SYNTHESIS OF STEROIDS OF THE PROGESTERONE SERIES[1]

MAXIMILIAN EHRENSTEIN

The George S. Cox Medical Research Institute, School of Medicine, University of Pennsylvania, Philadelphia 4, Pennsylvania

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The purpose of this review is the discussion of steroidal compounds which are structurally related to progesterone (X), particularly the higher and lower homologs of progesterone. In addition, certain oxygen derivatives of progesterone and compounds less saturated than progesterone will be included. The physiological activities of these compounds will be cited insofar as they have been recorded. They will be expressed in terms of the Corner and Allen (1) test, which is based upon the endometrial changes produced by 1 mg. of progesterone (the international unit).

At the outset, a few of the familiar methods for the preparation of progesterone should be mentioned. Thus, a number of the oxidation products of cholesterol may be transformed into progesterone. Cholesterol (I), properly protected by acetylation in position 3 and bromination in positions 5,6, may be oxidized by means of chromic acid to a number of products, among which dehydroisoandrosterone (II) predominates (*cf.* 41). Minor oxidation products of practical importance are pregnenolone (III), 3(β)-hydroxy-Δ^5-etiocholenic acid (IV), and 3(β)-hydroxy-Δ^5-cholenic acid (VI). These four oxidation products may be transformed into progesterone (X). Pregnenolone (III) may be converted into this hormone (X) by means of an Oppenauer dehydrogenation.

The acetate of the 3(β)-hydroxy-Δ^5-etiocholenic acid (VII) may be transformed into the acid chloride (VIII), which on treatment with dimethylcadmium forms the acetate of pregnenolone (IX). Saponification and subsequent Oppenauer dehydrogenation yield progesterone (X) (*cf.* 21).

Recently, six methods were worked out in Miescher's laboratory (26, 29) for the transformation of 3(β)-hydroxy-Δ^5-cholenic acid (VI) into progesterone (X). Each of these methods involves from eight to eleven separate chemical steps.[2]

Dehydroisoandrosterone (II) was transformed into progesterone (X) by Butenandt and Schmidt-Thomé (4). The starting material was the acetate of dehydroisoandrosterone (XI). The cyanohydrin reaction furnished compound XII, which was dehydrated to compound XIII. A Grignard reaction yielded the methyl ketone XIV, which by partial hydrogenation with Raney nickel gave pregnenolone (III). Oppenauer dehydrogenation of this furnished pro-

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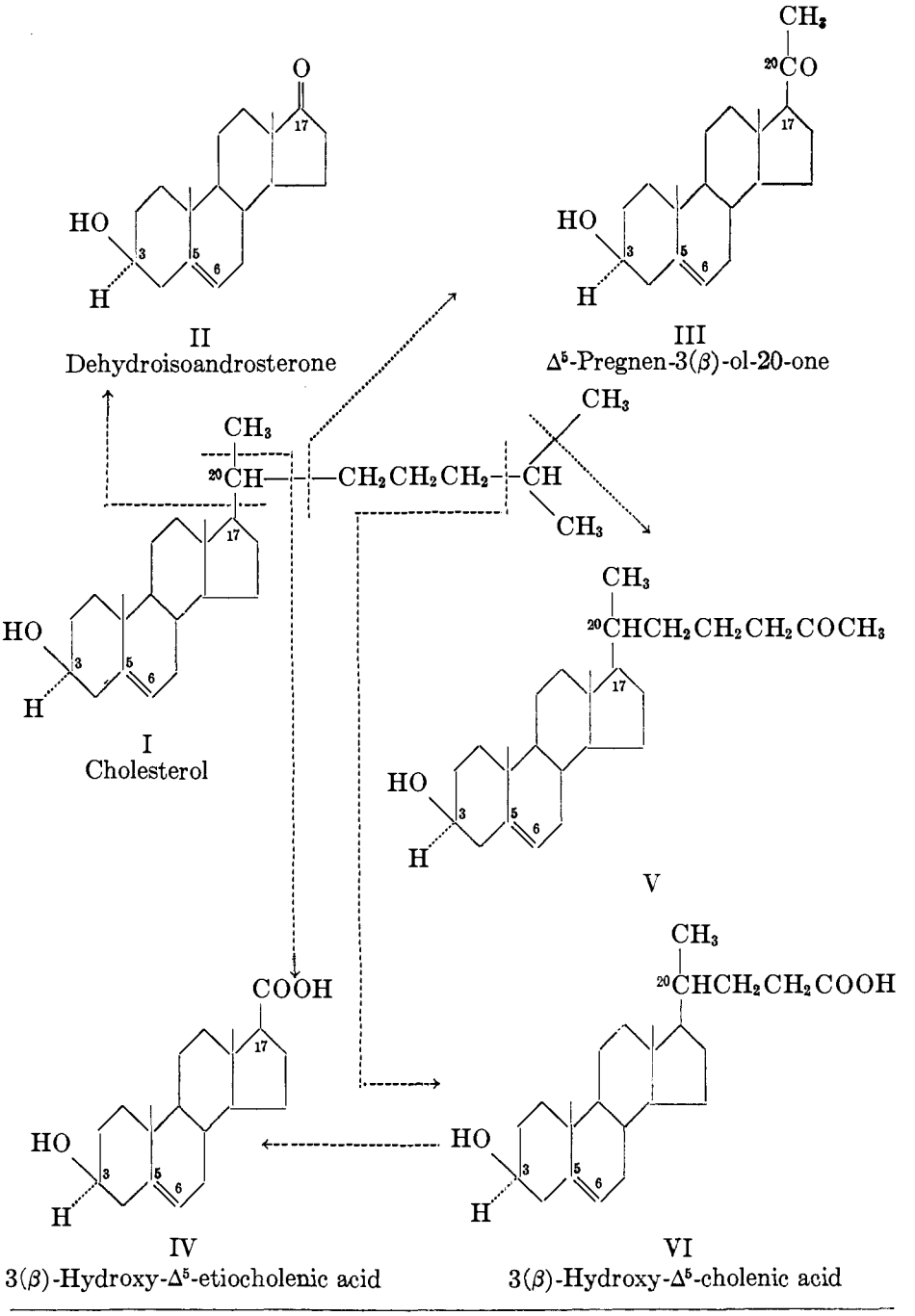
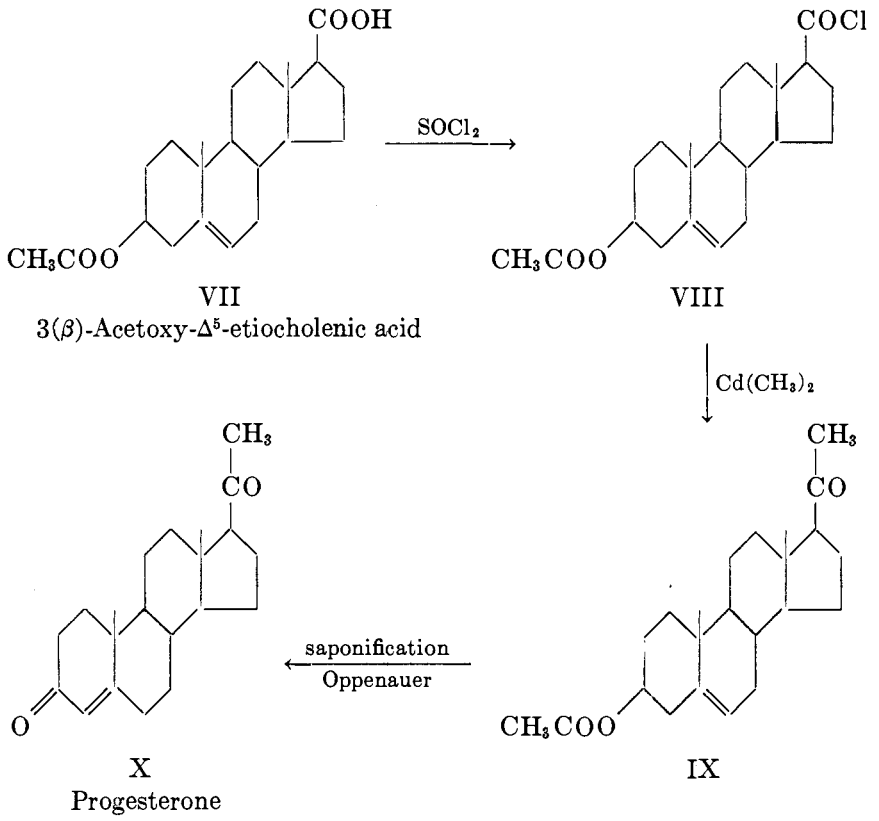
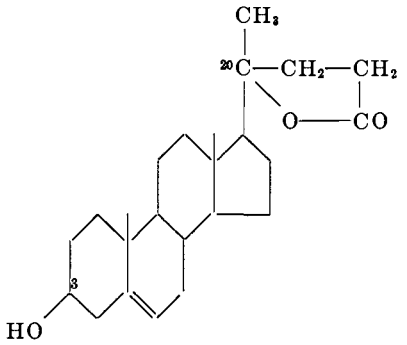
[2] While this paper was in press Billeter and Miescher (1a) established the chemical struc-



ture of another oxidation product of cholesterol as the 20-lactone of 3(β),20-dihydroxy-Δ5-cholenic acid:



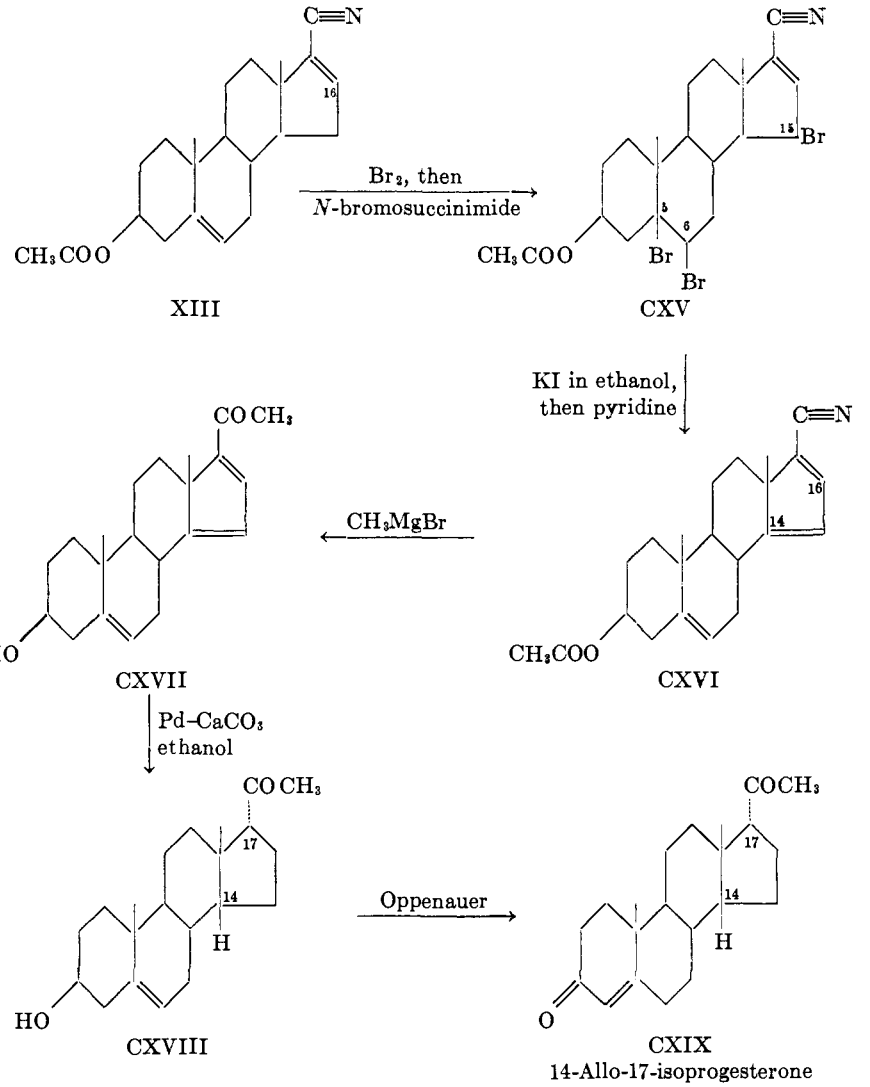
gesterone (X). The over-all yield of this transformation is claimed to be 40 per cent. When compound XIV was directly subjected to an Oppenauer reaction, the 16-dehydroprogesterone (XV) resulted. This substance, lacking the asymmetric center at carbon atom 17, possesses no progestational activity. It may be mentioned at this point that 17-isoprogesterone, which has a configuration



It can likewise be transformed into progesterone.

