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CHEMISTRY OF 19-NORSTEROIDS

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1. INTRODUCTION

In the production of highly active steroidal compounds, it has been found that their hormonal activity can be increased (*i*) by introducing into the steroid molecule additional substituents, such as halogens, alkyl groups, and hydroxy-groups not normally present in the natural compounds, or (*ii*) by preparing compounds in which certain structural units present in natural steroids are missing. This class of compounds includes the 19-norsteroids, which do not have the methyl group at $C_{(10)}$ of the steroid skeleton.

Some 19-nor-compounds have a considerably higher activity than their 19-methyl analogues. For practical application, however, it is not so much the generally higher level of physiological activity of 19-norsteroids which is of importance, as their highly specific action in comparison with the natural steroids. Thus compounds have been prepared having high anabolic or anti-oestrogenic activity but practically no androgenic action; highly active gestagens, hypotensive and contraceptive agents, etc., have also been obtained. The high physiological activity of 19-norsteroids has led to their rapid introduction into medical practice and to an increased number of preparative studies in this field. It is difficult to find a section of organic chemistry which has developed so rapidly in the last 5–10 years as the study of modified steroid hormones, and of 19-norsteroids in particular. The index to *Chemical Abstracts* for 1950 contains only three references to 19-norsteroids, while for 1960 there are about 200. The only existing review of the chemistry of 19-norsteroids[1], which covers work appearing up to 1958, is thus considerably out of date.

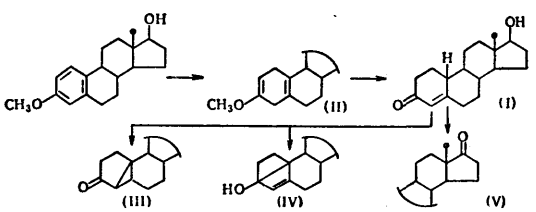
Because of limitations of space, we have used only reviews and the most important original papers in discussing the pharmacology and clinical use of 19-norsteroids, but the literature on their chemistry will be reviewed as fully as possible.

2. DERIVATIVES OF 19-NORANDROSTANE

(*a*) 19-Nortestosterone and Its Isomers

19-Nortestosterone (I) has been obtained by the Birch reduction of oestrone and oestradiol, alkaline treatment of 19-hydroxytestosterone, and various total syntheses.

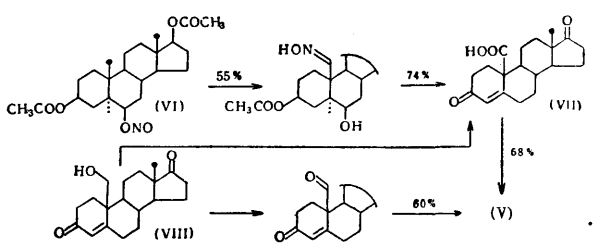
As starting materials Birch used ethers of oestradiol or oestrone. The reduction of glyceryl oestradiol ether by Birch's original procedure[2-4] gives (I) in yields of not more than 33%. Much better results are obtained from methyl oestradiol ether; hydrolysis of the resulting dihydro-derivative (II) with methanolic hydrogen chloride gives (I) in an overall yield of 80–90%.[5-8] The structure of (I) has been proved by its conversion to oestradiol by enzymatic dehydrogenation, and by its infrared and ultraviolet spectra[9-11]. The hydrogen atom at $C_{(10)}$ has the more stable, "natural" β-configuration, as has been shown by study of its optical rotatory dispersion[12,13] and nuclear magnetic resonance[14,15]. Oxidation of the 17-hydroxy--group of compound (III) with chromium(VI) oxide gives 19-norandrost-4-ene-3,17-dione (V).[6,16,17]. Photolysis of (I) in nitrogen produces a mixture of the 4,10- and 3,10--cyclosteroids (III) and (IV)†.[18]



19-Nortestosterone is obtained in practically quantitative yield by the alkaline treatment of 19-hydroxytestosterone, itself obtained by incubating testosterone with adrenal tissue or by partial synthesis from strophanthidin[19,20]. The 19-norandrostenedione (V) is also obtained by alkaline treatment of compounds oxidised at the 19-position. An important step in one preparation of (V)[21,22] is photolysis of 6β-hydroxy-3,17-diacetoxyandrostane nitrite (VI) (obtained from 3,17-diacetoxyandrost-5-ene) to the 19-aldoxime, which is dehydrated with phosphorus oxychloride in pyridine to give the corresponding nitrile; this is saponified and oxidised to produce the diketo-acid (VII), which is decarboxylated to the 19-norandrostenedione (V).

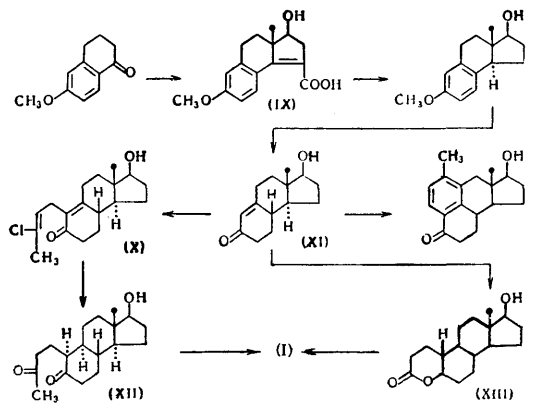
The compound (V) has also been prepared from the 6,19-oxide produced by oxidation with lead tetraacetate of the corresponding 5α-bromo-6β-hydroxy-compound[23].

Another method[24,25] starts from 19-hydroxyandrost-4--ene-3,17-dione (VIII), obtained by fermentation of the corresponding 19-deoxy-compound with *Corticium sasakii*. Oxidation of (VIII) with chromium (VI) oxide gives the diketo--acid (VII), which is converted to (V) as before. Mild oxidation gives the 19-aldehyde, which on heating with methanolic sodium hydroxide gives (V):



Various methods for the total synthesis of (I) from 1,2,3,4-tetrahydro-6-methoxy-1-oxonaphthalene have been described. In one of these[26,27] six steps yield the acid (IX), the laevorotatory isomer of which corresponds to the natural series. Decarboxylation of (IX) followed by selective hydrogenation gives a tricyclic compound containing the *B*, *C*, and *D* rings, which is reduced by Birch's method to the unsaturated ketone (XI). The usual method for attaching ring *A*, alkaline condensation with methyl vinyl ketone, gave only a product of cyclopentanophenalene structure when applied to (XI). Condensation with 1,3-dichlorobut-2-ene in the presence of sodium t-pentoxide gave compound (X), which on acid hydrolysis followed by catalytic hydrogenation yielded the diketone (XII); cyclisation of this with a mixture of hydrochloric and acetic acids was accompanied by epimerisation at $C_{(10)}$ and gave (I), identical in all respects with the natural compound.

Another method for preparing (I) starts from the racemic ketone (XI);[28] this is condensed with methyl acrylate in the presence of potassium t-butoxide to give an acid, which on catalytic hydrogenation and treatment with acetic anhydride gives the lactone (XIII), and this on reaction with methylmagnesium iodide followed by acidic cyclisation gives racemic (I):

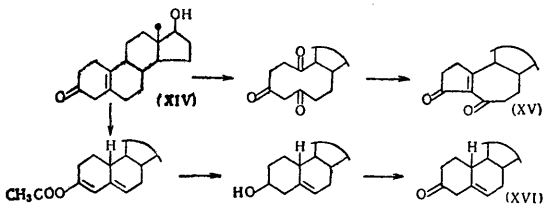


19-Nortestosterone (Nandrolone) has an anabolic activity equal to that of testosterone propionate, but its androgenic activity is only 6% of that of the latter; thus the ratio of anabolic to androgenic activity, which determines the clinical value of an anabolic agent, is 17 in 19-nortestosterone (taking that of testosterone propionate as unity). The product (I) also has strong anti-oestrogenic activity, weak gestagenic and anti-aldosteronic activity, and practically no oestrogenic, hypotensive, corticoidal, or anti--inflammatory activity[29-33].

