXX (124, 125).



When 17β-acetoxy-1α,2α-oxido-5α-androstan-3-one (CXXXI) was treated with *p*-toluenesulfonic acid in acetic anhydride, the expected 2,17β-diacetoxy-5α-androst-1-en-3-one (CXXXII) was isolated as a minor product. The major product from this reaction was identified as the diacetate of 1-methylestradiol (CXXXIII) (236).

Estrone has been prepared in 70% yield from 10β-carboxyestr-4-ene-3,17-dione (XXI). When the carboxy compound XXI was refluxed in pyridine containing 2 equiv of iodine, a mixture of estrone and 9(11)-dehydroestrone was obtained. Hydrogenation of this mixture gave estrone (415).



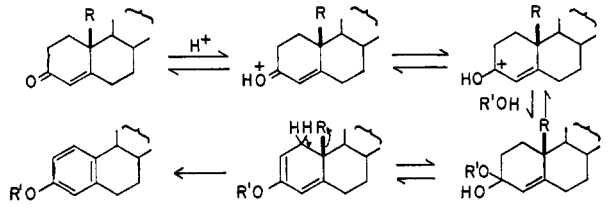
3. Aromatization of A Ring Involving Expulsion of C-10 Groups

a. Aromatization of 10-Substituted Estr-4-en-3-ones

These reactions can be carried out in either acidic or

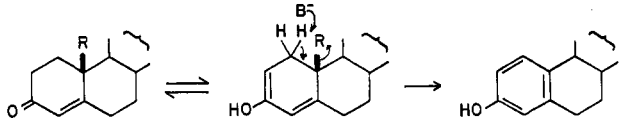
basic media. The acid-catalyzed reaction (Chart IX) probably proceeds *via* ketal or hemiketal formation, followed by rapid elimination of water or alcohol and loss of a proton at C-1 with expulsion of the C-10 substituent (3). In the base-catalyzed aromatization (Chart X), enolization of the 3-ketone and expulsion of the elements of acetic acid probably occur (3).

CHART IX



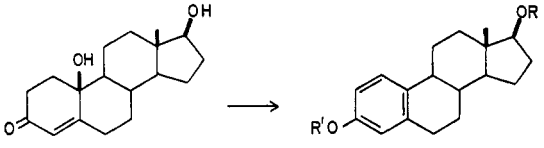
R = -OH, -OAc, -Br
R' = H or alkyl group

CHART X



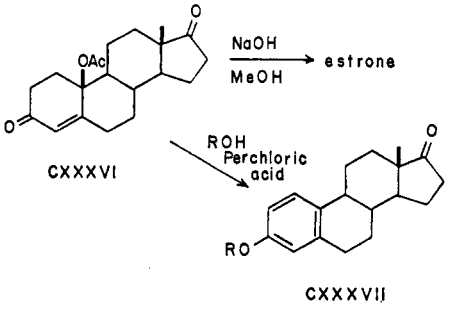
R = -OAc

This type of aromatization reaction was first carried out in 1956 when acid treatment of 10β,17β-dihydroxyestr-4-en-3-one (CXXXIV) was reported to give estradiol (CXXXV, R = R' = H) (305). Later, estradiol 17-acetate (CXXXV, R = Ac; R' = H) was obtained in 80% yield by treating CXXXIV with a mixture of hydrochloric and acetic acids at 5–10° (337). The rate of aromatization of CXXXIV with hydrochloric acid was found to be extremely slow at a concentration of H^+ below 3 *M* (242). Estradiol 3-methyl ether (CXXXV, R = H; R' = Me) was isolated in 85% yield when 10β,17β-dihydroxyestr-4-en-3-one (CXXXIV) was treated with methanol containing perchloric acid (150).



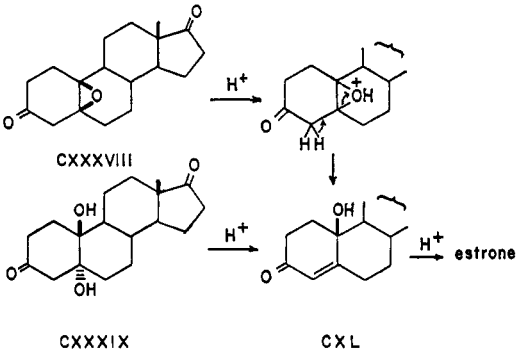
CXXXIV CXXXV

Both the acid- and base-catalyzed aromatizations of 10β-acetoxyestr-4-ene-3,17-dione (CXXXVI) were examined by Alvarez. Estrone was obtained in 98% yield when the 10β-acetoxy compound CXXXVI was treated in methanol with sodium hydroxide (3, 4). However, when the 10β-acetoxy compound CXXXVI was dissolved in anhydrous methanol containing a catalytic amount of perchloric acid and kept at room temperature for 48 hr, estrone methyl ether (CXXXVII, R = Me) was isolated in 80% yield. Similarly, when the reaction was performed in ethanol, estrone ethyl ether (CXXXVII, R = Et) was obtained in 72% yield, and estrone *n*-amyl ether (CXXXVII, R = *n*-amyl) was isolated in 44% yield when the reaction was carried out in *n*-amyl alcohol (3, 4).



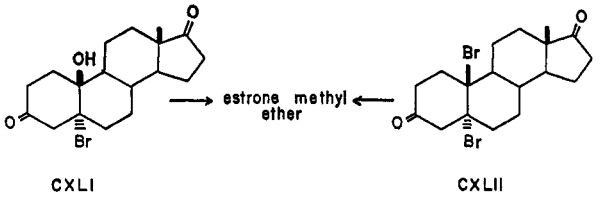
CXXXVI CXXXVII

At the same time as this work was being done, similar work was being performed in Italy. However, instead of starting with a 10-substituted estr-4-en-3-one, most of the work was carried out using 5,10-disubstituted 3-oxo-19-norsteroids. These compounds on treatment with acid yield aromatic A-ring steroids, and it can be postulated that they are converted to a 10-substituted estr-4-en-3-one during the reaction. For example, estrone was obtained in 87% yield when 5β,10β-oxidoestra-3,17-dione (CXXXVIII) was refluxed for 1 hr with acetone containing a few drops of concentrated hydrochloric acid (150). 5α,10β-Dihydroxyestra-3,17-dione (CXXXIX) when similarly treated gave a 90% yield of estrone. The 10β-hydroxy compound CXL can be postulated as an intermediate in these reactions.



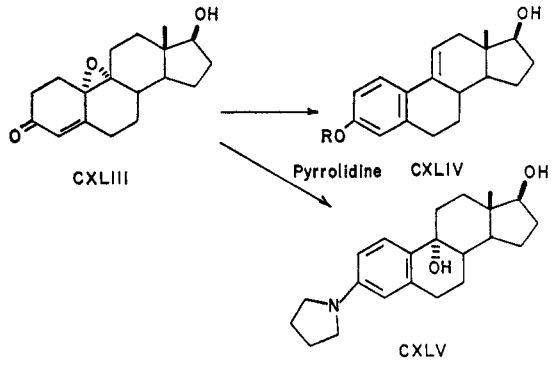
CXXXVIII CXXXIX CXL

Estrone methyl ether was obtained in 72% yield when 5α-bromo-10β-hydroxyestra-3,17-dione (CXLI) was heated in methanol for 30 min. Estrone methyl ether was similarly prepared from 5α,10β-dibromoestra-3,17-dione (CXLII) (*cf.* 306). Acid was not added to these reactions since the hydrogen bromide eliminated from the starting materials acts as a catalyst.



CXLI CXLII

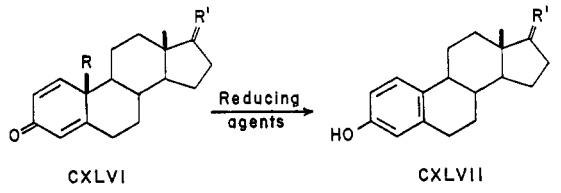
In a recent publication, 17β-hydroxy-9α,10α-oxidoestr-4-en-3-one (CXLIII) was reported to undergo aromatization of the A ring when treated with either acids or bases (137). When the epoxide CXLIII was treated with a 5% solution of potassium hydroxide in methanol, 9-dehydroestradiol (CXLIV, R = H) was isolated in 74% yield. However, when treated with methanol containing a catalytic amount of perchloric acid, the epoxide CXLIII yielded 9-dehydroestradiol 3-methyl ether (CXLIV, R = CH_3). The suggested mechanisms for these reactions are similar to those outlined in Charts IX and X, but in the above cases 9α-hydroxy compounds are presumably the intermediates to the 9-dehydrosteroids. When pyrrolidine was used as the base, it was possible to isolate 3-(1-pyrrolidino)estra-1,3,5(10)-triene-9α,17β-diol (CXLV).



b. Aromatization of 10-Substituted Estra-1,4-dien-3-ones

The general reaction CXLVI → CXLVII has rarely been used for the preparation of aromatic A-ring steroids since the 1,4-dien-3-ones (CXLVI) are usually derived from the aromatic compounds themselves. In the few reported instances of this type of reaction, the most common reducing agent is zinc in acetic acid. For example, treatment of 10β-hydroxyestra-1,4-diene-3,17-dione (CXLVI, R = OH, R′ = O) with zinc in acetic acid resulted in the formation of estrone (156) (CXLVII, R′ = O), and 10β,17β-dihydroxyestra-1,4-dien-3-one (CXLVI, R′ = OH (β), H (α); R = OH), when treated with zinc in acetic acid, yielded estradiol (CXLVII, R′ = OH (β), H (α)), (178). Estradiol was also formed when 10β-fluoro-17β-hydroxyestra-1,4-dien-3-one (CXLVI, R′ = OH (β), H (α); R = F) was treated with sodium borohydride or was hydrogenated using Raney nickel as a catalyst (285). Other catalysts have also been used to bring about the aromatization. For example, estrone was isolated after hydrogenation of 10β-acetoxyestra-1,4-diene-3,17-dione (CXLVI, R′ = O; R = OAc) (156) using palladium on charcoal.