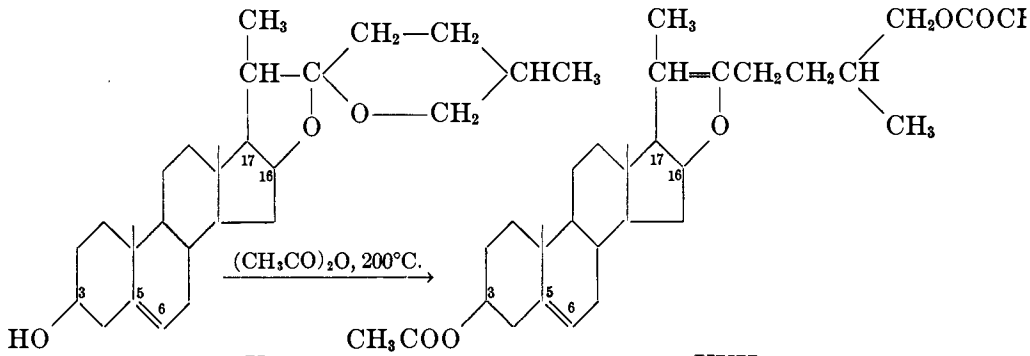
opposite to that of progesterone at carbon atom 17, is also physiologically inactive (*cf.* 5).[2a]

[2a] *Addition to proof, March 22, 1948:* In the meantime 14-allo-17-isoprogesterone (CXIX) has also been synthesized (32a). The starting material was the nitrile of 3(β)-acetoxy-$\Delta^{5,16}$-etiocholadienic acid (XIII). The 5,6-double bond was protected by adding bromine to it and a third bromine atom was introduced at carbon atom 15 by means of *N*-bromosuccinimide in the presence of light (CXV). The 5,6-double bond was reintroduced by boiling with potassium iodide in a solution of ethanol, and the resulting 15-monobromo compound was dehydrobrominated by refluxing it with pyridine. By this sequence of reactions a good yield of the nitrile of 3(β)-acetoxy-$\Delta^{5,14,16}$-etiocholatrienic acid (CXVI) was obtained. By treating this nitrile with methylmagnesium bromide the corresponding triene ketone (CXVII) was obtained, which was partially hydrogenated (palladium–calcium carbonate catalyst in ethanol) to 14-allo-17-iso-Δ^5-pregnen-3(β)-ol-20-one (CXVIII). Dehydrogenation of the latter compound by means of the Oppenauer method furnished the 14-allo-17-isoprogesterone (CXIX). It showed no progestational activity at a dosage level of 10 mg.



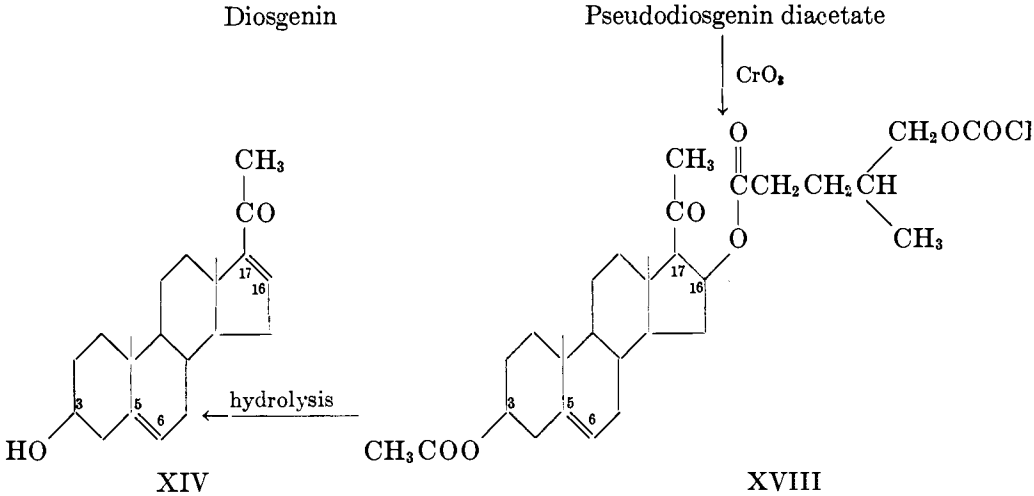
HCN
POCl₃
pyridine
CH₃COO
OH
C≡N
16
XI
Dehydroisoandrosterone acetate
XII
XIII
CH₃MgBr
COCH₃
Oppenauer
H₂
Raney nickel
HO
O
X
Progesterone
III
Δ⁵-Pregnen-3(β)-ol-20-one
XIV
Oppenauer
XV
16-Dehydroprogesterone

In his important work on sapogenins Marker and his associates (*cf.*, e.g., 24, 24a) transformed diosgenin (XVI), which is available from a number of plants, into progesterone (X).[2b] Diosgenin (XVI), on being heated with acetic anhydride at 200°C., was converted into pseudodiosgenin diacetate (XVII). This product was oxidized with chromic acid, the protection of the double bond being unnecessary. On hydrolysis with acid or alkali, the oxidation product XVIII furnished an almost quantitative yield of $\Delta^{5,16}$-pregnadien-3(β)-ol-20-one (XIV). This substance (XIV) had already been transformed into progesterone (XIV → III → X) by Butenandt and Schmidt-Thomé (4); hence the synthesis was complete.



XVI
Diosgenin

XVII
Pseudodiosgenin diacetate



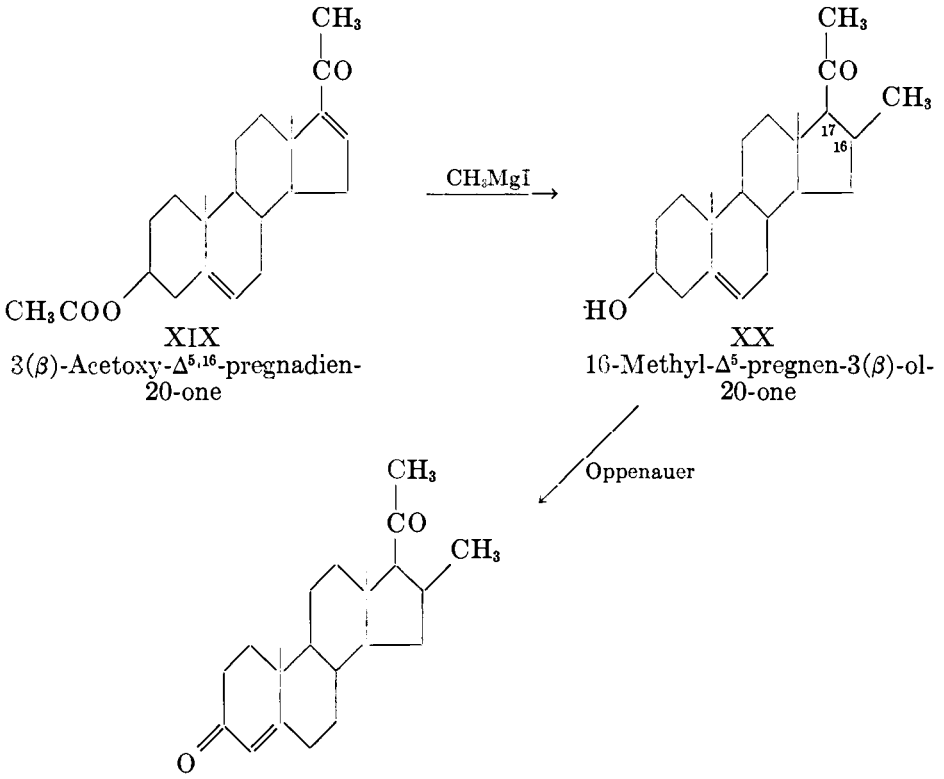
XIV
$\Delta^{5,16}$-Pregnadien-3(β)-ol-20-one

XVIII

In turning to the higher homologs of progesterone, those which are alkylated in position 16 will be discussed first. A number of such compounds were prepared by Marker and Crooks (23). The starting material was the acetate of

[2b] *Addition to proof, March 22, 1948:* Recently nologenin diacetate has also been transformed into progesterone (22a). The oxidation product of nologenin diacetate is identical with that of pseudodiosgenin acetate (XVIII), with the exception that it contains a hydroxyl group at carbon atom 17 instead of a hydrogen atom.

$\Delta^{5,16}$-pregnadien-3(β)-ol-20-one (XIX), which may be prepared from dehydroisoandrosterone acetate (XI) (4) or from diosgenin (XVI) (24). According to certain observations by Whitmore with Grignard compounds, it was to be expected that Grignard reagents would add to the double bond in the α,β-position to the keto group. This proved to be the case. With methylmagnesium iodide a 16-methyl-Δ^5-pregnen-3(β)-ol-20-one (XX) was obtained. A subsequent Oppenauer dehydrogenation furnished a 16-methylprogesterone (XXI) whose configurations at carbon atoms 16 and 17 remain uncertain. In an analogous fashion the 16-isopropyl- and 16-*tert*-butyl-progesterones were obtained. The physiological activities of these compounds are unknown.



XIX
3(β)-Acetoxy-$\Delta^{5,16}$-pregnadien-20-one

XX
16-Methyl-Δ^5-pregnen-3(β)-ol-20-one

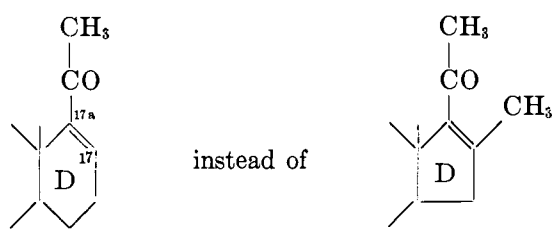
XXI
16-Methylprogesterone

Another, chemically different, 16-methylprogesterone was described by Wettstein (50). His procedure is based upon the observation that numerous α,β-unsaturated ketones react with diazomethane with the formation of a pyrazoline-ring system. The diazomethane simply adds to the double bond in the α,β-position to the keto group. Wettstein made the interesting observation that the α,β-unsaturated ketone arrangement in ring A of the steroids presents an exception, in that it does not participate in this reaction. For instance, when he took 16-dehydroprogesterone (XV), diazomethane readily added to the double bond in ring D, yielding the crystalline pyrazoline derivative XXIX. When this

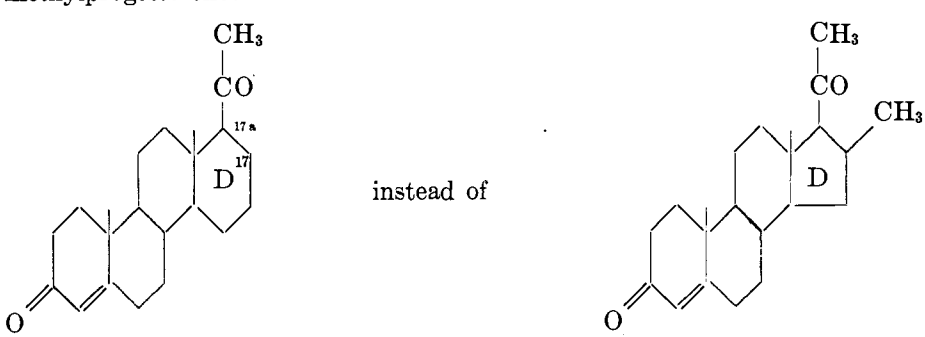
compound was subjected to thermal decomposition in a vacuum, a lively evolution of nitrogen took place near the melting point. The resulting product (XXX) was purified by subsequent distillation in a high vacuum. The reaction product (XXX) differs from the starting material (XV) in that it is methylated in position 16.