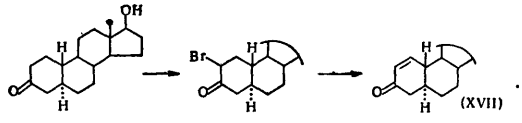
Since esterification of (I) produces compounds having a stronger and more lasting action on an organism, its esters have been widely investigated; they are usually prepared by treating (I) with the acid anhydride or chloride in the presence of pyridine or toluene-*p*-sulphonic acid. Esters of (I) have been described with the saturated aliphatic acids from formic to stearic[34-39], unsaturated aliphatic acids[35,37], and benzoic[40], hexahydrobenzoic[41,42], phenylacetic[35], and 3-phenyl- and 3-cyclopentyl-propionic acids[35,36]. The polyesters of (I) with succinic, glutaric, and phthalic acids are soluble in water, which is of importance for their practical application[35,43]. Esters have also been obtained with various amino-acids[44-46]. Of the esters of (I), only the 3-phenylpropionate (Durabolin) has found practical application as an anabolic agent, although good results in clinical trials have been shown also by the decanoate and the 3-cyclopentylpropionate[30-32].

† Here and subsequently, angular methyl groups will be represented by dots.

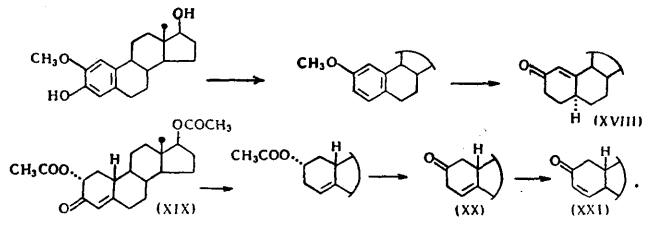
Isomers of (I) have been prepared for investigation of their physiological activity. Treatment with weak acids (oxalic or acetic), or ion-exchange resins of the Amberlite type, of the direct Birch reduction product of (II) gives an isomer of 19-nortestosterone having the double bond in the 5(10)-position (XIV).[6,47] This isomer has lower anabolic, androgenic, and gestagenic but higher oestrogenic activity than (I), and no anti-oestrogenic activity[31,48]. Ozonolysis of the acetate of (XIV) produces a triketone which on cyclisation in the presence of acetic acid gives compound (XV), which contains the so-called "abeosteroid" (*A*-nor-*B*-homosteroid) system[49]. The isomer of (I) with the double bond in the 5(6)-position (XVI) was obtained by sodium hydroborate reduction of the enol acetate of (I), with careful oxidation of the resulting 3,17-diol with chromium(VI) oxide. The physiological activity of this isomer is very like that of (I), apparently because of its ready isomerisation to the 4-en-3-one *in vivo*[50].



Compound (XVII), the isomer of (I) with the double bond in the 1(2)-position, was obtained from 4,5α-dihydro-19-nortestosterone by bromination followed by dehydrobromination, or by dehydrogenation by enzymes of *Pseudomonas testosteroni*. The 5β-epimer of (XVII) was prepared similarly[51-53]:



The isomer of (I) with the keto-group in the 2-position (XVIII) was obtained by reduction of 2-methoxyoestradiol, by way of the diethyl phosphate, to the 2-methoxy-compound, with subsequent Birch reduction; this isomer has very weak androgenic and anabolic activity[54,55]. Reduction of the keto-group of 2α-acetoxy-19-nortestosterone (XIX) by way of the corresponding ethylene thioketal gave an acetate which was hydrolysed and oxidised to the 4-en-2-one (XX); in acid medium this is converted into the 3-ene (XXI):[56,57]

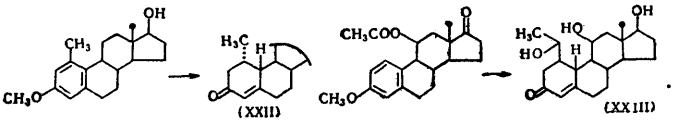


Reduction of 17-iso-oestradiol methyl ether with lithium in liquid ammonia has given the isomer of (I) with the 17-hydroxy-group in the α-configuration; this has neither androgenic nor anabolic activity[58].

Changing the position of the double bond or the keto-group or the configuration of the hydroxy-group in the molecule of (I) is thus seen to lead to a reduction in physiological activity.

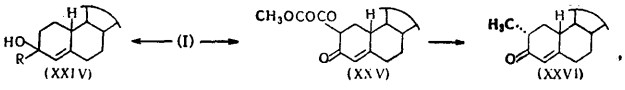
(*b*) Alkyl Derivatives of 19-Nortestosterone

The simplest *1-alkyl derivative* of (I) with a 1α-methyl group (XXII) has been prepared by Birch reduction of methyl 1-methyloestrone ether; the 1α,10β-configuration of (XXII) is based on its optical rotatory dispersion. 1α-Methyl-19-nortestosterone and its derivatives are not noticeably different in gestagenic and androgenic activity from their 1-demethyl analogues[59-61]. In the Birch reduction of 11β-acetoxyoestrone methyl ether the acetyl group migrates from the oxygen atom in the 11-position to the carbon at position 1 by a Claisen rearrangement type of mechanism, with the formation of compound (XXIII), which has anabolic, androgenic, and anti-oestrogenic activity[62,63].



2-Alkylation of (I) and its derivatives has been achieved by alkylation of the oxalyl derivative (XXV); the resulting 2α-methyl-19-nortestosterone (XXVI) has also been prepared by total synthesis by the method described above (Section 2*a*).[52,64,65]

3-Alkyl derivatives of (I) are obtained by reaction with chloroform and methyl- or butyl-magnesium bromide (XXIV):[6,67]

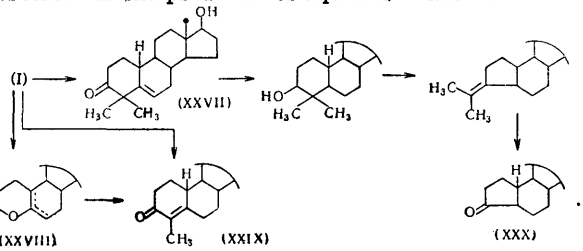


where R = CCl_3, CH_3, or C_4H_9.

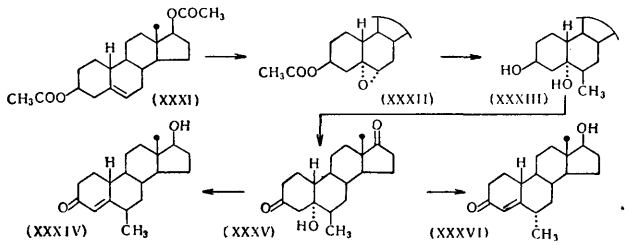
A *4-methyl group* is introduced into 19-nortestosterone by treatment of the lactone (XXVIII) — obtained from (I) by ozonolysis and lactonisation with acetic anhydride — with ethylmagnesium bromide, followed by alkaline cyclisation to 4-methyl-19-nortestosterone (XXIX).[68]

Reaction of the lactone (XXVIII) with ^{14}C-labelled methylmagnesium iodide followed by cyclisation gave 19-nor[4-^{14}C]testosterone, used as starting material for the production of oestrogens labelled in the 4-position[69-71]. Compound (XXIX), together with the 4,4-dimethyl derivative (XXVII), has been obtained also by alkylating (I) with methyl iodide in the presence of potassium t-butoxide[65,68,72]. The reduction product of the ketone (XXVII) treated with phosphorus pentachloride gives the isopropylidene derivative, which on ozonolysis produces *A*,19-dinortestosterone (XXX).[73,74]

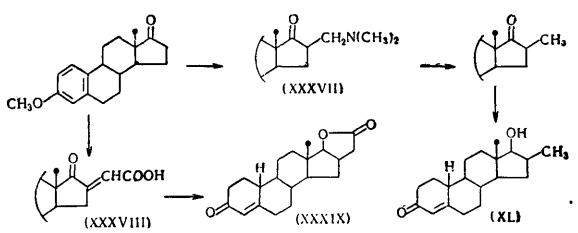
4-Alkyl-19-norandrostanes have been prepared also by catalytic hydrogenation of 1-hydroxy-4-methyloestra--1,3,5(10)-trien-17-one,[75] dehydration of 9α-hydroxyandrost-4-ene-3,17-dione,[76] and treatment of oestrone with allyl bromide in the presence of aqueous alkali[77].