Treatment of 10β-hydroxyestra-1,4-diene-3,17-dione (CXLVI, R = OH; R′ = O) with phosphorus tribromide resulted in a 10% yield of the unexpected



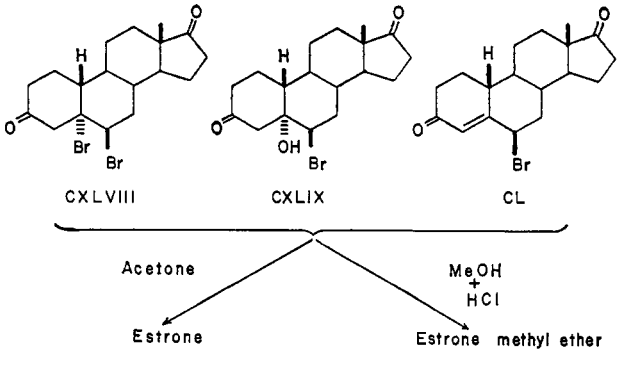
6-dehydroestrone. A mechanism has been proposed for this reaction (156).

Unlike the irradiation of C-19 steroidal 1,4-dien-3-ones where a mixture of ketonic and phenolic compounds is formed (see section VI.A.2.d), the irradiation of 10β,17β-diacetoxyestra-1,4-dien-3-one (CXLVI, R = OAc; R′ = OAc (β), H (α)) with monochromatic light of 254 mμ yielded estradiol 17-acetate (CXLVII, R′ = OAc (β), H (α)) as the major product (445).

4. A-Ring Aromatization of 19-Norsteroids Unsubstituted at C-10

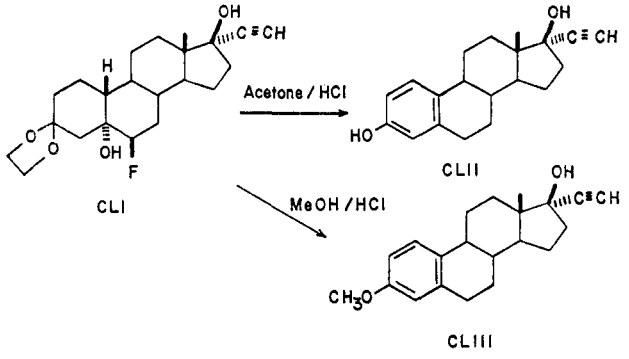
a. Aromatization of 5,6-Disubstituted 3-Oxo-19-norsteroids

The title compounds have been found to undergo aromatization of the A ring when heated in a suitable solvent in the presence of catalytic amounts of a strong acid (149). The most reactive of these compounds are the 6β-bromo derivatives. For example, estrone was isolated in 70–75% yield when 5α,6β-dibromoestra-3,17-dione (CXLVIII), 5α-hydroxy-6β-bromoestra-3,17-dione (CXLIX), or 6β-bromoestr-4-ene-3,-17-dione (CL) was heated under reflux for 3 hr in acetone containing a few drops of concentrated hydrochloric acid. These bromo compounds also spontaneously lose hydrogen bromide and aromatize even in the solid state at room temperature. The same compounds (CXLVIII, CXLIX, and CL) when refluxed in methanol for 30 min afforded estrone methyl ether (80–90% yield). The aromatization of halo derivatives other than bromo required an acid catalyst. For

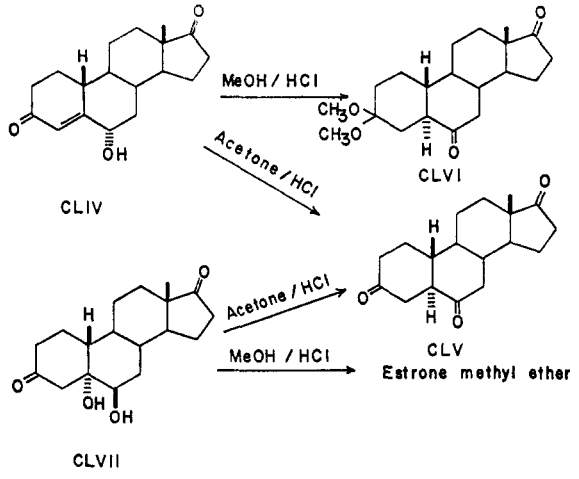


example, the ethylene ketal of 5α,17β-dihydroxy-6β-fluoro-17α-ethynylestr-3-one (CLI), when refluxed in acetone containing hydrochloric acid, gave a 60% yield of 17α-ethynylestradiol (CLII). 17α-Ethynylestradiol 3-methyl ether (CLIII) was obtained in 75%

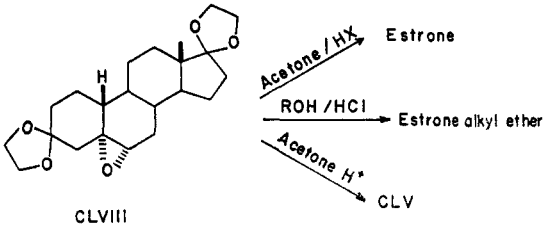
yield by heating the ketal CLI in methanol for 30 min with a small amount of hydrochloric acid.



6α-Hydroxyestr-4-ene-3,17-dione (CLIV) did not aromatize when heated in the presence of acids. 5α-Estra-3,6,17-trione (CLV) was obtained when the 6α-hydroxy compound CLIV was heated in acetone containing hydrochloric acid. The corresponding dimethyl ketal CLVI was obtained when the reaction was performed in methanol. The 5α,6β-diol CLVII also yielded the triketone CLV when treated in acetone, but when the reaction was carried out in methanol estrone methyl ether was obtained.



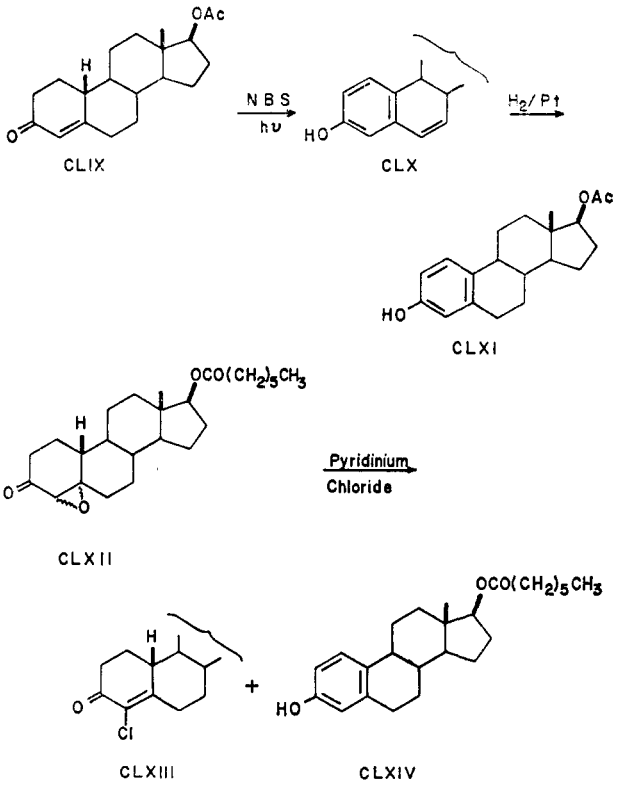
The epoxide CLVIII reacts in a similar way to the diol CLVII. When epoxide CLVIII was treated with acetone and a hydrogen halide, estrone was formed, indicating that oxide fission to a halohydrin is the first step in this reaction. However, treatment of the epoxide CLVIII in acetone containing acids such as sulfuric, *p*-toluenesulfonic, or perchloric resulted in the formation of the triketone CLV. When the epoxide was treated with an alcohol containing a hydrogen halide, the corresponding alkyl ether of estrone was formed. The reactions, which have been described in this section, were all carried out by Gardi and Pedrali who have proposed mechanisms to account for the various products (149).



b. Miscellaneous Reactions

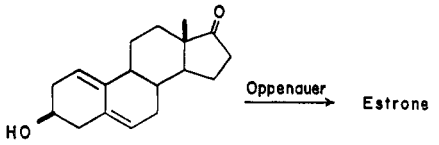
The aromatization of 17β-acetoxyestr-4-en-3-one (CLIX) to estradiol 17-acetate (CLXI) was effected by the use of N-bromosuccinimide in refluxing carbon tetrachloride, the reaction being catalyzed by light from a photoflood lamp. The intermediate, 6-dehydroestradiol 17-acetate (CLX), was hydrogenated using Adam's catalyst and the aromatic product (CLXI) was isolated in 60% yield (168).