In preparing his 16-methylprogesterone, Wettstein performed a similar sequence of reactions starting with $\Delta^{5,16}$-pregnadien-3(β)-ol-20-one (XIV) or its acetate (XIX). Taking the free alcohol (XIV), treatment with diazomethane furnished the pyrazoline XXII, which was decomposed to the 16-methyl derivative (XXIII). Subsequent acetylation furnished the acetate XXIV. The identical acetate was obtained also by starting with the acetate XIX, treating it with diazomethane, and subsequently decompositing the pyrazoline XXVIII. The diene acetate XXIV was partially hydrogenated with nickel as catalyst, yielding compound XXV. Though this hydrogenation may theoretically lead to four different isomers, actually only one compound was isolated. Various considerations, especially comparisons of optical rotations, make it probable that the isolated substance possesses a normal configuration at carbon atom 17. The configuration at carbon atom 16 remains unknown. Saponification of compound XXV yielded the 16-methyl-Δ^5-pregnen-3(β)-ol-20-one (XXVI), which by means of an Oppenauer dehydrogenation was transformed into a 16-methylprogesterone (XXVII). Physiological data on this 16-methylprogesterone are not available.

It is not impossible that the decomposition of the pyrazolines is associated with a ring enlargement. This would yield, instead of the methylated five-membered ring, a six-membered ring D:

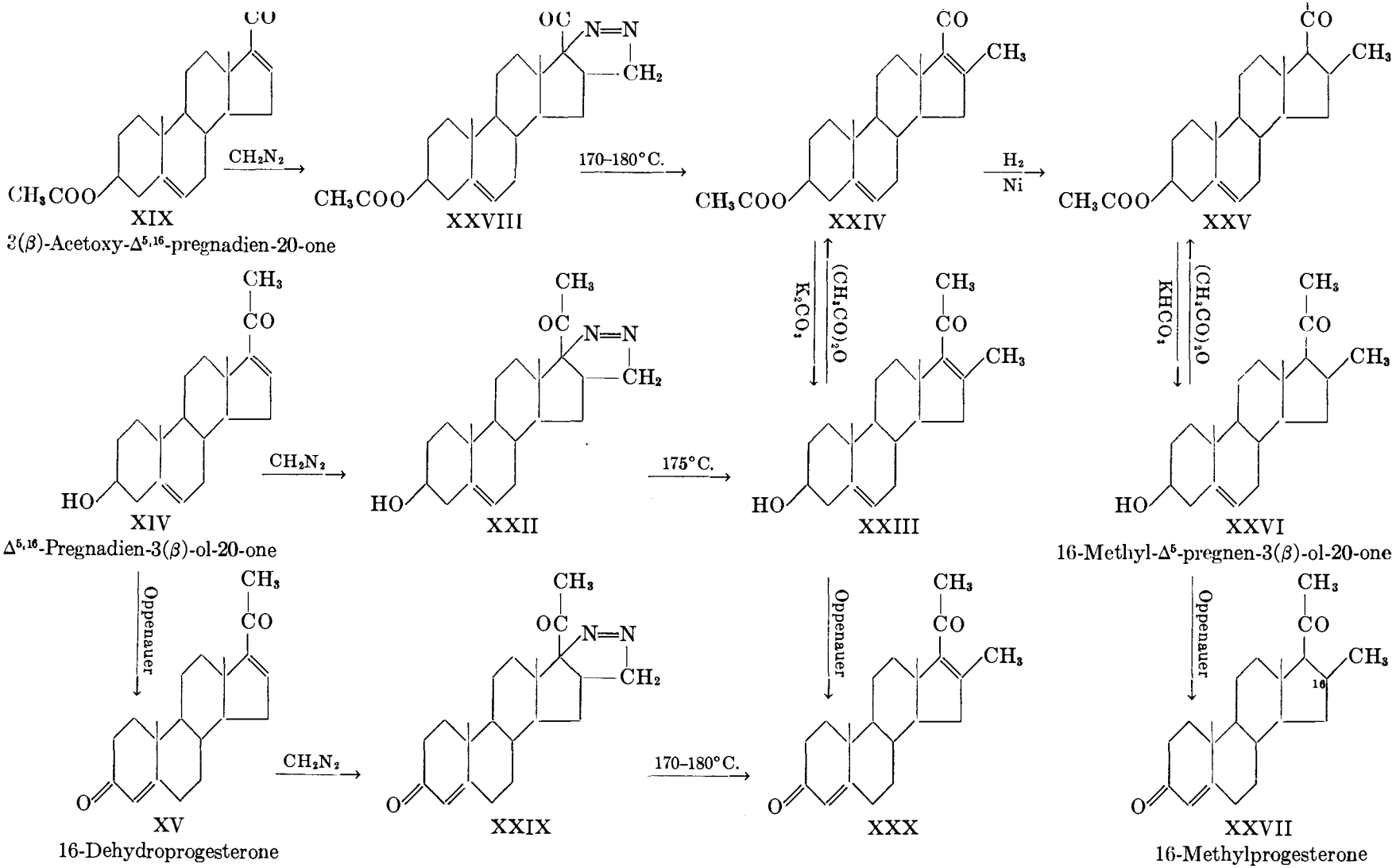


The end product might therefore be a D-homoprogesterone instead of a 16-methylprogesterone:

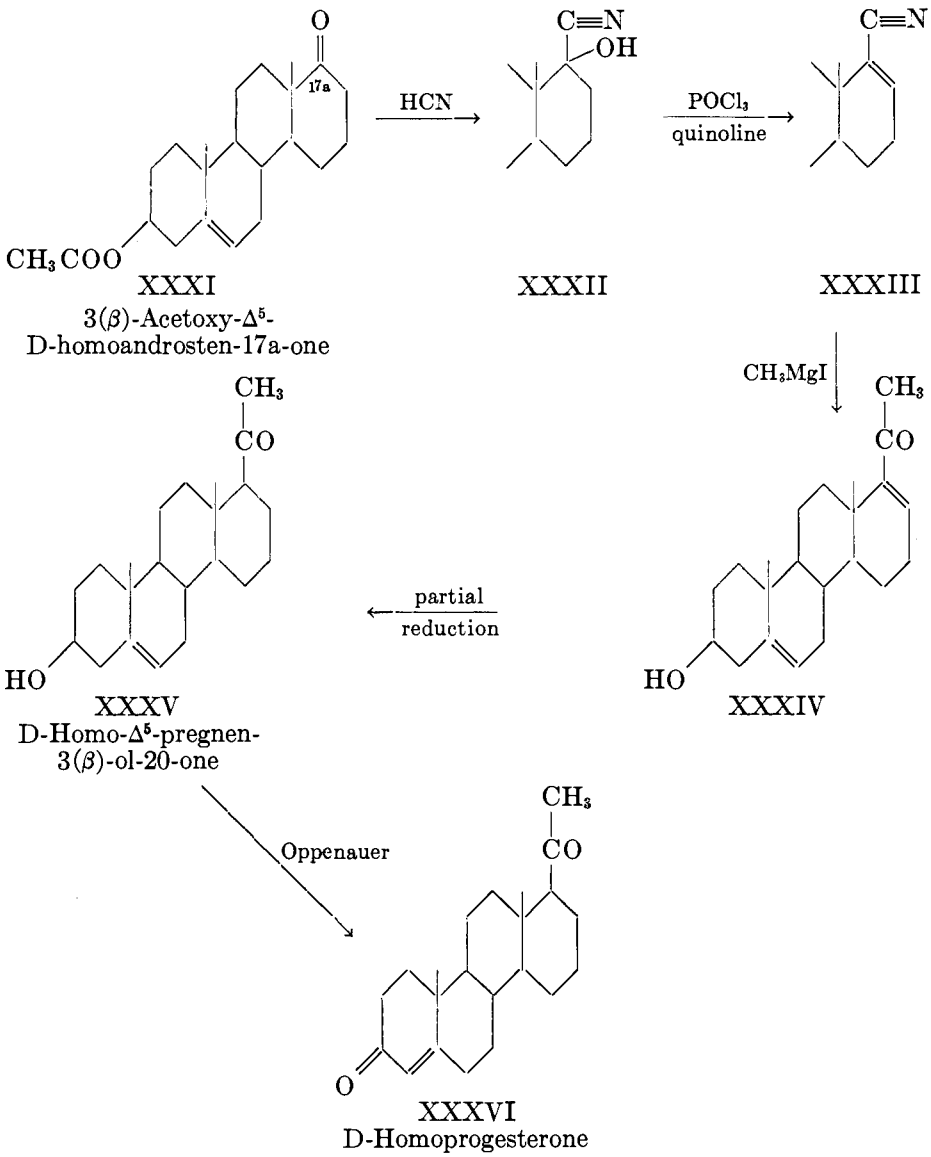


D-Homoprogesterone

XXVII
16-Methylprogesterone


CO
CH3COO
CH2N2
OC
N=N
CH2
170–180° C.
CH3
H2
Ni
XIX
3(β)-Acetoxy-Δ5,16-pregnadien-20-one
XXVIII
XXIV
XXV
HO
XIV
Δ5,16-Pregnadien-3(β)-ol-20-one
XXII
K2CO3
(CH3CO)2O
175° C.
XXIII
KHCO3
XXVI
16-Methyl-Δ5-pregnen-3(β)-ol-20-one
Oppenauer
O
XV
16-Dehydroprogesterone
XXIX
XXX
16
XXVII
16-Methylprogesterone

It may be mentioned that a D-homoprogesterone (XXXVI) and also a D-homodesoxycorticosterone are claimed by Ruzicka and Goldberg (39) in Swiss and American patents. In the American patent the preparation of the D-homoprogesterone is described only in the most general terms. No chemical characteristics of the intermediates or end product are given. In the disclosure it is stated that compounds of this type possess high physiological activity. According to the patent the preparation of D-homoprogesterone proceeds as follows:



XXXI
3(β)-Acetoxy-Δ⁵-D-homoandrosten-17a-one

XXXII

XXXIII

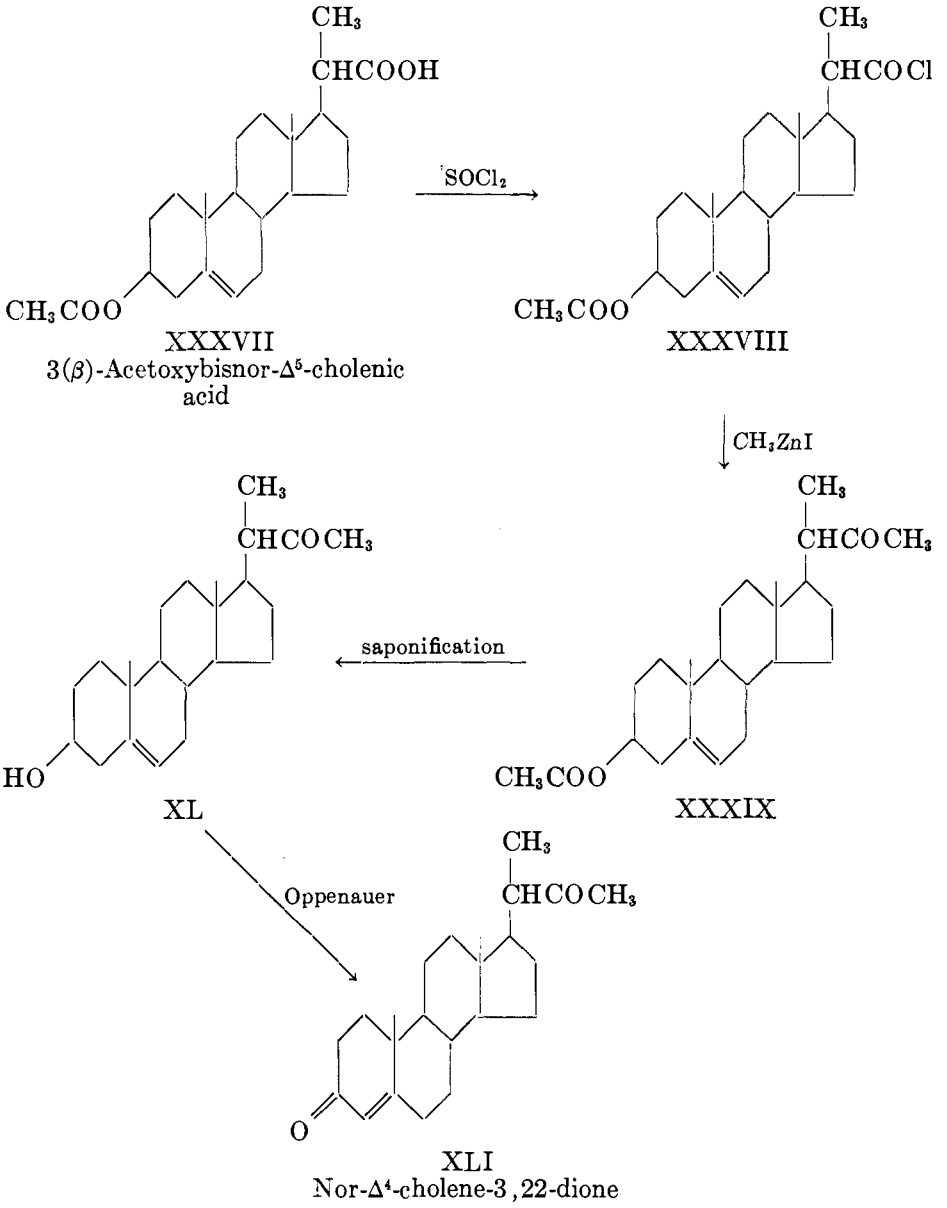
XXXIV

XXXV
D-Homo-Δ⁵-pregnen-3(β)-ol-20-one

XXXVI
D-Homoprogesterone

The method appears completely analogous to Butenandt's procedure (4) of

preparing progesterone from dehydroisoandrosterone. However, since the patent does not contain any details regarding the procedures nor any characteristics of the substances claimed, it appears somewhat doubtful whether these compounds have been sufficiently characterized. No publication covering the same substances has ever appeared in a chemical journal. It would certainly be interesting to prepare such compounds and test them for their physiological action. As is known, D-homoandrostane derivatives (*cf.*, e.g., 15a, 17) generally



XXXVII
3(β)-Acetoxybisnor-Δ⁵-cholenic acid

XXXVIII

XL

XXXIX

XLI
Nor-Δ⁴-cholene-3,22-dione

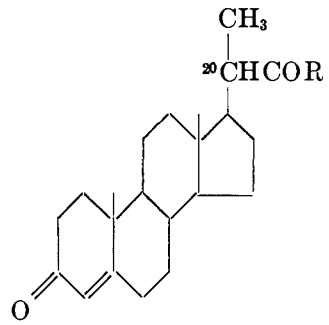
possess the same order of androgenic activity as the corresponding androstane derivatives. On the other hand, the D-homo analogs of estrone and estradiol (*cf.*, e.g., 16) seem to possess no estrogenic activity.

More is known regarding the physiological activity of the side-chain homologs of progesterone. The higher homologs derived from progesterone in this fashion fall in two groups.

In the first group carbon atoms appear introduced between carbon atom 17 and the keto group of the side chain. This will be illustrated by two examples.

(*a*) The higher homolog, nor-Δ^4-cholene-3,22-dione (XLI), was prepared by Wettstein (49) from 3(β)-acetoxybisnor-Δ^5-cholenic acid (XXXVII). This acid had been obtained previously by Fernholz in his studies on the degradation of stigmasterol. The acid chloride XXXVIII yielded with methylzinc iodide the ketone XXXIX, which was saponified to the free alcohol XL. The latter was dehydrogenated according to the Oppenauer method, yielding compound XLI.

Cole and Julian (6) have carried out analogous experiments on an extensive scale. Starting material for their work was the acid chloride XXXVIII, which was successfully treated with a number of dialkylcadmium compounds. They were even able to isolate end products (XLII) epimeric at carbon atom 20.

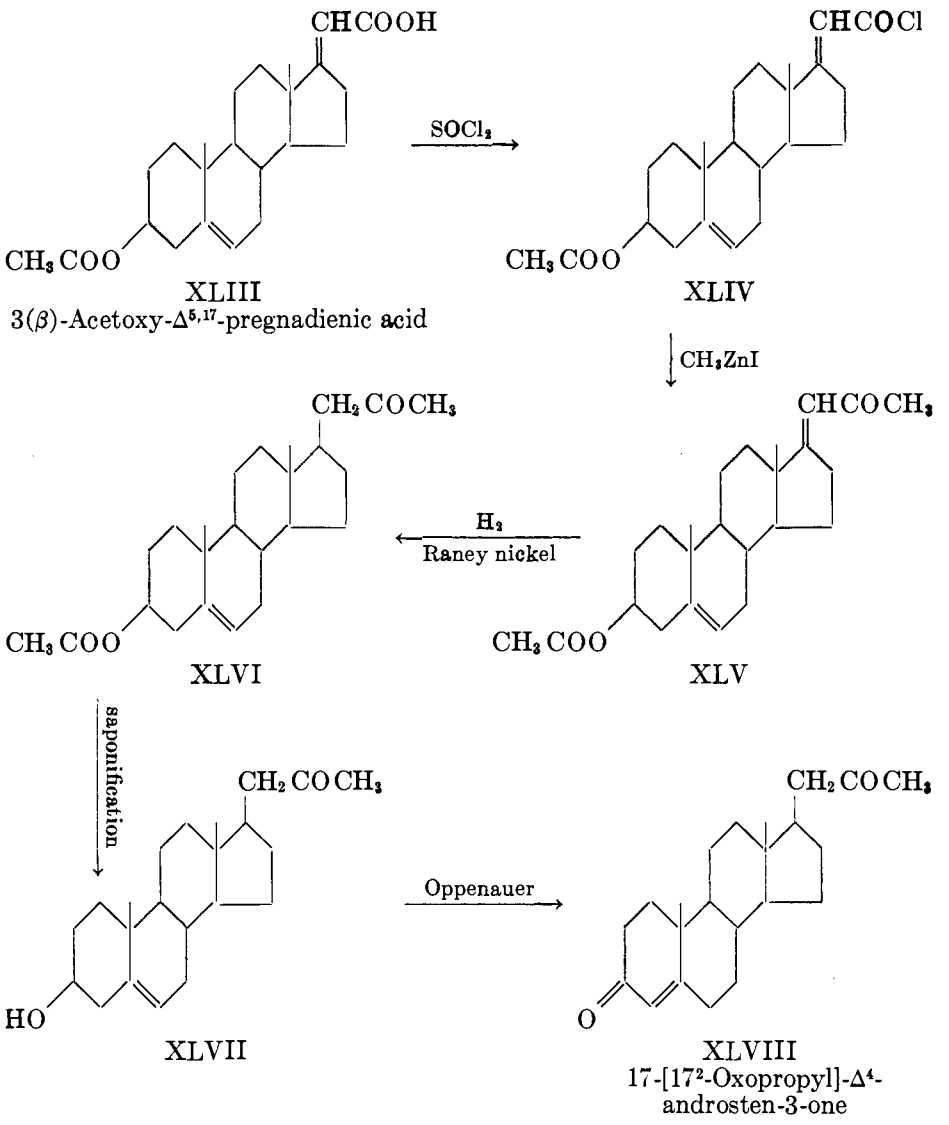


XLII
R = methyl, ethyl, isoamyl

All homologs of this series lacked progestational activity.

(*b*) The higher homolog 17-[17²-oxopropyl]-Δ^4-androsten-3-one (XLVIII) was prepared by Plattner and Schreck (36) from 3(β)-acetoxy-$\Delta^{5,17}$-pregnadienic acid (XLIII). This acid is accessible from dehydroisoandrosterone (II) by means of a Reformatzky reaction and subsequent dehydration (35). The acid chloride (XLIV) was treated with methylzinc iodide, yielding the ketone XLV, which by means of partial hydrogenation with Raney nickel furnished compound XLVI. The stereochemical configuration at carbon atom 17 remains uncertain. Saponification of compound XLVI furnished compound XLVII which, by means of an Oppenauer dehydrogenation, was transformed into the progesterone homolog XLVIII.

A second group of higher side-chain homologs is derived from progesterone, in that a radical replaces a hydrogen atom at carbon atom 21. Compounds of this



XLIII
3(β)-Acetoxy-$\Delta^{5,17}$-pregnadienic acid

XLIV

XLVI

XLV

XLVII

XLVIII
17-[17²-Oxopropyl]-Δ^4-androsten-3-one

type can easily be prepared from the acid chloride of 3(β)-acetoxy-Δ^5-etiocholenic acid (XLIX). Wettstein (48) reacted this compound with diethylzinc and propylzinc iodide, respectively, obtaining compounds La and Lb. A variant in the preparation of these substances consisted in treating the acid chloride (XLIX) with suitable malonic ester derivatives. Saponification of compounds La and Lb, followed by Oppenauer dehydrogenation, furnished 21-methylprogesterone (LIa) and 21-ethylprogesterone (LIb), respectively. 21-Methylprogesterone (LIa) was active with 3 mg. in the Clauberg test, i.e., equivalent to about 6 mg. in the Corner-Allen test, but 21-ethylprogesterone (LIb) proved to be physi-

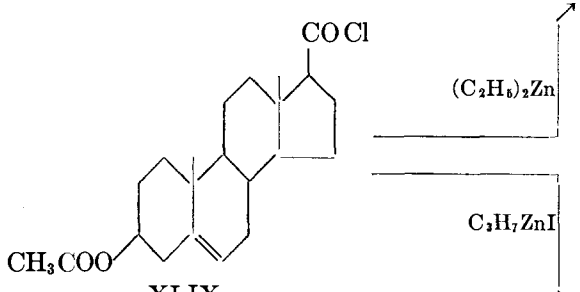
ologically inactive. Considering that progesterone is active at a dosage level of 1 mg., this indicates that lengthening of the side chain by substitution at carbon atom 21 decreases the physiological activity. It may be added that Marker and his associates (25) have prepared 21-benzalprogesterone (LIII) and 21-benzylprogesterone (LVII). Pregnenolone acetate (IX) was condensed with benzaldehyde to the benzal derivative LII, which by means of the Oppenauer dehydrogenation was transformed into 21-benzalprogesterone (LIII). When the benzalpregnenolone (LII) was acetylated (LIV), partially hydrogenated (LV), saponified (LVI), and finally treated according to Oppenauer, the end product was 21-benzylprogesterone (LVII). No physiological activity has been recorded for 21-benzalprogesterone (LIII) and 21-benzylprogesterone (LVII).

A lower member in the series of the side-chain homologs is 20-norprogesterone (LXII), which was prepared by Miescher, Hunziker, and Wettstein (30). In this homolog the methyl group of the side chain of progesterone is replaced by a hydrogen atom. The starting meterial for this synthesis was 21-acetoxy-Δ^5-pregnen-3(β)-ol-20-one (LVIII), which is known to be an intermediate in Reichstein's synthesis of desoxycorticosterone. Steiger and Reichstein (45) had already transformed this easily available substance into compound LXI in the following fashion: By means of the Meerwein–Ponndorff method the keto group was reduced to a secondary alcohol group; subsequent saponification yielded the triol LIX. Although two epimeric forms are possible at carbon atom 20, one of them predominated in the reaction mixture. It was transformed into the acetone compound LX which, by means of an Oppenauer dehydrogenation, furnished an α,β-unsaturated ketone. Subsequent hydrolysis of the acetonide yielded compound LXI. Oxidation under suitable conditions with periodic acid furnished the 20-norprogesterone (LXII). This substance was active at a dosage level of 10–20 mg. in the Clauberg test, which is the equivalent of about 20–40 mg. in the Corner–Allen test. Hence this lower homolog of progesterone possesses only very slight progestational activity.

Another lower homolog is 10-norprogesterone. It is derived from progesterone in that the angular methyl group at carbon atom 10 is replaced by a hydrogen atom. This compound was prepared by Ehrenstein (8) and found to be very active (1). The starting material was strophanthidin (LXIII), which possesses the general structural features of the cardiac aglycones. The structure is identical with that of periplogenin (LXIV), except that an aldehyde group instead of a methyl group is attached to carbon atom 10 (8). The configurational formulas of strophanthidin and periplogenin have been revised on the basis of recent investigations by Speiser and Reichstein (44).[3] All functional groups, i.e., the hydroxyl groups in positions 3,5,14 and the lactone ring in position 17, are probably attached in the β-position. Some of the intermediates described by Ehrenstein (8) had been reported in the literature previously (8).