5β-Methyl derivatives of (I) have been prepared by the Westphalen rearrangement and photolysis of 1-dehydrotestosterone acetate[78-80]. *6-Methyl homologues* of (I) have been obtained from the enol acetate of (I), the sodium tetrahydroborate reduction of which produces the dihydro derivative (XXXI), which is oxidised by monoperphthalic acid to the 5α,6α-oxide (XXXII); reaction of this with methylmagnesium iodide, and followed by oxidation of the resulting triol (XXXIII) with chromium(VI) oxide, gives the compound (XXXV), which is the main starting material for further preparations. Dehydration with thionyl chloride in pyridine, reduction of both keto-groups in the resulting ketone with lithium tetrahydroaluminate, and selective oxidation of the 3-hydroxy-group with manganese dioxide produce 6β-methyl-19-nortestosterone (XXXIV). Dehydration of compound (XXXV) with sodium hydroxide leads to a change of configuration, giving a diketone containing a 6α-methyl group; with the keto-group in the 3-position protected by formation of the ethyl enolate sodium tetrahydroborate reduction of the 17-keto-group and acid hydrolysis give 6α-methyl-19-nortestosterone (XXXVI):[81]



16β-Alkyl derivatives of (I) have been prepared from methyl oestrone ether, which by the Mannich reaction gives the amine (XXXVII), converted in two stages into methyl 16β-methyloestrone ether. Reduction of the 17-keto-group with sodium tetrahydroborate and of ring *A* by the Birch method gives 16β-methyl-19-nortestosterone (XL), which has high anabolic and antigonadotropic activity[82]. Condensation of methyl oestrone ether with glyoxylic acid produces the acid (XXXVIII); successive reduction with sodium tetrahydroborate, hydrogen over a platinum catalyst, and lithium in liquid ammonia has given the lactone of 16β-carboxymethyl-19-nortestosterone (XXXIX), which has antiandrogenic activity[83]:



17α-Alkyl derivatives of 19-nortestosterone (XLIII) are usually prepared by reaction of the appropriate Grignard reagent with 17-ketones of the 19-norandrostane series. Various methods have been worked out for preventing the 3-keto-group from being involved in the reaction, by varying the order in which reduction and alkylation are carried out and the methods of protecting the 3-keto-group:

A. Reaction of methyl oestrone ether with the Grignard reagent followed by Birch reduction of the 17α-alkyl derivative (XLI) to the compound (XLIII).[7,84-86]

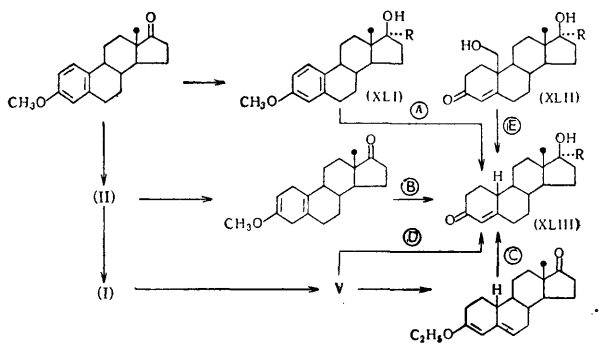
B. Oxidation with chromium(VI) oxide, or by the Oppenauer method, of the Birch reduction product of (II), reaction of the product with the Grignard reagent[87,88] or acetylene[89,90], and hydrolysis to a compound of the type (XLIII).

C. Oxidation of (I) with chromium(VI) oxide to the dione (V), protection of the 3-keto-group of (V) as the ethyl enolate, the pyrrolidine derivative, or the ethylene ketal[85,91-93], and reaction with the Grignard reagent or acetylene.

D. A specific method for 17α-ethynyl derivatives is the direct reaction of (V) with acetylene in the presence of alkaline reagents; this reaction proceeds only at the 17-keto-group[94].

Variants of these methods include reduction of unsaturated to saturated 17α-substituents either during the Birch reduction (method A) or by catalytic hydrogenation (methods B–D)[84,95-97].

E. A completely different method comprises perfusion of 17α-alkyltestosterones with adrenal tissue to obtain the 19-hydroxy-compounds (XLII), which after treatment with sodium hydroxide in aqueous methanol give 17α-alkyl-19--nortestosterones (XLIII).[98]

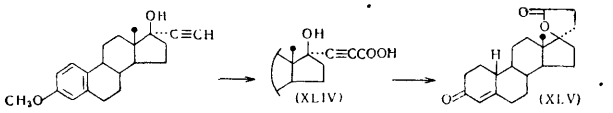


There exists a very large volume of literature on the physiological activity of 17α-alkyl-19-nortestosterones, including reviews[30-32,99,100]. The *anabolic activity* is at a maximum with the lower alkyl groups (CH_3, C_2H_5), when the ratio of anabolic to androgenic activity is 17 (testosterone propionate = 1). With lengthening of the alkyl chain, and the introduction of unsaturated substituents therein, both the anabolic and the androgenic activity are much decreased. 17α-Alkyl-19-nortestosterones are exceptionally active gestagens; as compared with progesterone they are 5–10 times as active when administered subcutaneously and more active by a factor of several powers of ten when administered orally. The gestagenic activity is greater with unsaturated substituents (vinyl, ethynyl, allyl, methallyl) and with substituents of the type –C≡CX, where X is alkyl or halogen.

Derivatives of (I) with 17α-alkyl substituents have practically no *oestrogenic* activity, but their 5(10)-ene isomers have 2–6% of the oestrogenic activity of oestrone. However, the 17α-alkyl-19-nortestosterones are powerful *anti-oestrogens*; thus in this respect the 17α-ethyl compound is 70 times as active as testosterone propionate and 12 times as active as progesterone[101,102]. Most compounds of this type inhibit ovulation and so are used as contraceptives[103–105]. The 17α-alkyl homologues of (I) are weak inhibitors of the growth of certain malignant tumours[106–108]. The 17α-alkyl-4-ene compounds also have a comparatively weak hypotensive action, which is completely absent in the 5(10)-ene isomers; neither series exhibits anti-inflammatory activity[109].

Four 17α-alkyl-19-nortestosterones are used medicinally and are prepared on an industrial scale: 17α-methyl--19-nortestosterone (Methyloestrenolone, Neosteron, Normethandrolone, Orgasteron) and 17α-ethyl-19-nortestosterone (Nilevar, Norethandrolone) mainly as anabolic agents, 17α-ethynyl-19-nortestosterone (Norlutin, Norethindrone, Norethisterone) as an oral progestative agent, and 17α-ethynyl-17β-hydroxyoestr-5(10)-en-3-one (Enovid, Norethynodrel, Ethynyloestrenolone) mainly as a contraceptive. The different types of activity of these compounds are compared in the Table; each has a fairly specific range of application.

If the steroid skeleton contains a 17-substituent of the type $[CH_2]_nCOOH$, cyclisation to form a spirolactone may occur. Thus the lactone of 17α-2′-carboxyethyl-19-nortestosterone (XLV) has been prepared by converting the Grignard derivative of 17α-ethynyloestradiol methyl ether to the acid (XLIV), catalytically hydrogenating this to the saturated acid, reducing its sodium salt with lithium in liquid ammonia, and hydrolysing the reduction product with hydrochloric acid[110,111]:



Compounds such as (XLV) are extremely active antagonists of mineralocorticoid hormones, especially (XLV) itself, known under the brand number SC-8109, which is four times as active as its 19-methyl analogue in blocking mineralocorticoids and has been used for treating various oedemas and primary hyperaldosteronism. The anticorticoidal activity is reduced if the double bond in the 4-position is hydrogenated or replaced by a 5(10)-double bond or if the lactone ring is expanded. The presence of an 11α--hydroxy- or 11-oxo-group greatly reduces the activity, while an 11β-hydroxy-group slightly increases it; it has also been reported that the introduction into SC-8109 of a 6-double bond and a 7-thioacetyl group increases the activity[111–113].