An 18% yield of estradiol 17-heptanoate (CLXIV) was unexpectedly isolated from the reaction of 17β-hydroxy-5ξ,6ξ-oxidoestr-3-one heptanoate (CLXII) with pyridinium chloride. The expected product, 17β-hydroxy-4-chloroestr-4-en-3-one heptanoate (CLXIII),



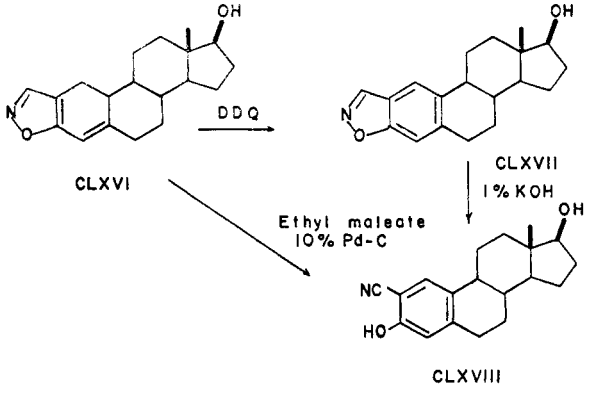
was also obtained in 13% yield (462). The Oppenauer oxidation has been used to prepare estrone in 82% yield from 3β-hydroxyestr-1(10),5-dien-17-one (CLXV) (414).

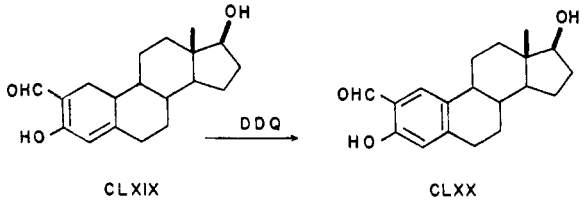
Several interesting dehydrogenation reactions leading to the formation of aromatic A-ring compounds have recently been reported by de Ruggieri, Gandolfi, and Guzzi (338). The isoxazole CLXVI when treated



CLXV

with ethyl maleate in refluxing dioxane containing palladium on carbon afforded 2-cyanoestra-1,3,5(10)-triene-3,17β-diol (CLXVIII). This reaction probably proceeds through the benzoisoxazole CLXVII which was isolated when the isoxazole CLXVI was dehydrogenated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Alkaline hydrolysis of CLXVII gave CLXVIII.



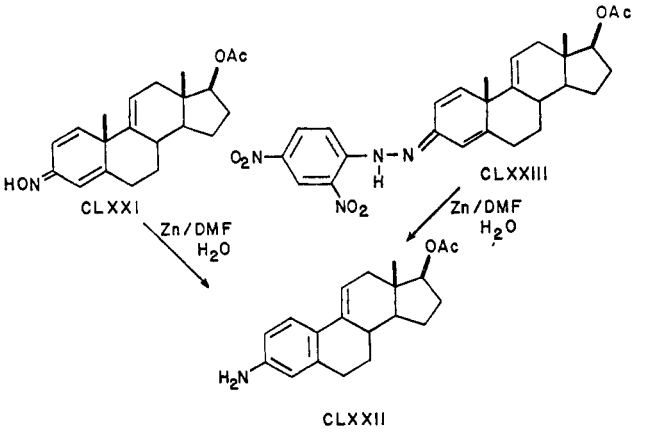


Dehydrogenation of 2-hydroxymethylene-17β-hydroxyestr-4-en-3-one (CLXIX) with DDQ gave the aromatic compound CLXX.

5. *Formation of Ring-A Aromatic Steroids with a Function Other than Oxygen at C-3*

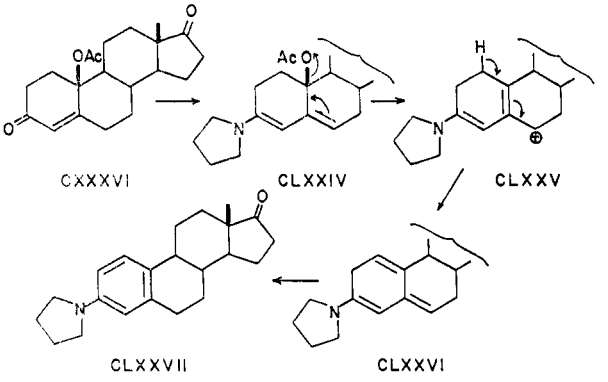
Interest in steroidal estrogens having any function other than oxygen at C-3 is of fairly recent origin (none were prepared until 1959), and as yet there are few examples of this type of compound to be found in the literature.

Tsuda and his co-workers (429) in their studies on the aromatization of cross-conjugated dienone systems with zinc (see section VI.A.2.b) have prepared 3-amino-17β-acetoxyestra-1,3,5(10),9(11)-tetraene (CLXXII) from 17β-acetoxyandrosta-1,4,9(11)-trien-3-one oxime (CLXXI). Treatment of CLXXI with zinc in refluxing dimethylformamide (DMF) in the presence of a small amount of water gave the aromatic amine CLXXII in 77% yield. The dinitrophenylhydrazone derivative CLXXIII with similar treatment also yielded CLXXII.



A-Ring anilino steroids had previously been prepared by Gold and Schwenk (157, 361) who synthesized 3-aminoestra-1,3,5(10)-trien-17-one and related compounds from the corresponding 10ξ-acetoxyestra-1,4-diene-3,17-dione by refluxing with benzylamine followed by treatment with dilute sulfuric acid. A similar reaction has been reported recently by Schmialek and Dannenberg (358), and a method for the preparation of 3-aminoestra-1,3,5(10)-trien-17β-ol has been described by Hecker (179, 180).

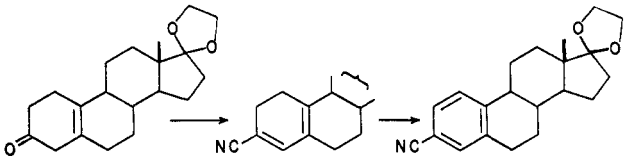
Alvarez and Ruiz (5) found that when a benzene solution of 10β-acetoxyestr-4-ene-3,17-dione (CXXXVI) was treated with a slight excess of pyrrolidine, complete aromatization of the A ring occurred yielding 3-(1-pyrrolidino)estra-1,3,5(10)-trien-17-one (CLXXVII). Aromatizations of CXXXVI with piperidine, diethylamine, and N,N-diethyl-1,2-ethylenediamine required the presence of an acid catalyst. The reaction has been assumed to proceed *via* enamine formation (CLXXIV), followed by anchimerically assisted elimination of acetate (CLXXIV → CLXXVII).



The formation of 3-(1-pyrrolidino)estra-1,3,5(10)-triene-9α,17β-diol (CXLV) in the base-catalyzed aromatization of 17β-hydroxy-9α,10α-oxidoestr-4-en-3-one (CXLIII) (137) has been discussed in section VI.A.3.a. This reaction has also been reported in the patent literature (300).

In 1964 Birch, Hughes, Kruger, and Subba Rao (38) reported a novel method for introducing a carbon func-

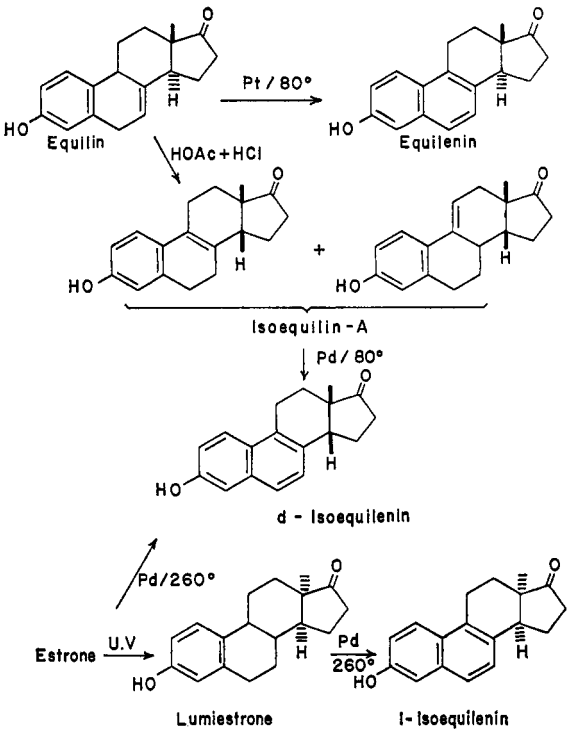
tion at C-3. Addition of hydrogen cyanide to the ketone CLXXVIII followed by dehydration gave CLXXIX, which was dehydrogenated with palladium on carbon to yield the 3-cyano aromatic compound CLXXX.