Jacobs (20) oxidized strophanthidin (LXIII) with potassium permanganate in a neutral solution of acetone and obtained the monobasic strophanthidinic acid (LXVI). Under these conditions the unsaturated lactone ring remained intact.

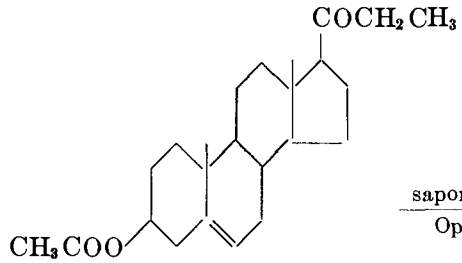
[3] *Cf.* the more recent article, "On the stereochemistry of strophanthidin and periplogenin" (36a).



XLIX
3(β)-Acetoxy-Δ⁵-etiocholenyl chloride

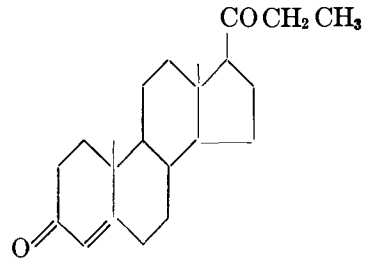
$(C_2H_5)_2Zn$

C_3H_7ZnI

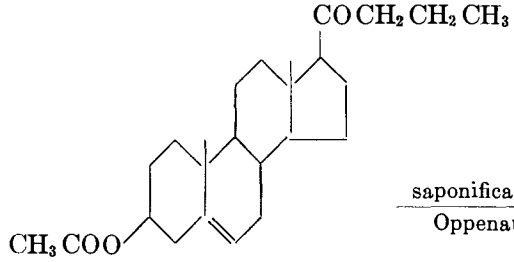


La

saponification
Oppenauer

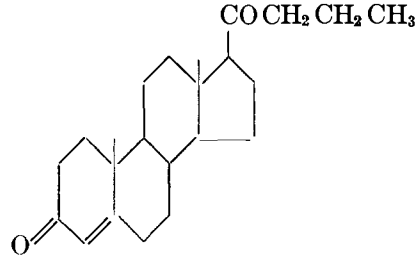


LIa
21-Methylprogesterone

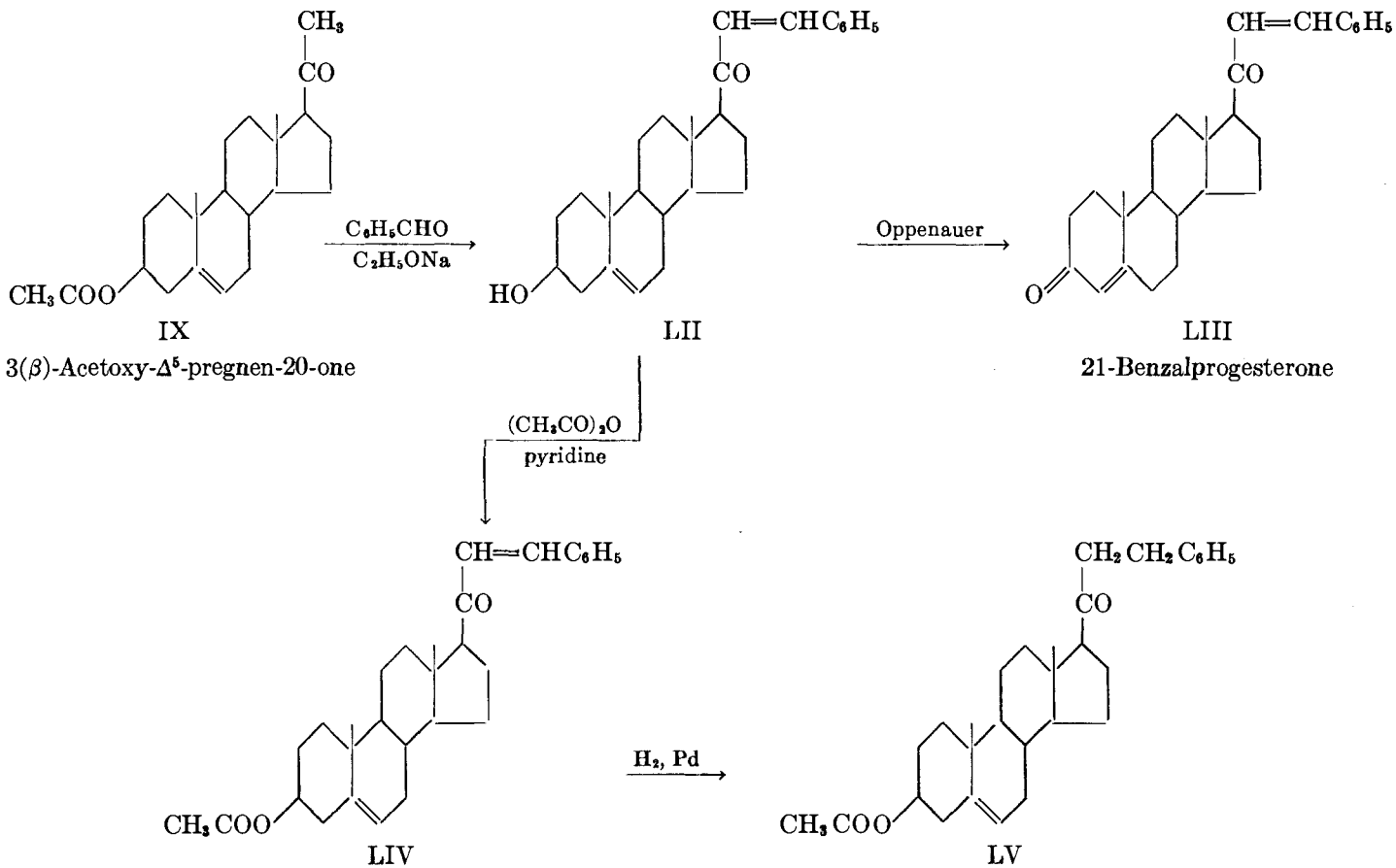


Lb

saponification
Oppenauer



LIb
21-Ethylprogesterone



IX

3(β)-Acetoxy-Δ⁵-pregnen-20-one

LII

LIII

21-Benzalprogesterone

LIV

LV

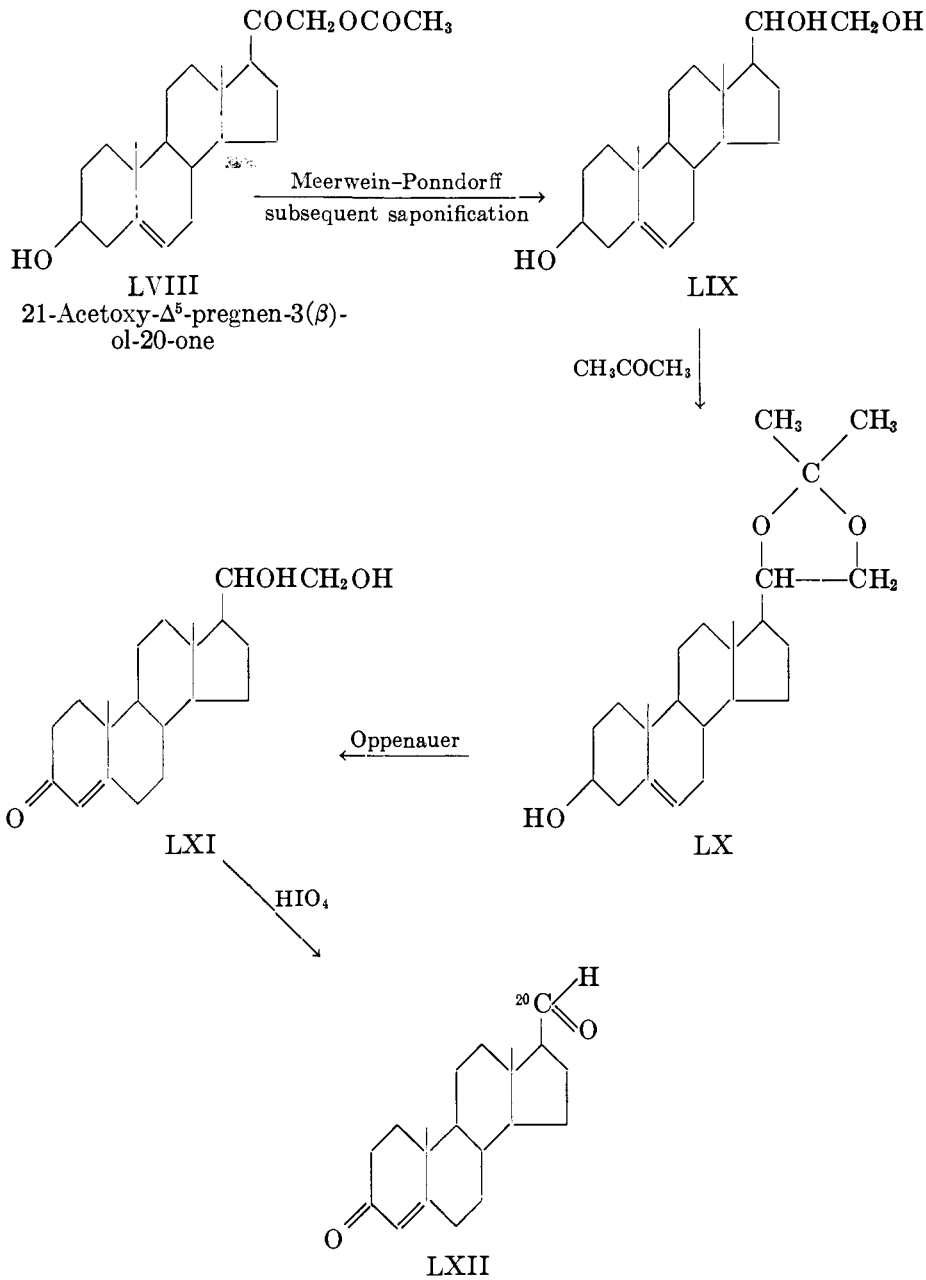
saponification

LVI

Oppenauer

LVII

21-Benzylprogesterone



LVIII
21-Acetoxy-Δ^5-pregnen-3(β)-ol-20-one

LIX

LXI

LX

LXII
20-Norprogesterone

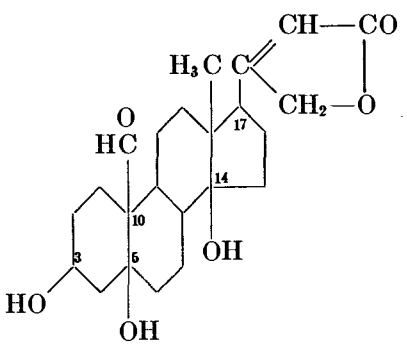
When the acid (LXVI) was subjected to oxidation with potassium permanganate in an alkaline solution, compound LXVII, which is an α-ketolactone acid, was obtained. Lactonization has occurred because the side chain attached to carbon atom 17 and the hydroxyl group at carbon atom 14 are in the *cis* position. On boiling this ketolactone acid LXVII with alkali, the lactone ring opened and

simultaneous epimerization took place at carbon atom 17, obviously by way of enolization of the carbonyl group adjacent to carbon atom 17. Through this epimerization the side chain at carbon atom 17 is placed in the so-called "iso position", which in this case is *trans* to the hydroxyl group at carbon atom 14, a configuration which prevents relactonization. Elderfield (14) subjected the dicarboxylic acid LXVIII to further degradation by means of hydrogen peroxide and obtained the dicarboxylic acid LXIX. Butenandt and Gallagher (3) dehydrated acid LXIX under mild conditions and obtained the unsaturated dicarboxylic acid LXX, which in turn was hydrogenated to the saturated dicarboxylic acid LXXI. The stereochemical configuration of this compound (LXXI), in particular at carbon atom 14, remains uncertain. According to recent observations by Ruzicka (*cf.*, e.g., 33, 34, 40, 44) the stereochemical course of the hydrogenation of Δ^{14}-unsaturated 17-carboxylic acids or their esters depends entirely on the configuration at carbon atom 17. A normal configuration at C_{17} leads to a *trans* linkage of rings C and D, whereas an iso configuration at C_{17} leads to a *cis* linkage. Provided the carboxyl group at carbon atom 10 does not influence this rule, the linkage between rings C and D in compound LXXI may be *cis*, as tentatively indicated in formula LXXI. However, this configuration cannot be assigned with certainty. The transformation of LXIX into LXXI was carried out simultaneously with practically identical results in the laboratories of both Butenandt (3) and Ehrenstein (8). The latter transformed the dibasic acid LXXI into the monoacetyl derivative LXXII and subjected it to a distillation in a high vacuum. Such treatment brings about simultaneous dehydration and decarboxylation. The double bond of the reaction product is probably in the 5,6-position, as indicated by formula LXXIII, although the alternatives LXXIIIa and LXXIIIb cannot be ruled out. The configuration at the asymmetric carbon atom 10 remains unknown. The acid chloride LXXIV was treated with methylzinc iodide, leading to the methyl ketone LXXV. Subsequent saponification yielded a 10-norpregnenolone (LXXVI). This reaction may have brought about an inversion of the configuration at carbon atom 17 leading from the iso to the normal arrangement,[4] though according to very recent evidence this appears improbable.[5] Dehydrogenation of the 10-norpregnenolone (LXXVI) according to the Oppenauer method yielded a 10-norprogesterone (LXXVII). By established methods the acid chloride LXXIV was also transformed into a 10-nor-11-desoxycorticosterone acetate. Although these two end products were non-crystalline, they have been fully characterized. The configurations at carbon atoms 10, 14, and 17 remain uncertain.[5a] It is perhaps a