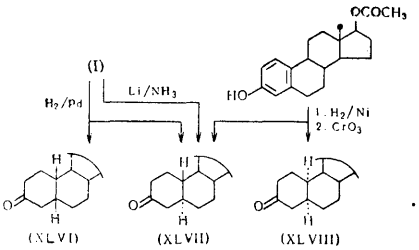
TABLE. Physiological activity of 17α-alkyl-19-nortestosterones.

Trade name	Type of activity						
	gestagenic	anabolic	androgenic	oestrogenic	anti-oestrogenic	inhibition of ovulation	hypotensive
Neosteron	++	++	+	0	++	+	0
Nilevar	++	++	+	0	++	+	+
Norlutin	++	+	+	0	+	+	0
Enovid	+	0	0	+	0	++	0

++ high activity
+ weak activity
0 practically no activity

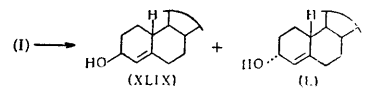
(*c*) Reduction Products of 19-Nortestosterone

Reduction of the double bond of (I) with lithium in liquid ammonia accompanied by decomposition of the reaction mixture by means of ammonium chloride gives the 5α,10β-dihydro-derivative (XLVII).[114] Catalytic reduction of (I) over ruthenium dioxide or palladium gives a mixture of the 5α,10β-isomer (XLVII) and the 5β,10β-isomer (XLVI).[114–117] A third series of isomers, with the 5α,10α-configuration (XLVIII), was obtained, together with an equal quantity of the 5α,10β-isomer (XLVII), by hydrogenating oestradiol 17-acetate over Raney nickel, followed by chromium(VI) oxide oxidation of the 3-hydroxy-group and hydrolysis of the 17-acetate residue[117]. Isomers having the 5β,10α-configuration would require a boat conformation for ring *B* and are apparently less stable; none have yet been prepared.



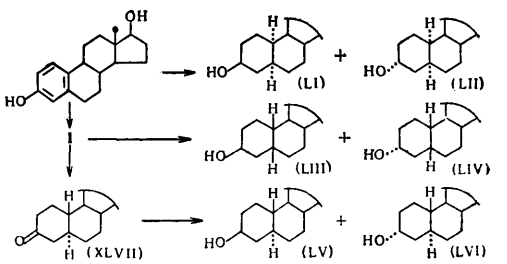
Hydrogenation of the 4-double bond of derivatives of (I) greatly reduces the anabolic, androgenic, and gestagenic activity, which also depend on the configuration at $C_{(5)}$ and $C_{(10)}$: the 5α,10β-compounds (XLVII) are the most active, and the 5β,10β-compounds (XLVI) the least; the 5α,10α--compounds (XLVIII) have a hormonal activity at all. The 5α,10β- and 5β,10β-dihydro-compounds also have strong anti-oestrogenic and hypotensive properties[101,118].

Reduction of the 3-keto-group of (I) with lithium tetrahydroaluminate or sodium tetrahydroborate gives a mixture of isomers containing the 3β-isomer (XLIX) and the 3α-isomer (L) in the ratio of about 2:1.[119,120] This reduction lowers the anabolic and androgenic activity but leaves the gestagenic activity apparently unaffected[30,31,50]:

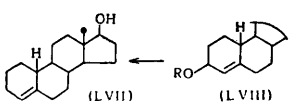


Complete reduction products of (I), the oestrane-3,17--diols, are found in human urine (5β,10β-series)[121–123], and are also products of the metabolism of (I) by homogenates of rat liver (5α,10β-series)[124]. The first preparations of this type of compound were achieved by exhaustive hydrogenation of oestrogen hormones over platinum oxide in alcohol containing hydrogen chloride[124–129] or over nickel–copper or nickel–chromium catalysts[130]. The products, as was shown later, were mixtures of diols of the 5β,10β-series with products of the hydrogenolysis of one or both hydroxy--groups.

All six possible isomers of oestrane-3,17β-diol of the 5α,10α-, 5β,10β-, and 5α,10β-series have now been prepared[114-117,131-133]. A mixture of isomers of the 5α,10α--series (LI) and (LII), with the 3β-hydroxy-isomer greatly predominating, was obtained by hydrogenating oestradiol over ruthenium dioxide; the isomers of the 5β,10β-series (LIII) and (LIV) were obtained as by-products. It is interesting that hydrogenation of oestradiol over Raney nickel gives approximately equal amounts of isomers of the 5α,10α- and 5α,10β-series; the direction of hydrogenation of oestrogens thus depends greatly on the catalyst used. Exhaustive hydrogenation of (I) over palladium on carbon gives a mixture of isomers (LIII) and (LIV) of the 5β,10β--series, with the former predominating; reduction of (I) with excess lithium in liquid ammonia leads exclusively to the 3β-hydroxy-isomer (LIII). Oxidation of the 3β-hydroxy--compounds (LI) and (LIII) with chromium(VI) oxide followed by reduction with sodium in propanol produces the corresponding 3α-isomers (LII) and (LIV). Finally, the mixture of isomers (LV) and (LVI) of the 5α,10β-series was obtained by hydrogenating the 4,5α-dihydro derivative (XLVII) over Raney nickel. Treatment of the toluene-*p*--sulphonate of the 3β-isomer (LV) with potassium acetate in dimethylformamide gives the 3α-isomer (LVI). While the isomers of the 5α,10α-series are inactive, the 5α,10β- and 5β,10β-compounds exhibit anabolic, androgenic, and hypotensive activity, but at a much lower level than the 4-en-3-one compounds.

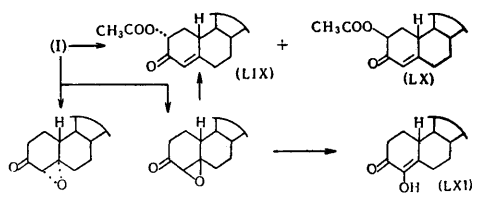


The simplest method for preparing *3-deoxy-compounds* of the 19-norandrostane series (LVII) is the Birch reduction of oestradiol in ethylamine or methylamine[134-136]; a more complex method consists in reduction of the methyl ethers or acetates (LVIII) to (LVII) with lithium in ethylamine[137-139]; (I) can also be converted into (LVII) by hydrogenolysis of the corresponding ethylene thioketal[56,140]. Finally, 3-deoxy-compounds with a double bond in the 2-position can be prepared by dehydration of the corresponding 3-hydroxy-compounds[133,141]. The 3-deoxy-compounds exhibit the same gestagenic activity as the 4-en-3--one compounds, and also anabolic and androgenic activity, but the level of this is unknown[140,141]:

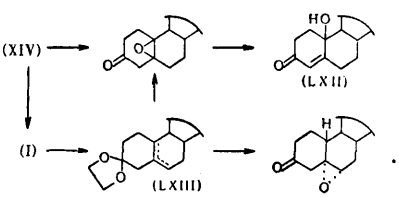


(*d*) Oxidation Products of 19-Nortestosterone

A preparative method for 2-hydroxy-compounds is lead tetraacetate oxidation of (I) acetate, to give a mixture of epimeric 2-acetoxy-derivatives in which the α-isomer (LIX) is present to a much greater extent than the β-isomer (LX).[142,143] Another method starts from the 4β,5β-oxide of (I), which undergoes rearrangement, under the influence of potassium acetate in acetic acid, to 2α-acetoxy-19-nortestosterone (LIX).[144-146] Opening of the 4β,5β-oxide ring with a mixture of sulphuric and acetic acids gives 4-hydroxy-19-nortestosterone (LXI), which has not gestagenic activity[147,148]; this compound is also obtained by the aerial oxidation of 4,5α-dihydro-19-nortestosterone (XLVIII) dissolved in t-butanol containing potassium t-butoxide, while under analogous conditions the 4,5β-dihydro-derivative (XLIX) gives the corresponding 1-en-2-ol:[149-151]