6. *Formation of Estrogens with Aromatic A and B Rings*

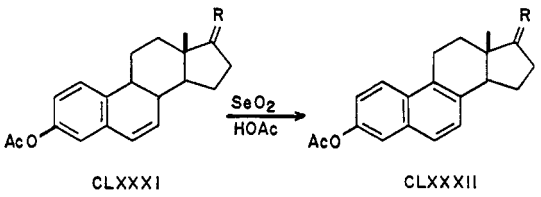
The dehydrogenations of equilin and estrone, leading to ring A, B aromatic compounds, as summarized in Chart XI, have been reviewed by Fieser and Fieser (140).

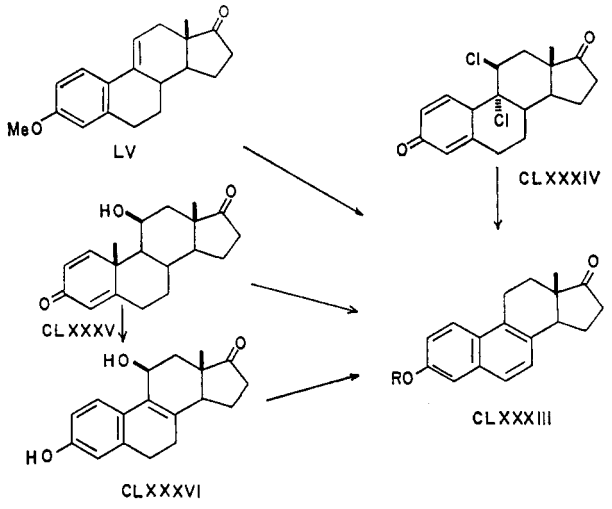
CHART XI



The first partial synthesis of equilenin from nonaromatic steroids was achieved in 1950. The final step was dehydrogenation with selenium dioxide of the acetate of 6-dehydroestrone (CLXXXI, R = O; see section VI.A.2.a) to give equilenin acetate (CLXXXII, R = O) in good yield (238). 17-Dihydroequilenin 17β-acetate (CLXXXII, R = OAc (β), H (α)) was similarly prepared from 6-dehydroestradiol 3,17-diacetate (CLXXXI, R = OAc (β), H (α)) (103, 104).

Equilenin methyl ether (CLXXXIII, R = Me) was formed in 30% yield when 9(11)-dehydroestrone methyl ether (LV) was treated with bromine (427). Treatment of the nonaromatic precursor, 9α,11β-dichloroandrosta-1,4-diene-3,17-dione (CLXXXIV), in refluxing dimethylformamide (DMF) has been reported (185) to give equilenin (CLXXXIII, R = H).





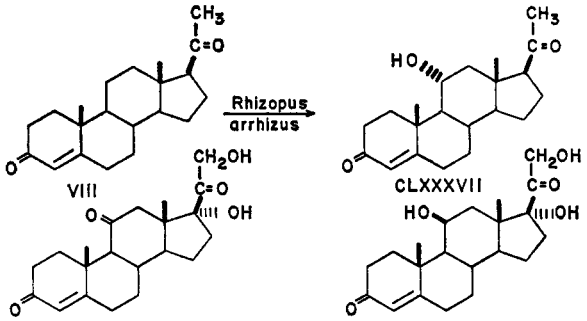
3,11β-Dihydroxyestra-1,3,5(10),8-tetraen-17-one (CLXXXVI), obtained from the diketone CLXXXV by reaction with zinc in dimethylformamide, was converted to equilenin (CLXXXIII, R = H) and equilenin methyl ether (CLXXXIII, R = Me) with hydrochloric acid and dimethyl sulfate, respectively. However, when 11β-hydroxyandrosta-1,4,8-triene-3,17-dione (CLXXXV) was treated with zinc in ethylene glycol, equilenin (CLXXXIII, R = H) was formed directly (428).

B. MICROBIOLOGICAL AROMATIZATIONS

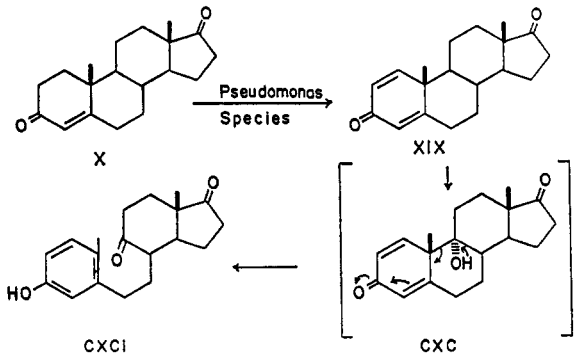
Microorganisms produce enzymes which are capable of catalyzing many reactions which are difficult to perform using ordinary chemical methods. Microbiological reactions are carried out with living, usually growing, cultures of microorganisms, and the compound to be converted is added to the growing culture. This compound is normally not essential for the growth of the microorganism; thus the microbial enzymes may be considered as highly selective chemical reagents which are often capable of performing chemically complicated reactions in a single step (418).

Although microbiological reactions, such as the formation of vinegar and the production of beer, have been known for centuries, it was only with the discovery of penicillin and other antibiotics, during and after the Second World War, that the field of chemical microbiology began to expand. The application of

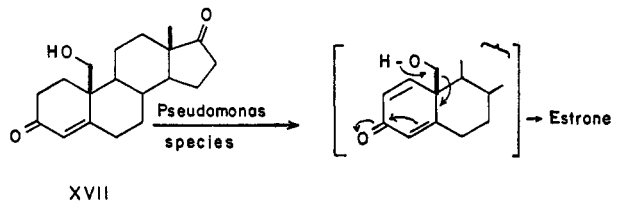
microbiological reactions to steroids was largely ignored until 1952 when Peterson and Murray (307) found that progesterone (VIII) was converted to 11α-hydroxyprogesterone (CLXXXVII) by incubation with cultures of *Rhizopus arrhizus*. At this time there was considerable interest in steroids with an oxygen function at C-11 since the clinical effects of cortisone (CLXXXVIII) and cortisol (CLXXXIX) in the treatment of rheumatic arthritis had just been discovered. The introduction of an oxygen function at the 11 position had previously required numerous chemical operations which could now be performed in a single microbiological step.



The first microbiological aromatization reaction of an alicyclic steroid with a C-19 methyl group was reported in 1958 by Dodson and Muir (106, 108) who isolated 9,10-seco-3-hydroxyandrosta-1,3,5(10)-triene-9,17-dione (CXCI) from the fermentation of androst-4-ene-3,17-dione (X) with a species of *Pseudomonas*. Several different types of microorganisms have since been found capable of effecting the same conversion (108, 360, 371). Dodson and Muir postulated (107–109, 371) that the reaction proceeds through the 1,4-diene (XIX, isolated) to the 9-hydroxylated compound (CXC, not isolated) which undergoes a reverse aldol-type reaction to give the secophenol (CXCI).

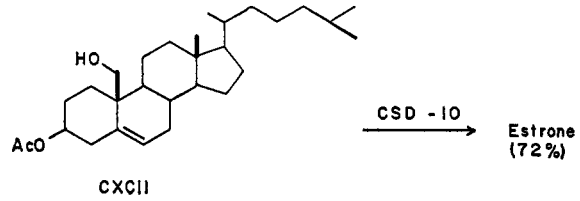


Fermentation of 19-hydroxyandrost-4-ene-3,17-dione (XVII) with this *Pseudomonas* species produced estrone (106, 108).



In order to use microbiological reactions for the preparation of steroidal estrogens, it is essential to begin with either a 19-nor- or preferably a 19-oxosteroid since 19-methylsteroids on fermentation yield the 9,10-secophenols. 19-Oxygenated steroids were found to be better substrates than 19-norsteroids for estrogen formation (253). Until the early 1960's it was difficult to prepare 19-nor compounds except by Birch reduction of aromatic A-ring steroids, and 19-oxo steroids could only be prepared from naturally occurring steroids with an oxygen function at C-19 (*e.g.*, strophanthidin) or by microbiological oxidation of a C-19 methyl group. Since there are very few naturally occurring C-19 oxygenated steroids and since this particular microbiological oxidation is nonselective, the microbiological preparation of estrogens was not an economical proposition. However, with the development of reactions which functionalized the C-19 methyl group (for reviews of these reactions see ref 187 and 459), 19-oxygenated steroids and 19-norsteroids are now readily available.

One of the most significant advances in the application of microbiological aromatization was achieved in 1965 when estrone was isolated in 72% yield from the fermentation of 3β-acetoxy-19-hydroxycholest-5-ene (CXCII, prepared from cholesterol in three chemical steps) with CSD-10 (372).