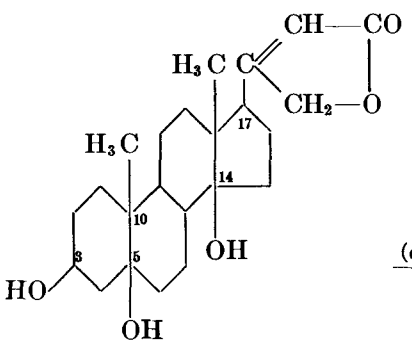
[4] For reasons *cf.* reference 8, page 441.

[5] 20-Keto-17-isosteroids with the iso configuration at carbon 14 appear to be stable towards acid and alkali (25a; *cf.* page 2025).

[5a] *Addition to proof, March 22, 1948:* In two recent publications (5a, 32a) it is suggested that the 10-norprogesterone prepared by Ehrenstein (8) possesses the iso (allo) configuration at carbon atom 14 and the iso configuration at carbon atom 17, as tentatively expressed in formula LXXVII. This cannot be considered definitely proven, and the stereochemical arrangement at carbon atom 10 remains wholly uncertain. Experiments are under way in the author's laboratory to repeat the preparation of 10-norprogesterone with such modifications that the isolation of stereochemically uniform material will be possible.

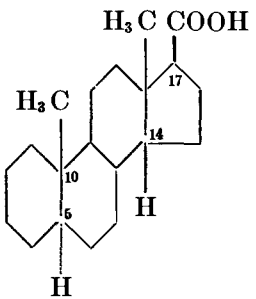


LXIII
Strophanthidin



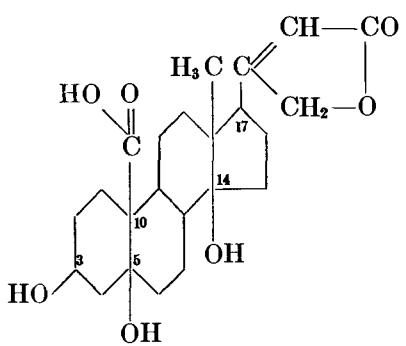
LXIV
Periplogenin

(cf. 8, 44)



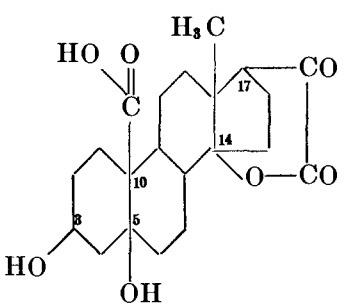
LXV
Etioallocholanic acid

$KMnO_4$ (neutral)



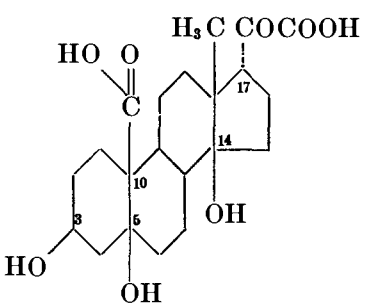
LXVI
Strophanthidinic acid

$KMnO_4$ (alkaline)



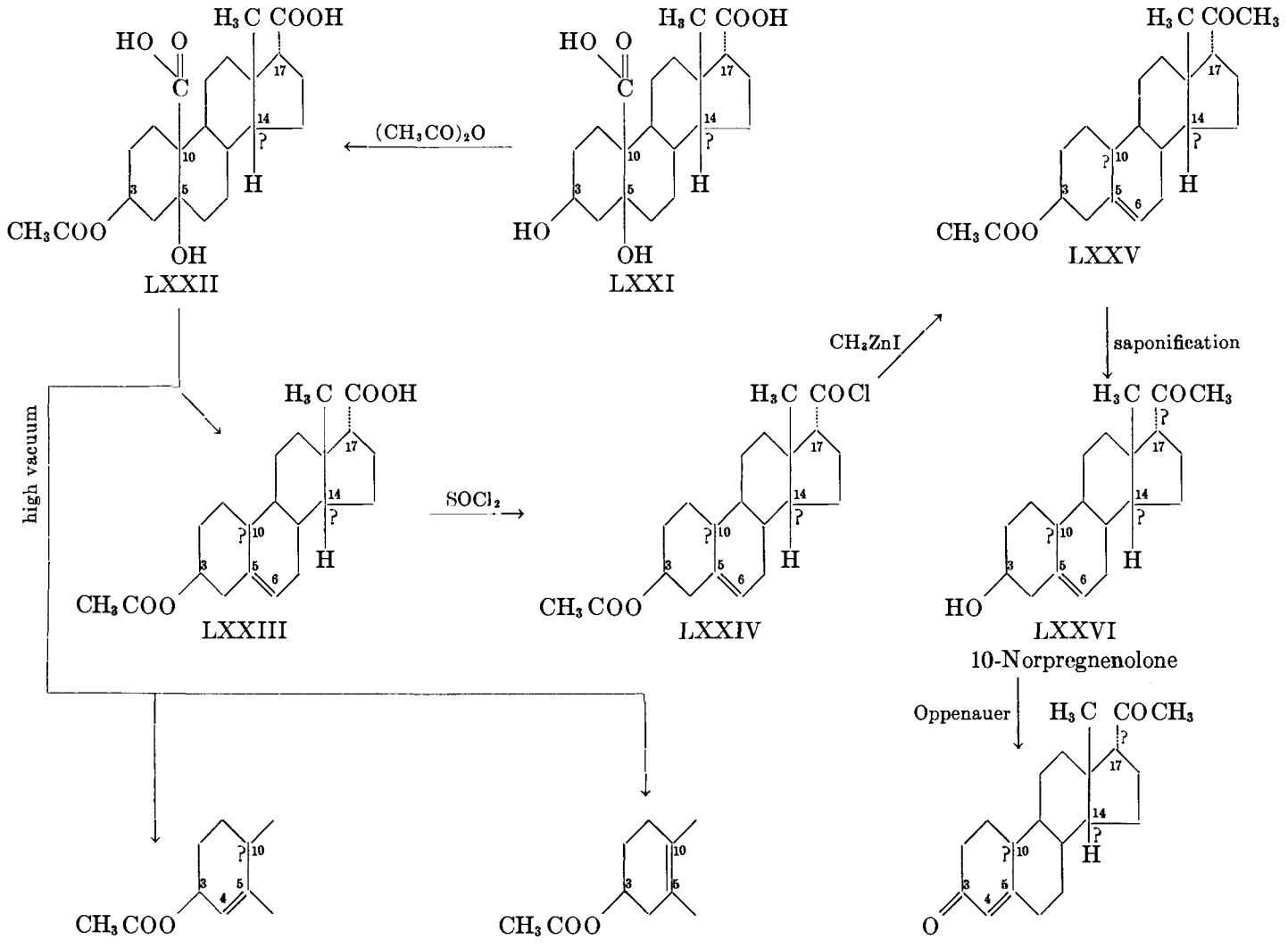
LXVII

alkali

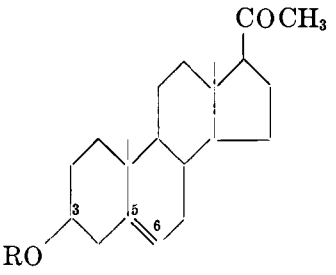


LXVIII

H2O2
H3C COOH
HO O
C
OH
OH
HO
LXIX
HCl
H3C COOH
HO O
C
OH
HO
LXX
H2
Pt
H3C COOH
HO O
C
H
OH
HO
LXXI

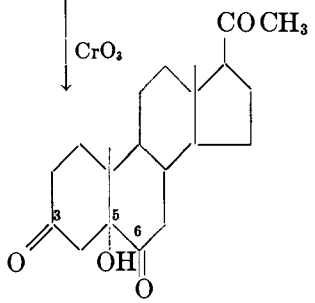

LXXII
LXXI
LXXV
LXXIII
LXXIV
LXXVI
10-Norpregnenolone
(CH3CO)2O
SOCl2
CH2ZnI
saponification
high vacuum
Oppenauer

stereochemical mixture. The 10-norprogesterone was tested for progestational activity (1) and found to be at least as active as progesterone. This physiological finding indicates that the angular methyl group between rings A and B is not essential for progestational activity. Considering that this preparation of 10-norprogesterone may be a stereochemical mixture, one of its components may



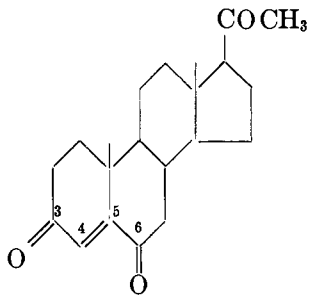
III: R = H, Δ^5-pregnen-3(β)-ol-20-one
IX: R = CH_3CO, 3(β)-acetoxy-Δ^5-pregnen-20-one

III

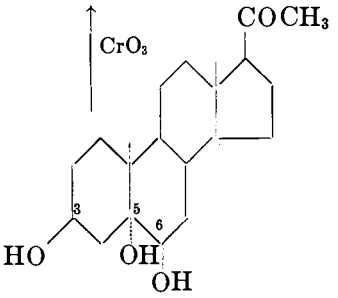


LXXX
Allopregnan-5-ol-3,6,20-trione

HCl



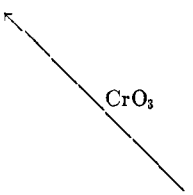
LXXXI
6-Oxoprogesterone [Δ^4-pregnene-3,6,20-trione]