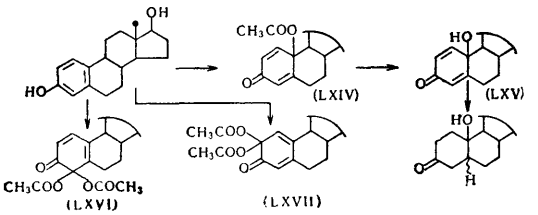


An oxygen substituent is introduced into the 6-position by fermentation of (I) with *Rhizopus nigricans* and by the perbenzoic acid oxidation of the enol acetate of (I).[152,153] Derivatives of (I) with a 10β-hydroxy-group have been obtained by several methods, for example from the 5β,10β-oxide obtained by the monoperphthalic acid oxidation of the 5(10)-ene (XIV).[154] This oxide is also prepared from 19-nortestosterone ethylene ketal (LXIII), which is a mixture of the 5(6)-ene and the 5(10)-ene in the ratio 2 : 1, as has been shown by epoxidation to the 5α,6α- and 5β,10β--oxides[155]. Opening the 5β,10β-oxide ring by boiling with methanolic potassium hydroxide produces 10β-hydroxy-19--nortestosterone (LVII).[154] The compound (LXII) has been prepared also by direct oxidation of the 5(10)-ene (XIV) with perbenzoic acid or osmium tetroxide, and, as a by--product, by fermenting (I) with *Rhizopus nigricans*[52]. The compound (LXII) possesses gestagenic and anabolic activity at a level several times lower than that of (I):[31,154]



The 10-hydroxy-derivatives of (I) with a double bond in the 1(2)-position are obtained by the lead tetraacetate oxidation of oestrone and oestradiol[156-164]; a mixture of the three products comprising the quinol acetate (LXIV) and the *gem*-diacetates (LXVI) and (LXVII) was obtained in a total yield of about 25%. The compound (LXIV) has oestrogenic activity and is apparently an antagonist of gestagenic agents; the compound (LXVI) exhibits oestrogenic properties which do not produce the usual anti-hormonal reactions. Reduction of the acetate (LXIV) with zinc dust in acetic acid or by catalytic hydrogenation gives oestrone; its hydrolysis under mild conditions produces 10β,17β-dihydroxy-oestra-1,4-dien-3-one (LXV), which is more stable than

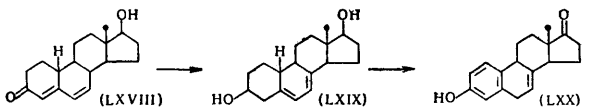
the acetate (LXIV); thus hydrogenation over palladium proceeds with retention of the 10-hydroxy-group, giving the 5ξ-tetrahydro-derivative:



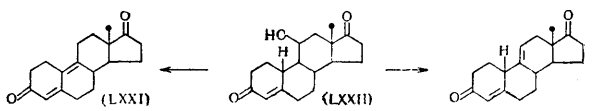
The 11α-hydroxy-derivative of (I) is obtained when the latter is fermented with *Rhizopus nigricans* [113], and also by the Birch reduction of oestrogens containing a 11α-hydroxy--group introduced by the same method [165]. 11β-Hydroxy--compounds are obtained by direct 11β-hydroxylation of (I) by perfusion with blood plasma or adrenal tissue [113], reduction of 11β-hydroxyoestrogens [69,165], and removal of the side-chain from 19-norcorticosteroids [166,167]. The 11α- and 11β-hydroxy-derivatives of (I) possess anabolic and androgenic activity [31,62]. Fermentation of (I) with *Mucor griseocyanus* and with *Penicillium urticae* give the 14α- and 15ξ-hydroxy-derivatives respectively [168,169]. Birch reduction of the methyl ether of oestriol gives 16α-hydroxy--19-nortestosterone, which has neither anabolic nor androgenic activity [170,171].

(*e*) Dehydrogenation Products of 19-Nortestosterone

The enzymatic introduction of a 1-double bond into ring *A* of 19-nortestosterone by means of *Pseudomonas testosteroni* [53,172,173], *Septomyxa affinis* [174,175], *Bacillus sphaericus* [176], *Corynebacterium simplex* [71,171], or *Protaminobacter alboflavum* [178] is accompanied by immediate aromatisation of the initially formed 1,4-diene into oestradiol. The 6-dehydro-derivative (LXVIII), which has a strong gestagenic action, is obtained from (I) by bromination followed by dehydrobromination, by dehydrogenation with benzoquinone or chloranil, or by oxidation with manganese dioxide [179,180]. Equilin was first prepared from compound (LXVIII) by reduction of its enol acetate with sodium tetrahydroborate to (LXIX), which by the Oppenauer oxidation gave the diketone, the 7(8)-double bond being preserved; enzymatic dehydrogenation of this with *Corynebacterium simplex* produced equilin (LXX): [179,181]

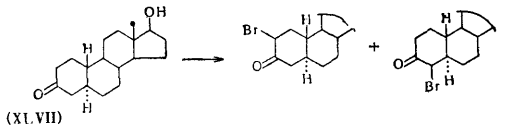


Direct bromination of (I) or its 5(10)-ene isomer in pyridine gives a high yield of the 9,10-dehydro-derivative (LXXI), also obtained by dehydration of the 11β-hydroxy--compound (LXXII) under severe conditions. Dehydration of (LXXII) under mild conditions gives the 9,11-dehydro--derivative. All these compounds possess considerable anabolic, gestagenic, and anti-oestrogenic activity [48,167,182,183].

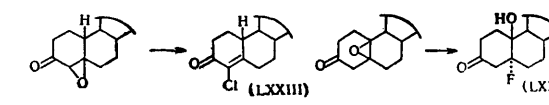


(*f*) Halogen Derivatives of 19-Nortestosterone

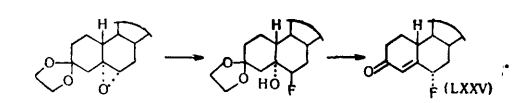
The anabolically active 2-halogeno-derivatives of (I) are prepared by direct halogenation of the 4,5α-dihydro-derivative (XLVII). The absence of the screening effect of a 19-methyl group considerably alters the stereochemical direction of bromination: while 4,5α-dihydrotestosterone gives only the equatorial 2α-bromo-ketone, bromination of the 19-nor-analogue (XLVII) gives a mixture of the axial 2β- and 4β-bromo-ketones in the ratio 1.5–2 : 1: [51,52]



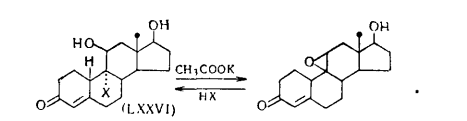
The main method for preparing a 4-halogeno-derivative of (I) is treatment of the 4β,5β-oxide with the corresponding aqueous hydrogen halide [116,144,145,184]. 4-Chloro-19-nortestosterone (LXXIII) has been obtained by direct chlorination of (I) [185] and by treating it with isocyanuryl chloride [186] or t-butyl hypochlorite [187]. Reaction of the pyrrolidine derivative of (I) with perchloryl fluoride has been suggested [188] for preparation of the 4-fluoro-derivative. 4-Chloro-19-nortestosterone has a ratio of anabolic to androgenic activity of 28 (activity of testosterone propionate = 1); it also has marked anti-oestrogenic action and weak gestagenic activity [144,148]. The opening, with boron trifluoride, of the ring of the 5β,10β-oxide obtained from the 5(10)-ene isomer of (I) gives the 5α-fluoro-10β--hydroxy-derivative (LXXIV), which has one-quarter of the gestagenic activity of Norlutin [154,155].