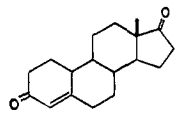
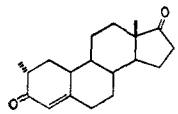
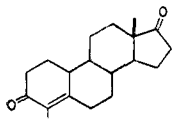
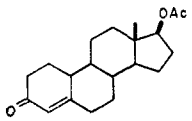
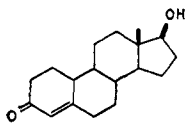
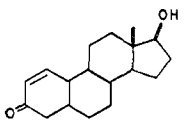
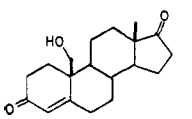
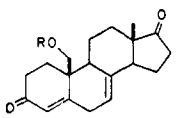
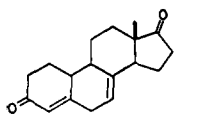
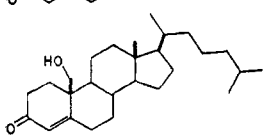
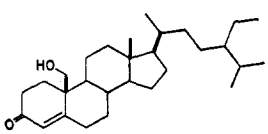


Other microbiological aromatizations leading to the formation of steroidal estrogens are tabulated in Table II.

VII. Heterocyclic Derivatives of Steroidal Estrogens

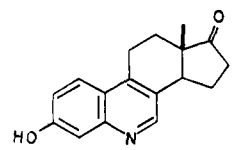
Until 1963 when the total synthesis of 6-azaequilenin (CXCIII) was achieved (64, 65), the only previously recorded heterocyclic analog of a naturally occurring steroidal estrogen was 4-azaestradiol 17-acetate (CXC-IV), first prepared in 1959 (433). Since 1963 there has been a phenomenal increase in the number of publications describing syntheses of heterocyclic de-

TABLE II

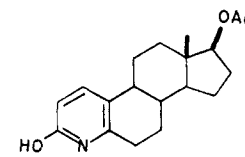
Substrate	Microorganism	Product	Yield, %	Ref
	*Septomyxa affinis*	Estrone Estradiol	55 12	276
	*Septomyxa affinis*	2-Methyl-estrone	17	308
	*Septomyxa affinis*	4-Methyl-estrone	13	308
	*Corynebacterium simplex*	17-β-Estradiol acetate	77	254
	*Pseudomonas testosteroni*	Estrone + little estradiol	67	262
	*Pseudomonas testosteroni*	Estrone + little estradiol	..	263
	Steroid-1-dehydrogenase isolated from *Nocardia restrictus*	Estrone	20	371
	*Nocardia restrictus*	Equilin	20	24
	*Corynebacterium simplex*	Equilin	60	470, 471
	*Nocardia restrictus* CSD-10	Estrone Estrone	8 30	373 373
	CSD-10	Estrone	10	373

rivatives of estrogens. The preparation of compounds of this type is only one aspect of the rapidly developing field of modified steroidal hormones.

Although the relationship between chemical structure and biological activity has not yet been established, several theories, such as the receptor theory of drug action, have been postulated (336), and the applications of such theoretical concepts have led to the synthesis of many modified steroidal hormones, some of which are now in use as drugs. Most of the heterocyclic analogs of the steroidal estrogenic hormones have been prepared as a result of such theories, but, because their syntheses are of recent origin, it is too early to say if any of them have clinical applications.



CXCIII



CXCIV

Interest in heterocyclic steroids over the last few years has resulted in the publication of several reviews. Alauddin and Martin-Smith (1) and Martin-Smith and Sugrue (275) have written reviews on the biological activities of nitrogen-containing steroids; Singh, Parashar, and Padmanabhan (377) surveyed the synthesis of azasteroids using the Beckmann rearrangement and the Schmidt reaction; and Tökés (421) has discussed the insertion of heteroatoms into the steroid nucleus. Reviews by Tilak (420) and Rosseels (335) cover the very early work in this field.

In this review the preparation of heterocyclic analogs of the naturally occurring steroidal estrogens are discussed in parts A and B, and related heterocyclic compounds are listed in Tables III, IV, and V. Only those steroids which have heteroatoms as part of the nucleus are discussed. Steroids having a heterocyclic ring attached to the nucleus have been reviewed by de Ruggieri, Gandolfi, Guzzi, Chiaramonti, and Ferrari (339).

In the total syntheses discussed in parts A and B all structural formulas are drawn to represent one enantiomer although, in fact, all compounds are racemic.

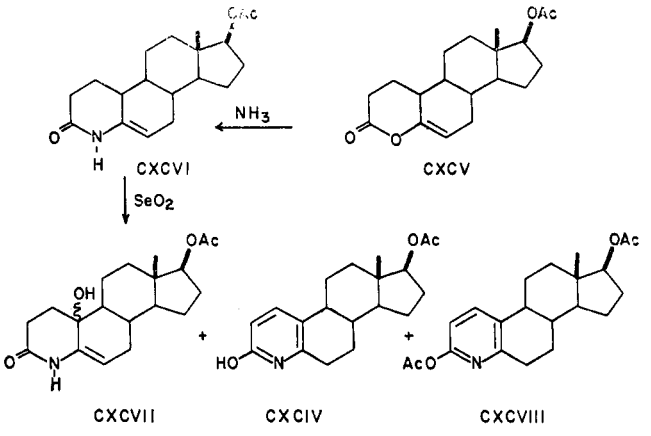
A. AZA ANALOGS OF STEROIDAL ESTROGENS

Azasteroids are by far the most common of the heterocyclic steroids. This is probably due to the fact that an –NH– group is approximately the same size as a methylene group. Consequently the insertion of a nitrogen atom into the steroid nucleus does not distort the shape of the molecule to any great extent. In the following discussion the aza analogs of the steroidal estrogens are grouped according to the position of the nitrogen atom in the nucleus.

1. Nitrogen in Position 4

A 10% yield of 4-azaestradiol 17-acetate (CXCIV) and a 5% yield of 4-azaestradiol 3,17-diacetate (CXCVIII) were isolated from the selenium dioxide oxidation of 17β-acetoxy-4-azaestr-5-en-3-one (CXCVI) (433, 434). The latter was prepared by treatment of 17β-acetoxy-4-oxaestr-5-en-3-one (CXCV) (168) with am-

monia. The major product from this selenium dioxide oxidation was 10ξ,17β-dihydroxy-4-azaestr-5-en-3-one 17β-acetate (CXCVII).

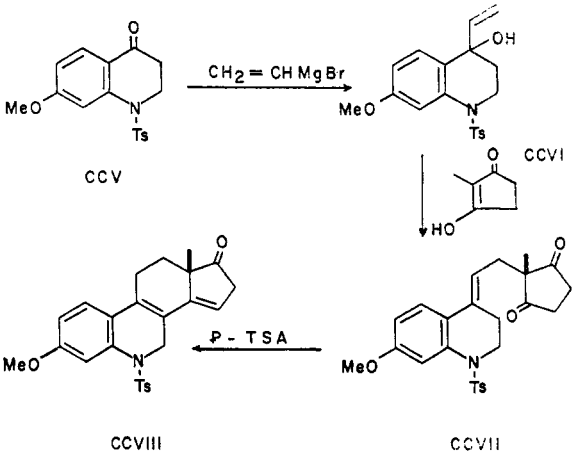


2. Nitrogen in Position 6

The first preparation of 6-azaequilenin (CXCIII) was a 15-step synthesis from *m*-anisidine (CXCIX) by Burckhalter and Watanabe (64, 65) in 1963 (see Chart XII). *m*-Anisidine (CXCIX) with ethyl orthoformate gave the formamidine (CC) which when heated with cyclohexane-1,3-dione gave the tricyclic diketone CCI. Ring closure of CCI with polyphosphoric acid gave the ketone CCII. Application of Johnson's modification of the Stobbe procedure (230, 231) to CCII gave 6-aza-15-carbethoxy-14,15-dehydroequilenin methyl ether (CCIII) in six steps. Sodium borohydride reduction of CCIII to the 17β-hydroxy derivative prevented the 14,15 double bond from shifting to the 15,16 position during hydrolysis. After hydrolysis the hydroxy ester was decarboxylated to CCIV. Hydrogenation of CCIV over palladium on carbon, followed by oxidation and demethylation, gave 6-azaequilenin (CXCIII).

In 1964 a total synthesis of 6-azaequilenin (CXCIII), which was based on an adaptation of Torgov's estrone synthesis (7, 423), was published independently by Smith, Douglas, and Walk (385), and by Huisman, Speckamp, de Koning, and Pandit (206). The method described by the two groups of workers is virtually identical, but, because the Dutch group has developed this synthesis to include the preparation of other 6-aza derivatives of the steroidal estrogens (394), for example, 6-azaestrone, the following discussion deals mainly with their work.

Treatment of the quinolone CCV[3] (395) with vinylmagnesium bromide gave the vinyl alcohol CCVI which was condensed with 2-methylcyclopentane-1,3-



dione to give the diketone CCVII. Cyclodehydration of CCVII with *p*-toluenesulfonic acid afforded CCVIII in good yield. The scheme outlined in Chart XIII shows how CCVIII was converted to 6-azaequilenin (CXCIII) and 6-azaestrone (CCXVII).