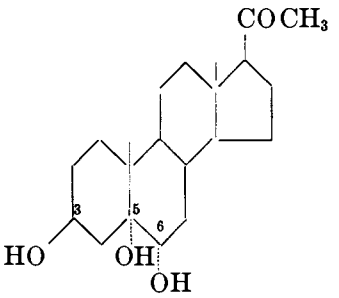


LXXVIII
Allopregnane-3(β),5,6(β)-triol-20-one

H_2O_2 | saponification

IX

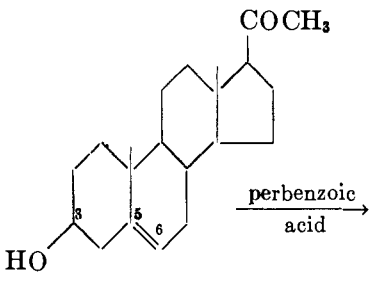




LXXIX
Allopregnane-3(β),5,6(α)-triol-20-one

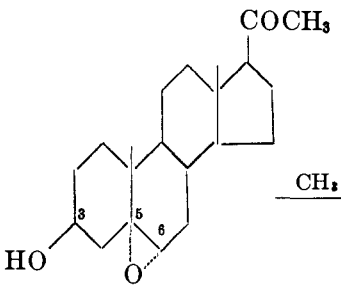
OsO_4

III



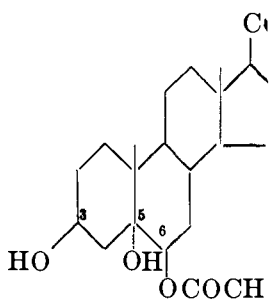
III

Δ^5-Pregnen-3(β)-ol-20-one



LXXXVI

5,6(α)-Oxidoallopregnan-3(β)-ol-20-one

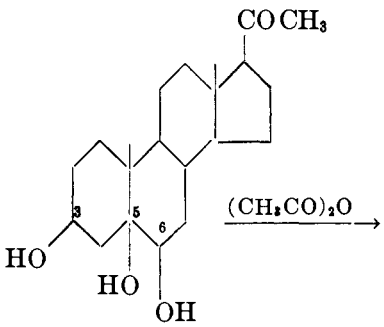


LXXXIII

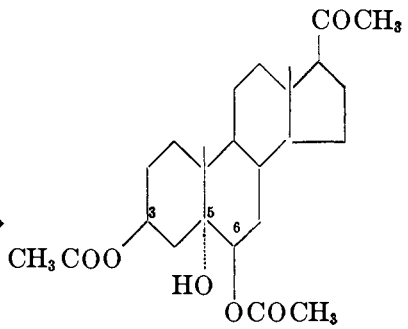
6(β)-Acetoxyallopregn
3(β),5-diol-20-one

partial saponification

CrO_3

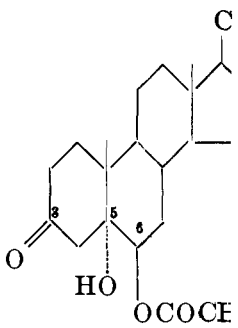


LXXVIII



LXXXII

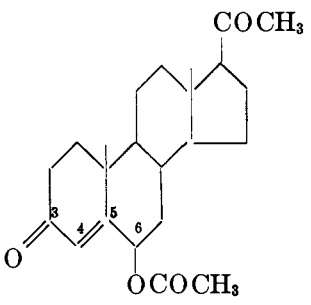
3(β),6(β)-Diacetoxyallopregnan-5-ol-20-one



LXXXIV

6(β)-Acetoxyallopr
5-ol-3,20-dion

HCl



LXXXV

6(β)-Acetoxyprogesterone

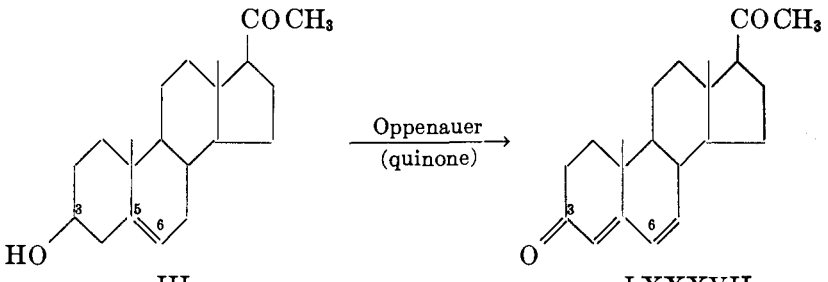
represent a very active progestational compound. It should be emphasized that the over-all yield of this procedure for the preparation of 10-norprogesterone is very small.

In the remaining part of this review some oxygenated progesterones and dehydroprogesterones will be discussed. Progesterones hydroxylated in position 21 will be omitted, however, because compounds of this type belong to the series of the adrenal cortical hormones. As is known, some of the adrenal cortical hormones, e.g., desoxycorticosterone, produce slight progestational action (42).

6-Oxoprogesterone (LXXXI) was prepared by Ehrenstein (7, 9). Hydroxylation of pregnenolone (III) by means of hydrogen peroxide or osmic acid yields two triols, LXXVIII and LXXIX, respectively, which differ in their configuration at carbon atom 6. Oxidation of these different triols with chromic acid leads to an identical allopregnan-5-ol-3,6,20-trione (LXXX), which by dehydration was transformed into 6-oxoprogesterone (LXXXI). The progestational activity of this compound is less than one-fifth that of progesterone. On the other hand, a slight estrogenic effect has been recorded (7).

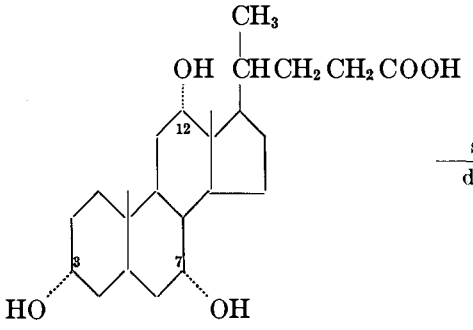
Two methods of preparing the acetate of 6(β)-hydroxyprogesterone (LXXXV) have been described (9, 10, 12). Acetylation of the triol LXXVIII furnished the diacetate LXXXII, which by partial saponification yielded the monoacetate LXXXIII. Partial saponification is usually a rather unsatisfactory procedure. Hence the preparation of the monacetate LXXXIII was later simplified by transforming pregnenolone (III) into the α-oxide (LXXXVI) and subjecting the latter to acetolysis. Oxidation of the monoacetate LXXXIII yielded compound LXXXIV, which by dehydration was transformed into the acetate of 6(β)-hydroxyprogesterone (LXXXV). This compound, tested in two different laboratories (G. W. Corner, A. W. Makepeace), was found to possess one-fifth to one-third the activity of progesterone.

6-Dehydroprogesterone (LXXXVII) was prepared by Wettstein (47). Pregnenolone (III) was subjected to the Oppenauer procedure with the modification of using quinone as hydrogen acceptor. Under such vigorous conditions there takes place not merely a dehydrogenation of the secondary alcohol group, but also the introduction of another double bond. No yields of this reaction are stated. The physiological activity of 6-dehydroprogesterone (LXXXVII) is about one-third to one-half that of progesterone.



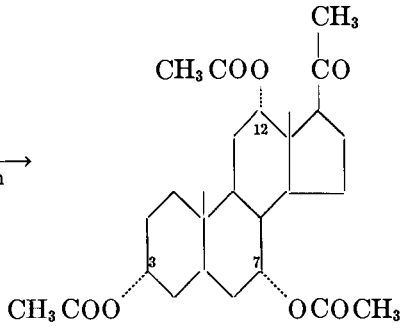
III
Δ⁵-Pregnen-3(β)-ol-20-one

LXXXVII
6-Dehydroprogesterone



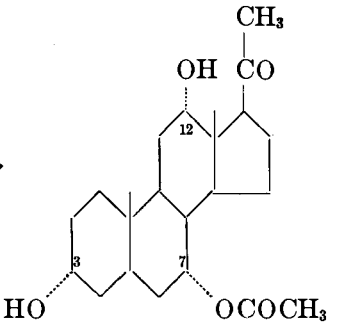
LXXXVIII
Cholic acid

side chain degradation →



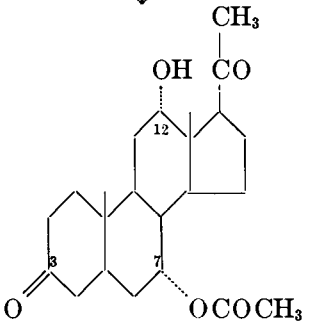
LXXXIX
3(α),7(α),12(α)-Triacetoxypregnan-20-one

KOH →



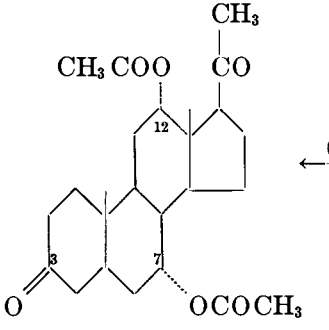
XC
7(α)-Acetoxypregnane-3(α),12(α)-diol-20-one

Oppenauer ↓



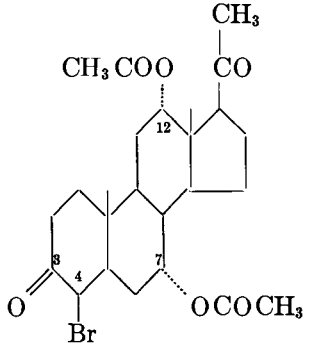
XCI
7(α)-Acetoxypregnan-12(α)-ol-3,20-dione

← $(CC_3HO)_2O$

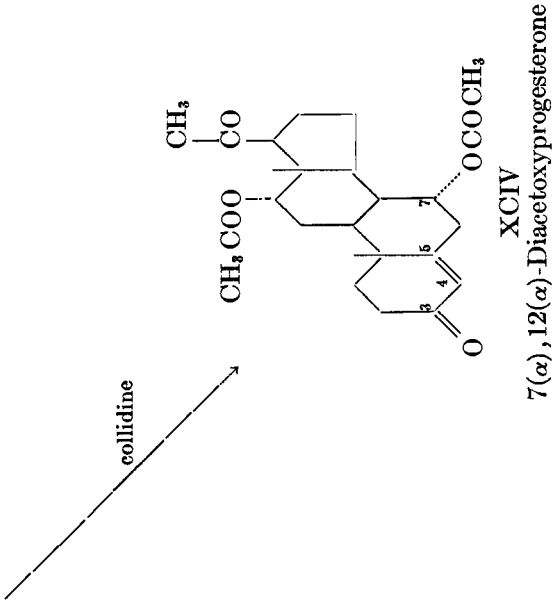


XCII
7(α),12(α)-Diacetoxypregnane-3,20-dione

← Br_2



XCIII
4-Bromo-7(α),12(α)-diacetoxypregnane-3,20-dione



XCIV

7(α), 12(α)-Diacetoxyprogesterone

The diacetate of 7(α),12(α)-dihydroxyprogesterone (XCIV) was prepared by Ehrenstein and Stevens (9, 11) by a procedure starting with cholic acid (LXXXVIII). A side-chain degradation involving many steps yielded 3(α),7(α),12(α)-triacetoxypregnan-20-one (LXXXIX), a compound which is now much more easily available by means of Miescher's new degradation method (27, 28). It was partially saponified to compound XC.[6] Subsequent Oppenauer dehydrogenation is selective in that only the hydroxyl group at carbon atom 3 is involved. Hence compound XCI[6] resulted, which by acetylation was transformed into the diacetate XCII. Subsequent bromination yielded the impure bromo compound XCIII, which by dehydrobromination was transformed into the diacetate of 7(α),12(α)-dihydroxyprogesterone (XCIV). The end product was obviously not quite pure. Owing to lack of sufficient material it could not be tested physiologically.

11-Oxoprogesterone (C) and 11(β)-hydroxyprogesterone (XCIX) were prepared by Reichstein and Fuchs (38). When corticosterone (XCV) was treated with toluenesulfonyl chloride in pyridine, the toluenesulfonate XCVI was obtained, which partly reacted with the pyridine hydrochloride to form the 21-chloro compound (XCVII). The mixture of these two substances when treated with sodium iodide furnished the 21-iodo compound (XCVIII), which was reduced with zinc and acetic acid to 11(β)-hydroxyprogesterone (XCIX). This compound was found to have less than one-sixth the activity of progesterone. Treating 11(β)-hydroxyprogesterone (XCIX) with chromic acid furnished 11-oxoprogesterone (C), the physiological activity of which is unknown.[7] Recently Wettstein and Meystre (51) described the transformation of desoxycholic acid into 11-oxoprogesterone, a procedure which required eighteen different chemical steps.