Halogen is introduced into the 6-position of (I) by ring--opening of the 5α,6α-oxide with hydrogen fluoride or boron trifluoride; the resulting fluorohydrin is dehydrated with anhydrous hydrogen chloride, with accompanying inversion at $C_{(6)}$, to give 6α-fluoro-19-nortestosterone (LXXV): [155]

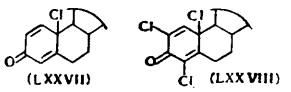


Reaction of the 9,11-dehydro-derivative of (I) with hypobromous acid produces the bromohydrin (LXXVI; X = Br), which with potassium acetate gives the 9β,11β-oxide; ring--opening of this with hydrogen fluoride, hydrogen chloride, or hydrogen iodide gives the corresponding 9α-halogeno--11β-hydroxy-derivatives of (I), which exhibit anabolic activity [189,190]:



Reaction of oestradiol with isocyanuryl chloride or *N*-chlorosuccinimide gives 10β-chloro-Δ^1-19-nortestosterone (LXXVII) in 25% yield; with the former, the

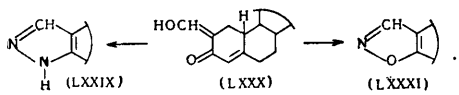
2,4,10β-trichloro-derivative (LXXVIII) is obtained as a by-product, and with the latter, a dichloro-derivative of undetermined structure. With perchloryl fluoride, oestradiol forms 10β-fluoro-Δ^1-19-nortestosterone, which is slightly more stable than its 10β-chloro-analogue (LXXVII); thus it can be hydrogenated to the saturated ketone without loss of the 10β-fluoro-atom. Compounds (LXXVII) and (LXVIII) have oestrogenic and anti-androgenic activity[191,192].



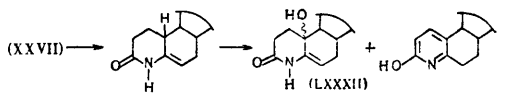
(*g*) Heterocyclic Derivatives of 19-Nortestosterone

Structurally the heterocyclic derivatives of (I) fall into two groups — those in which the heterocyclic system is fused to ring *A*, and those in which a carbon atom of the skeleton is replaced by a hetero-atom.

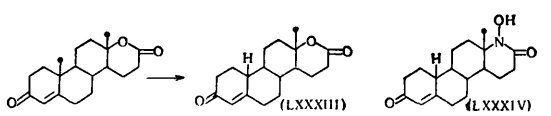
Derivatives of the first group are prepared by treating the 2-hydroxymethylene derivative (LXXX) or its 4,5α-dihydro-analogue with hydrazine hydrate to produce pyrazo--derivatives (LXXIX), or with hydroxylamine to produce isoxazolo-derivatives (LXXXI); the former have high anabolic and oestrogenic activity, and the latter high gestagenic activity[193-196]:



The lactone (XXVIII), obtained by ozonising the acetate of (I), is converted into the 4-aza-derivative by passing a stream of ammonia through a benzene solution. This compound is oxidised by selenium dioxide to (LXXXII), together with small amounts of 4-aza-oestradiol mono- and di-acetates[197,198]:

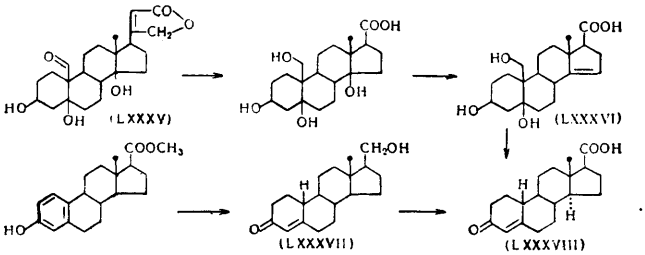


The analogue of (I) with an oxygen atom in ring *D* (LXXXIII) has been obtained from an oxidation product of testosterone, the so-called testololactone; perfusion of adrenal tissue with this gives the 19-hydroxy-compound, which loses formaldehyde under the conditions of the Oppenauer reaction to form the compound (LXXXIII).[199] Photolysis of the nitrite of (I) has given the compound (LXXXIV) with a nitrogen atom in ring *D*.[200]

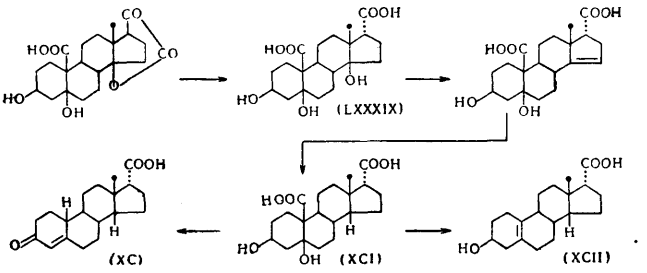


3. 19-NORETIANIC ACIDS

The 3-oxo-19-norandrost-4-ene-17β-carboxylic acid (LXXXVIII) has been prepared from strophanthidin (LXXXV): reduction of the latter with aluminium amalgam followed by oxidation with neutral potassium permanganate produced the tetrahydroxy-acid with a normal configuration of the side-chain; removal of the 14-hydroxy-group by heating with ethanolic hydrogen chloride gave the unsaturated acid (LXXXVI), which, like other 17β-substituted steroids, is catalytically hydrogenated to the 14α-dihydro-compound; successive treatment of this with *N*-bromoacetamide and Girard T reagent gives the acid (LXXXVIII).[201-203] In another method, methyl 3-hydroxy-19-norandrosta--1,3,5(10)-triene-17β-carboxylate is subjected to Birch reduction to obtain the compound (LXXXVII), which is oxidised by chromium(VI) oxide to the acid (LXXXVIII):[204]



An isomer of the acid (LXXXVIII), 3-oxo-19-nor-14β--androst-4-ene-17α-carboxylic acid (XC), has been obtained from strophanthidin (LXXXV) by a modified method[205-212]. Oxidation of strophanthidin 3-acetate with alkaline potassium permanganate gives a 33% yield of the lactone of the keto-carboxylic acid; treatment of this with alkaline hydrogen peroxide results in opening of the lactone ring, inversion at $C_{(17)}$ to the α-isomer, which is more stable for the *cis-C/D* series, and further oxidation to the dicarboxylic acid (LXXXIX). Dehydration of this acid with hydrogen chloride gives the 14(15)-ene, which, like other 17α-steroids, is catalytically hydrogenated to the 14β-compound (XCI), and this when oxidised with *N*-bromoacetamide loses the 5-hydroxyl and the 19-carboxyl to form the acid (XC). Thermal dissociation of the diacetate of (XCI) followed by hydrolysis produces the hydroxy-acid (XCII). The isomeric etianic acids (LXXXVIII), (XC), and (XCII) have been used as starting materials for the production of the corresponding 19-norprogesterone isomers (see Section 4).



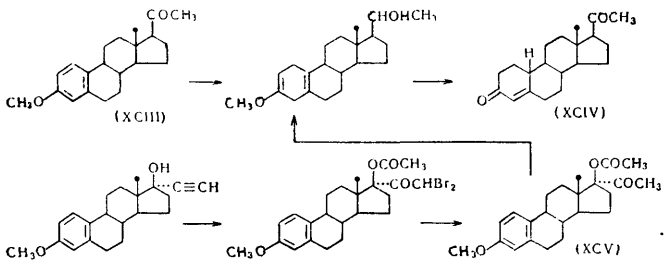
4. DERIVATIVES OF 19-NORPREGNANE

(*a*) 19-Norprogesterone

This compound has been obtained by total synthesis by a modified Woodward method[213], and by partial synthesis by four other methods. The starting material for the first of these was 5α-pregnane-3,20-dione; this was converted into the methoxy-ketone (XCIII), which by Birch reduction

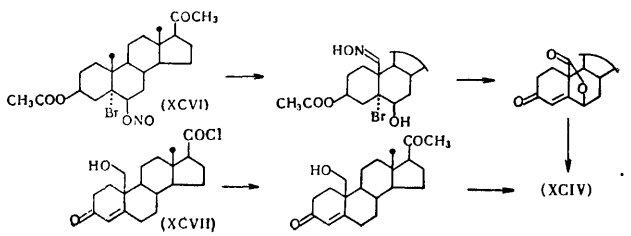
gave a compound with a 20ξ-hydroxy-group. Hydrolysis of the latter with hydrochloric acid and oxidation with chromium(VI) oxide gave 19-norprogesterone (XCIV) in a yield of 55% based on (XCIII).[214,215]