Catalytic reduction of CCVIII over palladium on

(3) Smith, Douglas, and Walk (385) used the benzenesulfonate derivative.

CHART XII

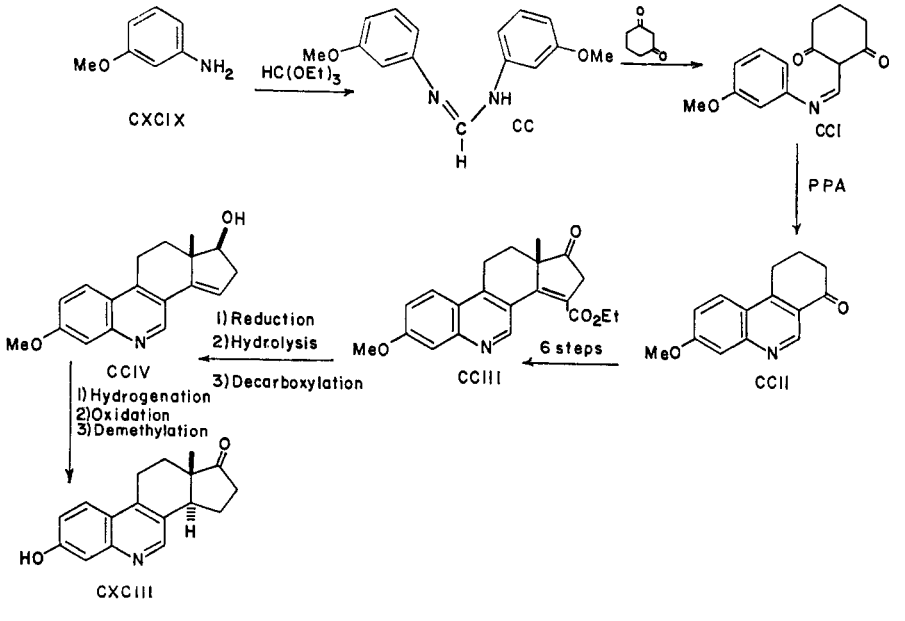
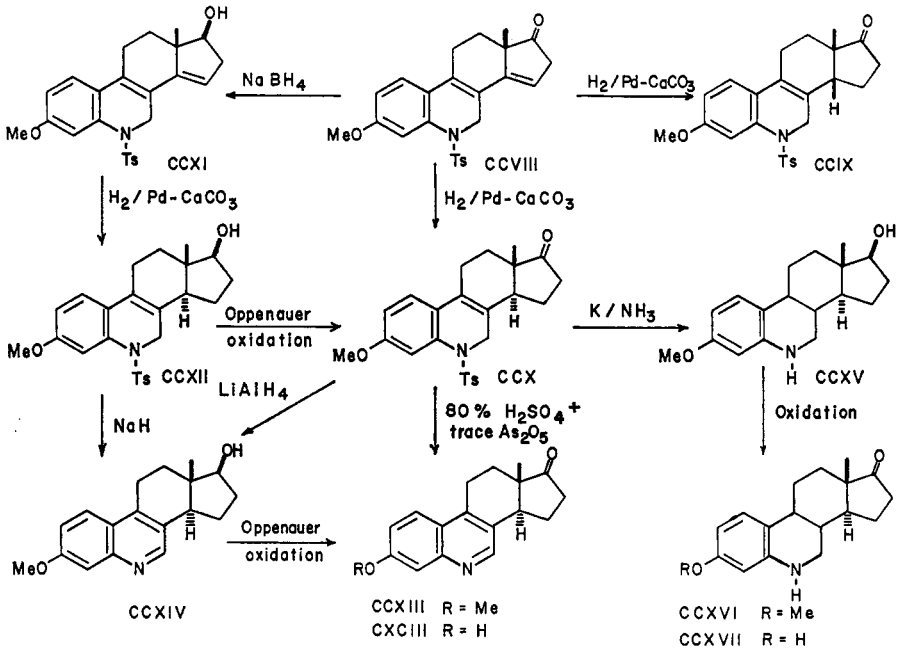


CHART XIII



calcium carbonate gave a mixture of two 14,15 dihydro ketones, one the 14β-compound CCIX and the other the 14α-compound CCX. Contrary to the observation in the analogous carbocyclic system (120, 460), the major product of this reduction was the 14β-compound CCIX. The bulk of the tosyl group was suggested as a reason for this unexpected reversal.

To overcome this unfavorable distribution of isomers, the tosyl ketone CCVIII was reduced with sodium borohydride (30) to the 17β-alcohol CCXI which on hydrogenation gave the 14α-alcohol CCXII in 73% yield. Oppenauer oxidation of CCXII afforded ketone CCX which was converted, in low yield, to 6-azaequilenin methyl ether (CCXIII) by refluxing with 80% sulfuric acid containing a trace of arsenic pentoxide. A better approach to the azaequilenin methyl ether (CCXIII) was *via* the quinoline derivative CCXIV, obtained by oxidative detosylation of CCXII. CCXIV was also obtained by treating the tosyl ketone CCX with lithium aluminum hydride in tetrahydrofuran. Oppenauer oxidation of CCXIV gave 6-azaequilenin methyl ether (CCXIII) which, on demethylation with pyridine and hydrochloric acid, yielded 6-azaequilenin (CXCIII).

When the ketone CCX was treated in liquid ammonia with a two- to threefold excess of potassium, a 35% yield of the 6-azaestradiol derivative CCXV was isolated. Oppenauer oxidation of alcohol CCXV afforded 6-azaestrone methyl ether (CCXVI) which could be demethylated to the unstable 6-azaestrone (CCXVII). A similar preparation of 6-azaestrone has recently been described (432).

3. *Nitrogen in Position 8*

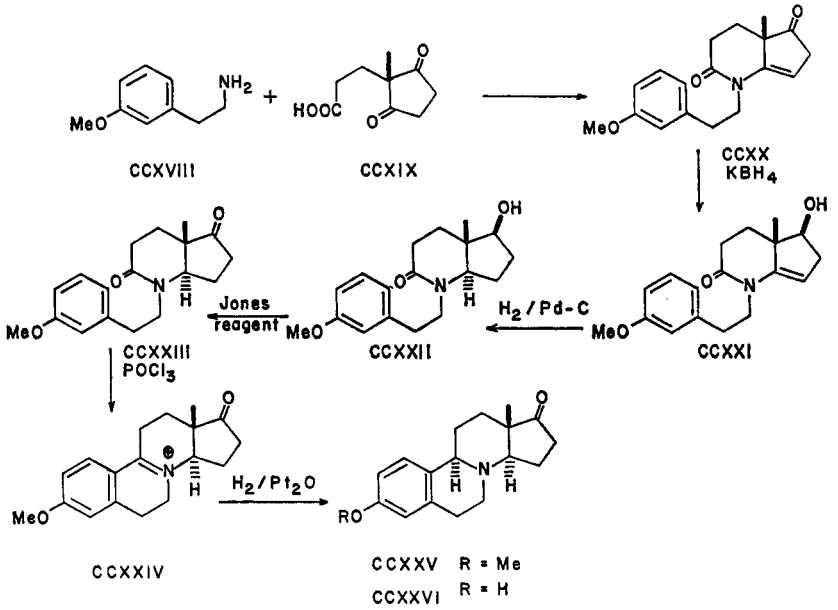
To date there are three reported total syntheses of 8-azaestrone. The first of these was described in preliminary form in 1963 by Meltzer, Lustgarten, Stanaback, and Brown (278). A detailed report of their synthesis, as outlined in Chart XIV, has recently been published (62, 277). 8-Azaestrone was the first azasteroid synthesized in which the nitrogen atom is common to two rings.

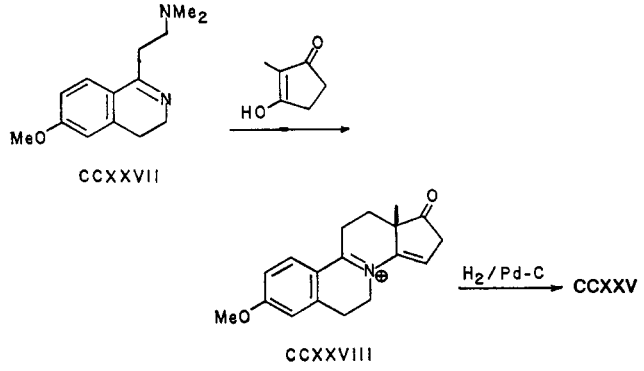
Condensation of *m*-methoxyphenethylamine (CCXVIII) with the diketone CCXIX resulted in a 50% yield of the lactam CCXX. In order to achieve stereospecific reduction of the 14,15 double bond to the 14α isomer, lactam CCXX was reduced with potassium borohydride to its 17β-hydroxy derivative (CCXXI). This hydroxy compound (CCXXI) when hydrogenated over palladium on carbon gave a 75% yield of the *trans*-alcohol CCXXII which was oxidized with Jones reagent to the lactam CCXXIII. Treatment of lactam CCXXIII with phosphorus oxychloride gave a good yield of the quaternary salt CCXXIV which was catalytically reduced to 8-azaestrone methyl ether CCXXV. Demethylation afforded 8-azaestrone (CCXXVI). Infrared and nmr evidence suggest that the 8-azaestrone obtained from this synthesis exists in the 9α,13β,14α configuration as shown in CCXXVI.