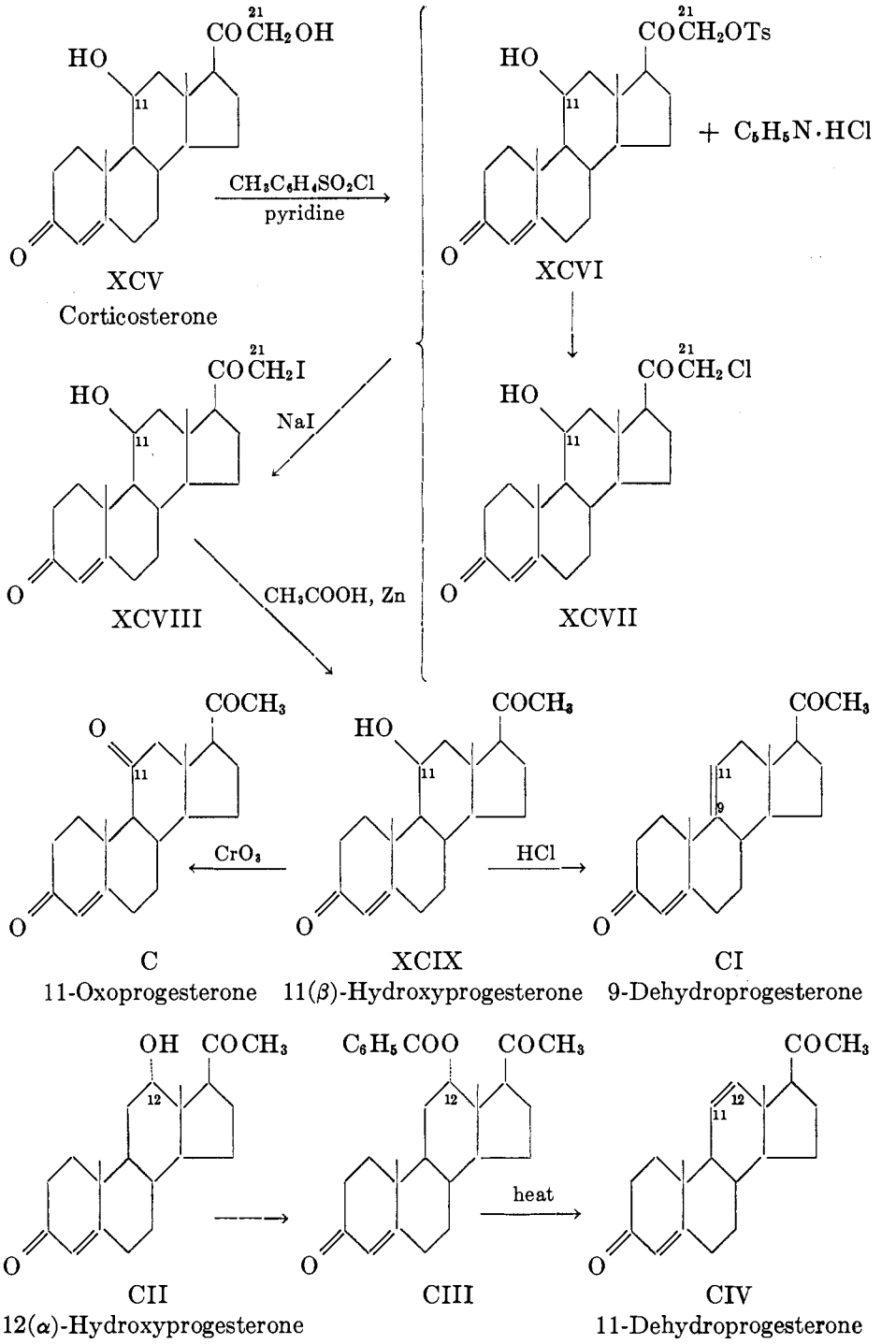
By boiling 11(β)-hydroxyprogesterone (XCIX) with glacial acetic acid and concentrated hydrochloric acid Shoppee and Reichstein (43; *cf.* also 18) obtained a yield of about 65 per cent of 9-dehydroprogesterone (CI). Four milligrams of this substance was active in the Corner–Allen test.

11-Dehydroprogesterone (CIV) was prepared from 12(α)-hydroxyprogesterone (CII) by Hegner and Reichstein (18). 12(α)-Hydroxyprogesterone in turn was obtained from desoxycholic acid by way of a degradation of the side chain and further transformations of the resulting methyl ketone (2). It (CII) is said to possess no appreciable progestational activity (13). To prepare the 11-dehydro compound, 12(α)-hydroxyprogesterone (CII) was benzoylated and the benzoate (CIII) subjected to a thermal decomposition. 11-Dehydroprogesterone (CIV) produced the Corner–Allen reaction with 2 mg. or less.

17(α)-Hydroxyprogesterone (CV), originally thought to possess the β-configuration, was isolated from adrenal extracts by Pfiffner and North (31, 32) and later also by von Euw and Reichstein (46). It possesses no progestational activity. Prins and Reichstein (37) prepared the same substance by partial

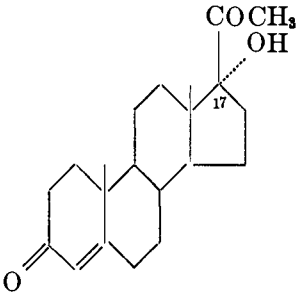
[6] Formulas XC and XCI have been reinterpreted according to Lardon (22); *cf.* also reference 9.

[7] For 11-oxoprogesterone *cf.* also Hegner and Reichstein (19).

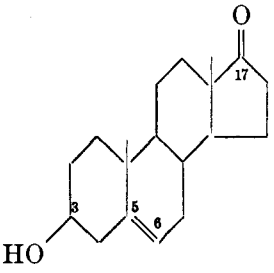

21
CO CH2 OH
HO
11
O
CH3C6H4SO2Cl
pyridine
XCV
Corticosterone
21
CO CH2 OTs
HO
11
O
+ C5H5N·HCl
XCVI
21
CO CH2 I
HO
11
O
NaI
CH3COOH, Zn
XCVIII
21
CO CH2 Cl
HO
11
O
XCVII
COCH3
O
11
O
CrO3
C
11-Oxoprogesterone
COCH3
HO
11
O
HCl
XCIX
11(β)-Hydroxyprogesterone
COCH3
11
9
O
CI
9-Dehydroprogesterone
OH
COCH3
12
O
CII
12(α)-Hydroxyprogesterone
C6H5COO
COCH3
12
O
heat
CIII
COCH3
12
11
O
CIV
11-Dehydroprogesterone

synthesis, which will not be reviewed because there are too many steps involved.

The 17(β)-hydroxyprogesterone (CVIII) to which the α-configuration was originally assigned was prepared by Goldberg *et al.* (15) by hydration of ethinyltestosterone (CVII) in the presence of mercuric *p*-toluenesulfonamide. No data are available regarding the physiological activity of this 17(β)-hydroxyprogesterone (CVIII). As is generally known, the intermediate 17-ethinyltestosterone (anhydrohydroxyprogesterone, pregneninolone) (CVII) is an orally effective progestational compound which is accessible from dehydroisoandrosterone (II) (*cf.* 41).

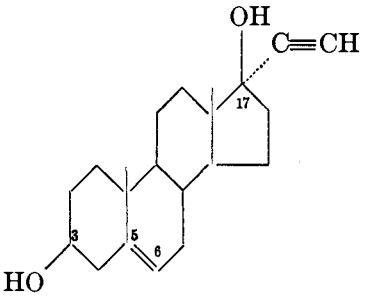


CV
17(α)-Hydroxyprogesterone

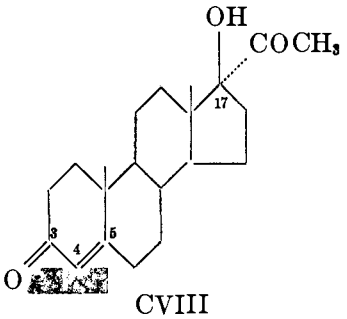


II
Dehydroisoandrosterone

K + CH≡CH →



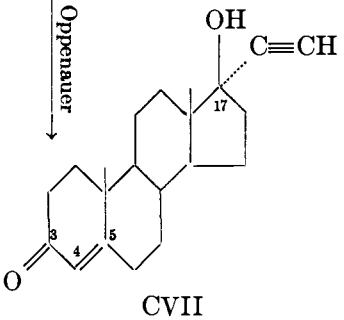
CVI



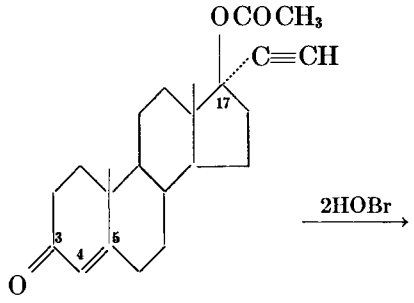
CVIII
17(β)-Hydroxyprogesterone

← $(C_7H_7SO_2NH)_2Hg$

Oppenauer ↓

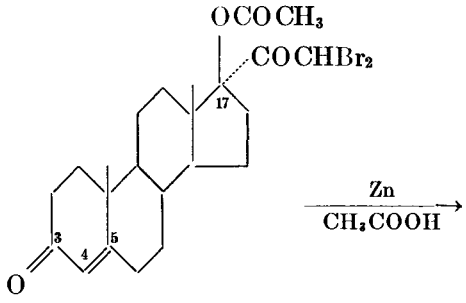


CVII
17-Ethinyltestosterone
[anhydrohydroxyprogesterone, pregneninolone]



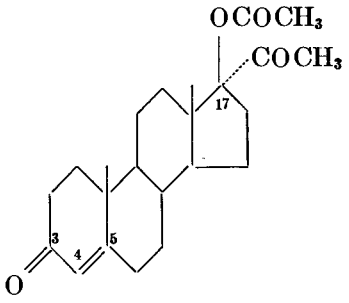
CIX

2HOBr



CX

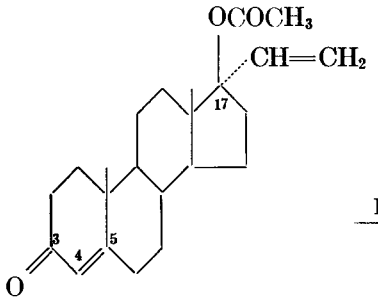
Zn
CH_3COOH



CXI

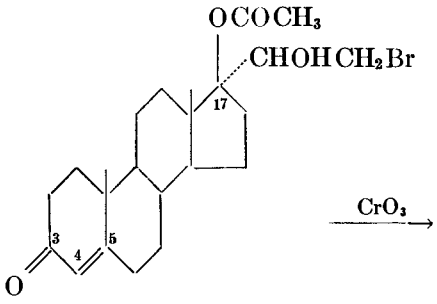
17(β)-Acetoxyprogesterone

Zn
CH_3COOH



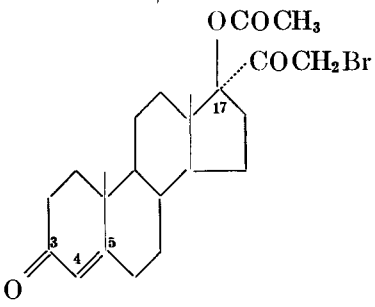
CXII

HOBr



CXIII

CrO_3



CXIV

17(β)-Acetoxyprogesterone (CXI) was first described by Ruzicka (39a, 39b). Recently Salamon and Reichstein (40a) succeeded in preparing this compound from either the acetate of ethinyltestosterone [17(β)-acetoxy-Δ^4-pregnen-20-ine-3-one] (CIX)(39b) or 17(β)-acetoxy-$\Delta^{4,20}$-pregnadien-3-one (CXII) (37a). When reacted with hypobromous acid, compound CIX yielded the dibromo ketone CX, which on treatment with zinc dust in a solution of glacial acetic acid furnished 17(β)-acetoxyprogesterone (CXI). On the other hand, the diene CXII yielded with hypobromous acid the monobromo compound CXIII, which was oxidized by means of chromic acid to the bromodiketone CXIV. On treating the latter with zinc in a solution of glacial acetic acid 17(β)-acetoxyprogesterone (CXI) resulted.

In conclusion it may be stated that of the homologs of progesterone only 10-norprogesterone appears to manifest outstanding progestational activity. Unfortunately it is difficult to prepare. Most of the oxygenated progesterones reviewed produce no significant physiological action. With the exception of 16-dehydroprogesterone all dehydroprogesterones known at present show appreciable progestational activity. They appear to be only slightly less active than progesterone.

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