In another method, 17α-ethynyloestradiol methyl ether is converted with *N*-bromoacetamide by the Favorsky reaction into a dibromo-ketone. Debromination with zinc dust produces the 17α-acetyl derivative (XCV), which when reduced with lithium in liquid ammonia eliminates the 17-acetoxy-group and isomerises the other 17-substituent to produce the 20ξ-hydroxy-compound, which is then converted into (XCIV):[216]

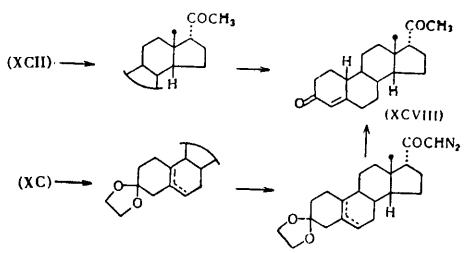


In a third method of preparing (XCIV), hydroxypregnenone is treated successivly with hypobromite and nitrosyl chloride to obtain the 5α-bromo-6-nitrite (XCVI), which on photolysis produces the 19-aldroxime; hydrolysis, oxidation, and dehydrobromination then gives the Δ⁴-3-oxo-lactone, which with zinc in acetic acid produces (XCIV).[22]

In the fourth method, the 19-hydroxyetienoyl chloride (XCVII) is converted by diazomethane into the corresponding diazo-ketone, which is reduced by hydrogen iodide to 19-hydroxyprogesterone. Treatment of this with aqueous sodium hydroxide gives (XCIV), identical with the product obtained by other methods[19,217-220]. 19-Norprogesterone has approximately eight times the gestagenic activity of progesterone and thirteen times its anti-oestrogenic activity[215,221,222]:



The isomer of (XCIV) with the 14β,17α-configuration (XCVIII) was the first 19-norpregnane to be synthesised; it was obtained in low yield from strophanthidin in 1944.[223] The synthesis was subsequently much improved, and is now carried out as follows[203-205]:

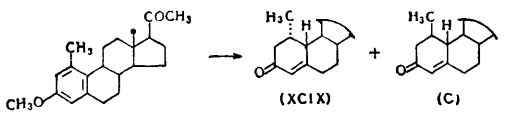


The etienic acid (XCII) treated with oxalyl chloride gives the acid chloride, which on reaction with dimethylcadmium followed by hydrolysis produces the corresponding keto-alcohol, and this is oxidised by the Oppenauer method to 19-nor-14β,17α-progesterone (XCVIII). The ketone (XCVIII) has also been prepared from the ethylene ketal of the acid (XC) by successive treatment with oxalyl chloride and diazomethane to give the diazo-ketone, which is reduced to compound (XCVIII) in a total yield of 25%. Compound (XCVIII) has about eight times the gestagenic activity of progesterone[224,225].

Even such considerable structural changes as removal of the 19-methyl group, *cis*-conjunction of rings *C* and *D*, and α-configuration of the side-chain, which is the inverse of the natural configuration, are thus seen to produce a considerable increase in hormonal activity over that found in the natural compound. In this respect it is interesting that the 15-methyl analogue of (XCVIII), 14β,17α-progesterone, has no gestagenic activity[226], demonstrating that there is no simple additive method for correlating physiological activity with structural changes in the steroid molecule.

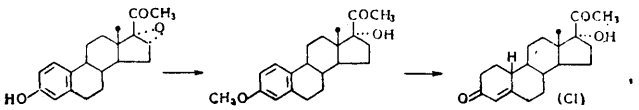
(*b*) Derivatives of 19-Norprogesterone

The compounds reviewed in this section are generally obtained analogously to the corresponding derivatives of (I). Thus reduction of 17β-acetyl-3-methoxy-1-methyloestra-1,3,5(10)-triene with lithium in liquid ammonia followed by chromium(VI) oxide oxidation of the resulting 20ξ-hydroxy-compound gives a mixture of the gestagenically active 1α-isomer (XCIX) and inactive 1β-isomer (C) of 1-methyl-19-norprogesterone[60,227]. 16α-Methyl-19-norprogesterone was prepared similarly[228].



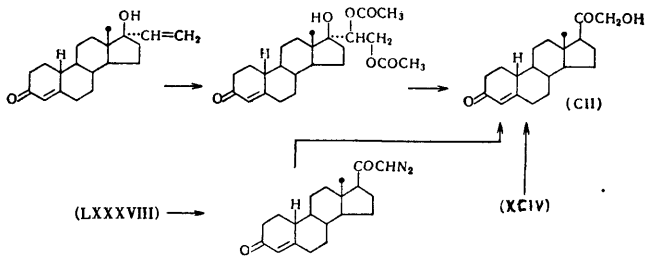
3-Deoxy-derivatives of 19-norprogesterone[137,139], Westphalen rearrangement products[80,229], and 9,10-dehydro-[182] and 4-chloro-19-norprogesterone[184] have been prepared analogously to the corresponding compounds of the 19-nor-androstane series. Fermentation of 19-norprogesterone with *Rhizopus nigricans* gives the 11α-hydroxy-derivative, and with *Curvularia linata* the 11β-hydroxy-derivative[230,231]. Fermentation with *Bacillus sphaericus* or *Corynebacterium simplex* gives the corresponding phenol[176,230,231]. Finally, the enzymes of *Helicostylum piriforme* and *Mucor griseocyanus* give the 14α-hydroxy-derivative[231] and those of *Penicillium urticae* a 15ξ-hydroxy-derivative[232].

17α-Hydroxy-19-norprogesterone (CI), which has high progestative activity, has been prepared from the 16α,17α-oxide; this is converted in three steps to the 17α-hydroxy-compound, which is reduced by the Birch method to (CI) in a total yield of up to 35%.[167] Fermentation of 17α-hydroxyprogesterone with *Corticium sasakii* or with adrenal homogenates and alkaline treatment of the resulting 19-hydroxy-compound also produces (CI).[25,233]

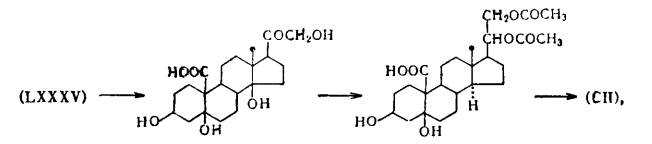


(*c*) 19-Nordeoxycorticosterone

The simplest method for obtaining this compound is 21-hydroxylation of 19-norprogesterone with enzymes of *Aspergillus niger*; the yield reaches 48%.[234] In another method, 17α-vinyl-19-nortestosterone is oxidised with osmium tetroxide and then acetylated to the 20,21-diacetoxy--derivative, which on boiling with zinc dust in toluene gives (CII).[204,235] In a third method, the acid (LXXXVIII), obtained from strophanthidin (see Section 3), is converted into the acid chloride, and this is treated with diazomethane to produce the diazo-ketone, which on heating with acetic acid gives (CII).[204,218]. Application of these reactions to the 14β,17α-isomer of (XC), which is also obtained from strophanthidin, gives the corresponding isomer of (CII), which is devoid of mineralocorticoid activity[205,223]:



Recently an original method for preparing 19-nordeoxycorticosterone (CII) directly from strophanthidin (LXXXV) has been proposed: ozonolysis of (LXXXV) gives the required side-chain directly, with simultaneous oxidation to the 10-carboxylic acid. Removal of the 14-hydroxy-group with hydrogen chloride yields the 14(15)-unsaturated compound, which when hydrogenated over a platinum catalyst forms the triacetate. Selective hydrolysis of this compound followed by chromium(VI) oxide oxidation with simultaneous decarboxylation gives the acetate of (CII).[236] 19-Nordeoxycorticosterone acetate, when tested for retention of sodium in adrenalectomised rats, was five times as active as its 19-methyl analogue[233,237].