The second total synthesis for 8-azaestrone was published in 1965 by Clarkson (88). Condensation of the dimethylaminoisoquinoline (CCXXVII, prepared in three steps from *m*-methoxyphenethylamine (CCXVIII) with 2-methylcyclopentane-1,3-dione gave a 55–60% yield of the dienamine CCXXVIII, which on hydrogenation over palladium on carbon afforded only 8-azaestrone methyl ether (CCXXV) in excellent yield.

The third 8-azaestrone synthesis was published recently by Meyers and Sircar (282). As can be seen

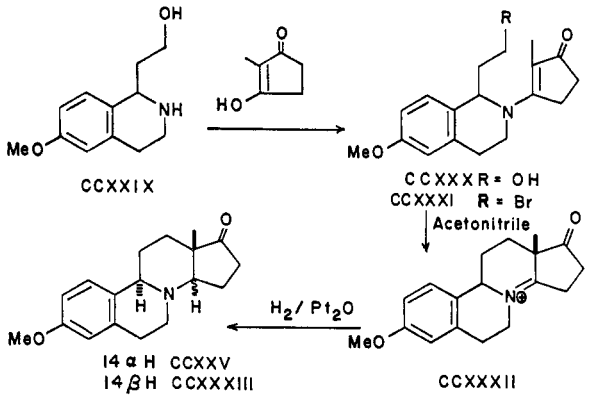
CHART XIV





from Chart XV, this synthesis is similar in some respects to that of Clarkson.

CHART XV

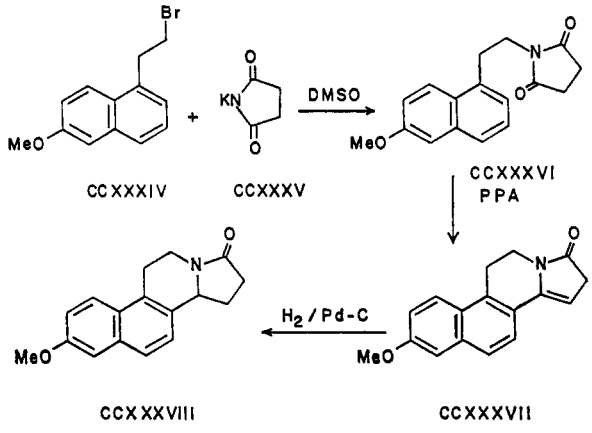


The isoquinoline alcohol CCXXIX, when condensed with 2-methylcyclopentane-1,3-dione, gave a 94% yield of the enamino ketone CCXXX which was quantitatively transformed to the bromide CCXXXI. The latter was cyclized in acetonitrile to give the unstable iminium salt CCXXXII which was reduced to a 55:45 mixture of 14α- (CCXXV) and 14β- (CCXXXIII) 8-azaestrone methyl ethers. The stereochemical assignments of CCXXV and CCXXXIII were based on infrared and nmr evidence.

4. *Nitrogen in Position 13*

When a nitrogen atom occupies position 13, the C-18 methyl group is absent. In 1965 Birch and Subba Rao (39) published a simple total synthesis of 13-aza-18-norequilenin methyl ether (CCXXXVIII). Their synthesis is shown in Chart XVI.

CHART XVI



Condensation of the bromide CCXXXIV with potassium succinimide (CCXXXV) in dimethyl sulfoxide (DMSO) gave the succinimide compound CCXXXVI which cyclized in polyphosphoric acid to 14-dehydro-13-aza-18-norequilenin methyl ether (CCXXXVII). Hydrogenation of the latter gave 13-aza-18-norequilenin methyl ether (CCXXXVIII).

Later in 1965, Kessar, Singh, and Kumar (241) published a different synthesis of 13-aza-18-norequilenin methyl ether (Chart XVII).

TABLE III
AZASTEROIDS

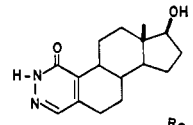
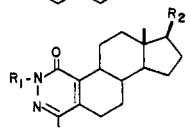
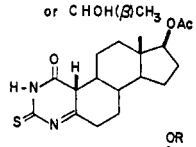
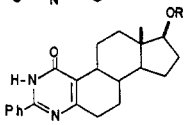
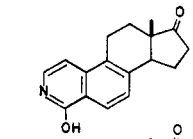
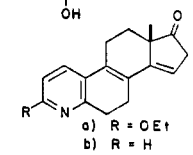
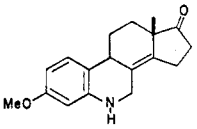
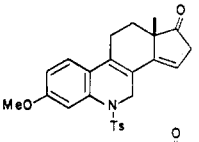
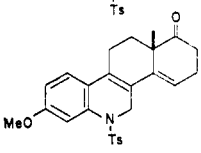
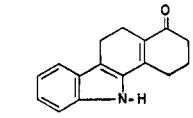
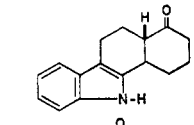
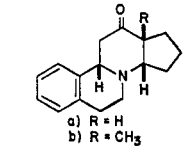
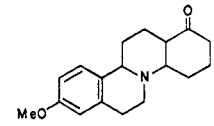
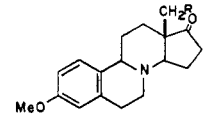
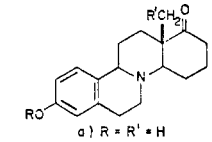
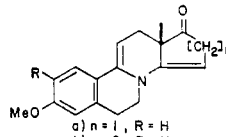
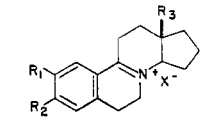
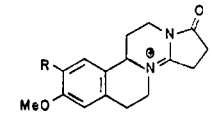
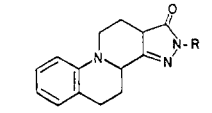
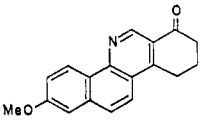
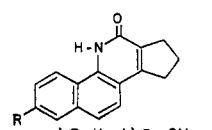
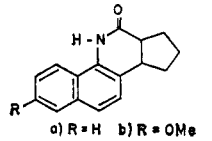
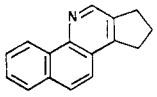
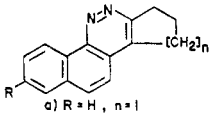
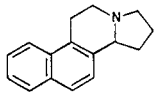
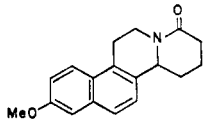
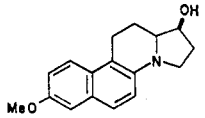
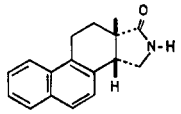
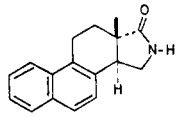
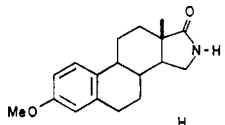
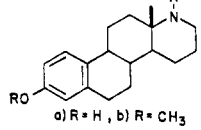
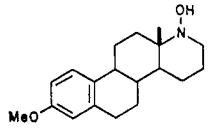
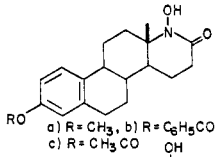
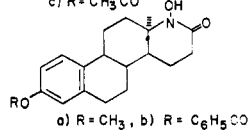
Position(s) of N atom(s)	Structural formula	Method of prepn[a]	Ref
2, 3		PS	75
2, 3	 R_1 = H or Me; R_2 = OH, $COCH_3$ or $CHOH(\beta)CH_3$	PS	311
2, 4		PS	77, 310
2, 4	 a) R = H; b) R = $COCH_3$	PS	310
3		PS	291
4	 a) R = OEt; b) R = H	TS	381
6		TS	442
6		TS	207
6		TS	207
6-B-nor		TS	420
6-B-nor		TS	420
8	 a) R = H; b) R = CH_3	TS	281, 391
8		TS	297
8	 a) R = Me; b) R = Et	TS	88, 209, 277
8	 a) R = R' = H; b) R = Me, R' = H; c) R = R' = Me; d) R = Me, R' = Et	TS	88, 209, 277
8	 a) n = 1, R = H; b) n = 2, R = H; c) n = 1, R = OMe; d) n = 2, R = OMe	TS	208
8	 R_1 = H, OH or OMe; R_2 = OH or OMe; R_3 = H or Me; X = Br or I	TS	61, 277
8, 13	 a) R = H; b) R = OMe	TS	63
9, 15, 16	 a) R = H; b) R = C_6H_5	TS	234, 357
11		TS	240
11	 a) R = H; b) R = OMe	TS	90
11	 a) R = H; b) R = OMe	Sodium amalgam reduction of above compd	90

TABLE III (*Continued*)

Position(s) of N atom(s)	Structural formula	Method of prepn[a]	Ref
11		Reduction of above compd followed by dehydrogenation	90
11, 12	 a) R = H, n = 1 b) R = OMe, n = 1 c) R = H, n = 2 d) R = OMe, n = 2	TS	48 458
13		TS	356
13		TS	39
14		TS	233
16		PS	23
16		PS	23
16		PS	29
17a-D-homo	 a) R = C_6H_5CO b) R = C_6H_5CO, CH_3, H	Beckmann rearrangement of corresponding 17-oxime	237 319
17a-D-homo	 a) R = H, b) R = CH_3	Lithium aluminum hydride reduction of b(R = CH_3 and H) above	319
17a-D-homo		Thermal decompn of N-ethyl oxide derivative	316
17a-D-homo	 a) R = CH_3, b) R = C_6H_5CO c) R = CH_3CO	Photolysis of corresponding 17-nitrite deriv gives mixt of 13α and 13β compds; see following example	330 331
17a-D-homo	 a) R = CH_3, b) R = C_6H_5CO	See above	302 330

[a] PS indicates partial synthesis, *i.e.*, the compound has been prepared by degrading one ring (either ring A or D) of a tetracyclic steroid followed by recyclization. TS indicates total synthesis. All heterocyclic estrogens which have a heteroatom in ring B or C have been prepared by total synthesis.

The amine CCXXXIX, when condensed with β-carbomethoxypropionyl chloride, gave the amide CCXL which on cyclization gave a mixture of ketone CCXLI and diketone CCXXXVI. Hydrogenation of CCXLI followed by thermal cyclization afforded 13-aza-18-norequilenin methyl ether (CCXXXVIII). It is interesting to note that these workers were unable to cyclize CCXXXVI under conditions similar to those successfully employed by Birch and Subba Rao.

B. 6-OXAESTRONE METHYL ETHER

Considering the growing interest during recent years in the synthesis of heterocyclic steroids it is surprising that so few oxaestrogens have been prepared. In 1964

CHART XVII

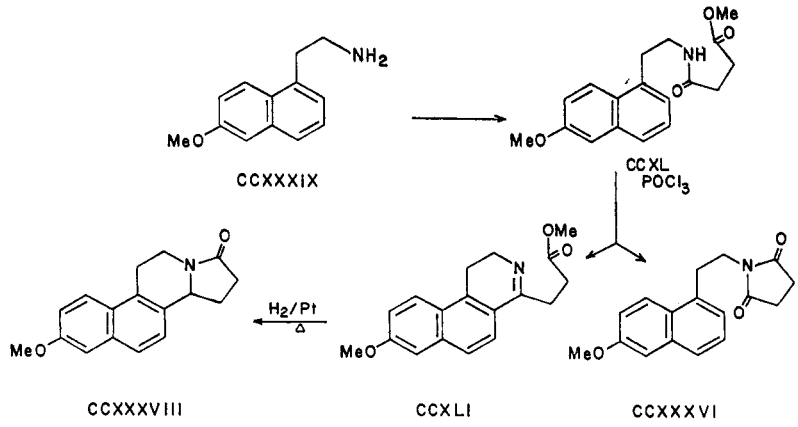
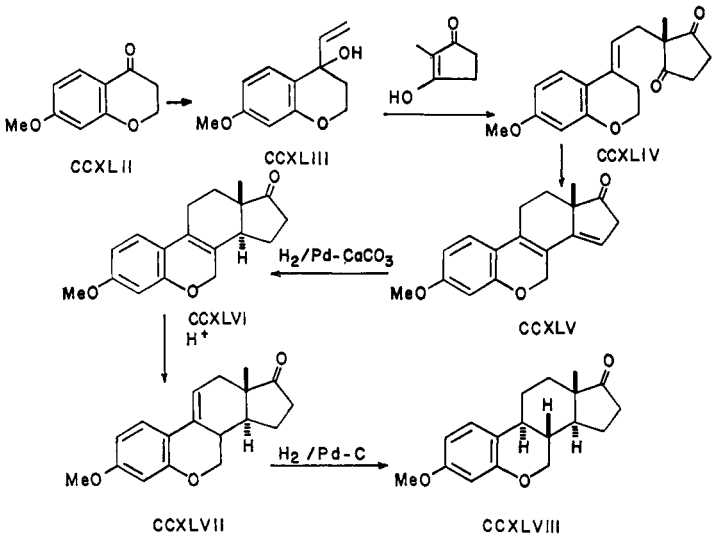


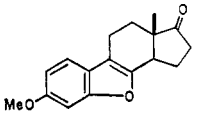
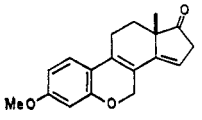
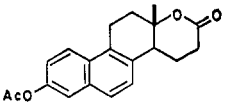
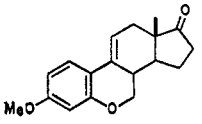
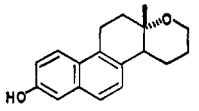
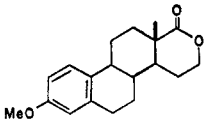
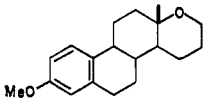
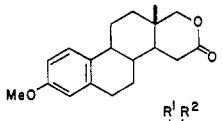
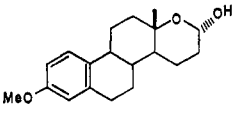
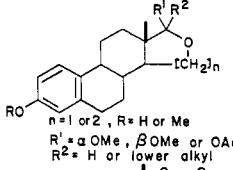
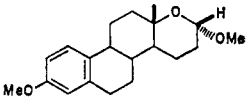
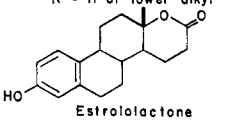
CHART XVIII



Smith, Douglas, and Walk (204, 384, 385) described a total synthesis of 6-oxaestrone methyl ether (CCXLVIII, see Chart XVIII) which is very similar to their synthesis of 6-azaequilenin mentioned in section VII.A.2.

Vinylmagnesium chloride converted the chromanone

TABLE IV
OXASTEROIDS

Position of O atom	Structural formula	Method of prepn[a]	Ref	Position(s) of N atom(s)	Structural formula	Method of prepn[a]	Ref
6-B-nor		TS	37 420				
6		TS	205	17a-D-homo		Peracid on equilenin acetate	221[b]
6		From above compd by saturation of Δ^{14} bond and isomerization with acid	383	17a-D-homo		Decompn of the bishydroperoxide deriv of 17-keto-steroid	436[b]
17-D-homo		PS	425	17a-D-homo		Sodium borohydride redn of corresponding lactone	309
17-D-homo		PS	200	17a-D-homo		Diisobutylaluminum hydride reduction of estrololactone 3-methyl ether	26
16- and 17-D-homo		PS	27 28	17a-D-homo		By treatment of the above lactol with methanol containing *p*-toluenesulfonic acid	26
17a-D-homo		Usually by treatment of estrone with peracid	196 220 239 450[b]				

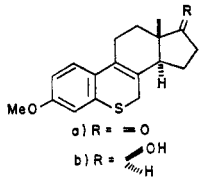
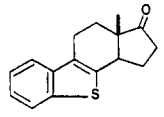
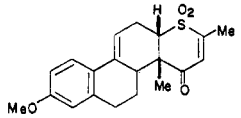
[a] TS indicates total synthesis; PS indicates partial synthesis. [b] See also ref 421.

CCXLII into the alcohol CCXLIII, which on condensation with 2-methylcyclopentane-1,3-dione gave the seco-oxasteroid CCXLIV. Cyclodehydration of the latter compound in ethanolic hydrochloric acid afforded the oxaestrapentaene (CCXLV) which was selectively hydrogenated over 2% palladized calcium carbonate to the oxaestratetraene (CCXLVI). Ethanolic hydrochloric acid transformed CCXLVI to its $\Delta^{9(11)}$ isomer (CCXLVII) and subsequent hydrogenation over 10% palladized carbon gave 6-oxaestrone methyl ether (CCXLVIII). There is no chemical evidence for the stereochemical assignment of CCXLVIII; the configuration given is based on analogy with the product (estrone) formed in the corresponding carbocyclic synthesis.

C. OTHER HETEROCYCLIC STEROIDAL ESTROGENS

The compounds listed in Tables III–V are not heterocyclic analogs of the steroidal estrogens; however, they may be regarded as heterocyclic derivatives of these compounds since they all possess the following features: (a) tetracyclic structure, (b) aromatic A ring, (c) heteroatom as part of steroid nucleus.

TABLE V
THIASTEROIDS

Position of S atom	Structural formula	Method of prepn[a]	Ref
6		TS	451
6-B-nor		TS	94, 286, 420
17a-D-homo		TS	294

[a] TS indicates total synthesis.

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(5) Alvarez, F. S., and Ruiz, A. B., *J. Org. Chem.*, **30**, 2047 (1965).
(6) Amatsu, M., *Nippon Naibumpi Gakkai Zasshi*, **39**, 1009 (1964).
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