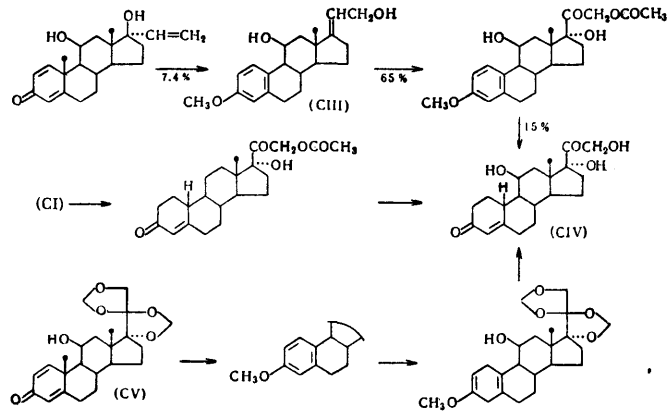


(*d*) 19-Norhydrocortisone

Three different methods have been proposed for the synthesis of 19-norhydrocortisone.

(i) 11β,17β-Dihydroxy-17α-vinylandrosta-1,4-dien-3-one is converted in five steps into the compound (CIII); successive oxidation of the side-chain with osmium tetroxide and *N*-methylmorpholine peroxide and acetylation of the product gave a compound having a dihydroxyacetone side-chain, the ethylene ketal of which is subjected to Birch reduction; acid hydrolysis of the product gives 19-norhydrocortisone (CIV). Oxidation of the 11β-hydroxy-group then yields 19-norcortisone[166].

(ii) 17α-Hydroxy-19-norprogesterone (CI) is treated with iodine in an alkali medium, and the resulting 21-iodo--derivative treated with potassium acetate to yield the 21-acetate. Introduction of the 11β-hydroxy-group by perfusion with adrenal homogenates gives 19-norhydrocortisone (CIV).[167,238]



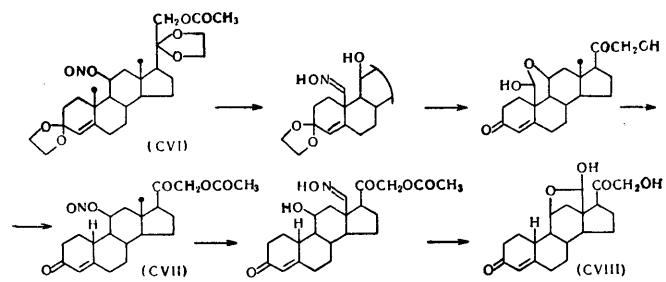
(iii) Pyrolysis of the bismethylenedioxy-derivative of prednisolone (CV) in mineral oil, followed by methylation, Birch reduction of the ether, and acid hydrolysis of the resulting dihydro-derivative gives 19-norhydrocortisone (CIV).[239]

19-Norhydrocortisone has one-tenth of the glucocorticoid activity and one-third of the anti-inflammatory activity of hydrocortisone, and one-quarter of the mineralocorticoid activity of deoxycorticosterone[166,167,240,241].

(*e*) 19-Noraldosterone

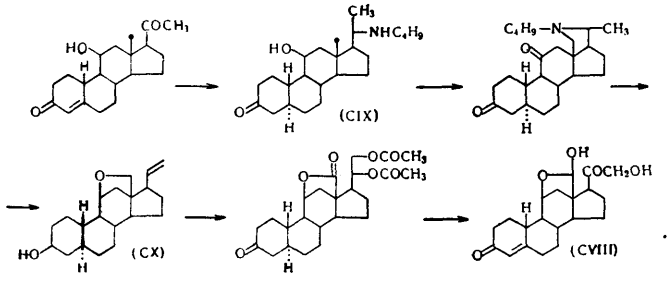
19-Noraldosterone (CVIII) has been prepared by two methods.

(i) The 11-nitrite 21-acetate of 3,20-bisethylenedioxy-pregn-4-ene-11β,21-diol (CVI) was photolysed to a mixture of 18- and 19-oximes; reaction of the latter with nitrous acid followed by hydrolysis gave the 19-aldehyde semi-acetal, which with alkali formed 19-norcorticosterone; photolysis of the 11-nitrite of this (CVII) produced the 19-oxime, which on removal of the oxime group by a known procedure[242,243] yielded 19-noraldosterone (CVIII). 17α-Hydroxy-19-noraldosterone was prepared analogously[244,245].



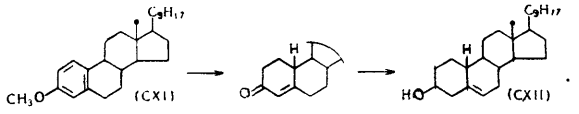
(ii) According to the patent literature[246-248], reductive amination of 11β-hydroxy-19-norprogesterone with butylamine gave the amine (CIX), which by chromium(VI) oxide oxidation and photolysis was converted into a 19-norconamine derivative; this was reduced with lithium tetrahydroaluminate, subjected to Hofmann degradation, and

treated with potassium hydroxide to obtain the 11β,18-oxide (CX). Successive oxidation of the 3-hydroxy-group with chromium(VI) oxide, of the 20(21)-double bond with osmium tetroxide, and of the 11β,18-oxide ring with ruthenium tetroxide gave the 11,18-lactone, which was brominated and then dehydrobrominated to obtain a double bond in the 4-position; formation of a hydroxyacetyl side-chain by hydrolysis and chromium(VI) oxide oxidation and, finally, reduction of the lactone group with lithium tetrahydroaluminate gave 19-noraldosterone (CVIII).

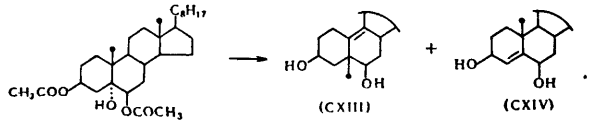


5. DERIVATIVES OF 19-NORCHOLESTEROL AND OTHER STEROIDS

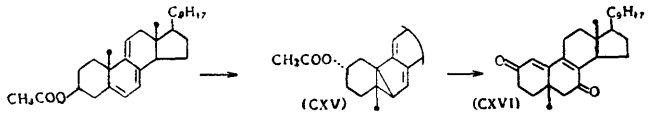
The simplest member of this series of compounds, 19-norcholesterol (CXII), has been prepared by Birch reduction of (CXI) to the 4-en-3-one and potassium tetrahydroborate reduction of the enol acetate. 7-Dehydro--19-norcholesterol has been prepared in an analogous manner[181,249]:



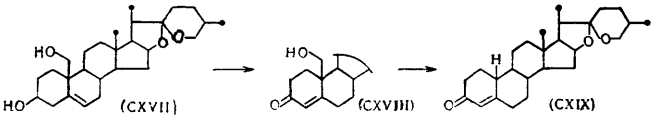
The Westphalen rearrangement is widely used for preparing derivatives of 19-norcholestane; it takes place by a mechanism similar to that of the Wagner–Meerwein rearrangement, and is accomplished by the action of a mixture of acetic anhydride and sulphuric acid or potassium bisulphate on 3,5,6-triols. This reaction has been employed to convert cholestane-3β,5α,6β-triol 3,6-diacetate into the so-called "Westphalen's diol", 5β-methyl-19-norcholest-9(10)-en-3β,6β-diol (CXIII);[250,251] in addition to a 61% yield of this compound, the reaction also gave the normal dehydration product (CXIV) in 9% yield. Under the experimental conditions, therefore, isomerism greatly predominates over dehydration[252]. The structure of Westphalen's diol was proved by spectroscopic methods and by numerous chemical reactions[253–263]. 6β-Acetoxy-5α--hydroxy-3β-methoxycholestane[264,265] and 3β-acetoxy-6β--fluoro(chloro, bromo)-5α-hydroxycholestane[266] have also been subjected to the Westphalen rearrangement.



Derivatives of 19-norergostane containing a 5-methyl group can be obtained by photochemical rearrangements. Thus photolysis of dehydroergosterol acetate produces the compound (CXV), which has been converted in three steps into the diketone (CXVI). Analogous treatment of the acetic ester of dehydrolumisterol (the $C_{(10)}$-epimer of dehydroergosterol) gives the isomer of the ketone (CXVI) with a 5α-methyl group; this photochemical rearrangement is thus fully stereoselective[267,268].

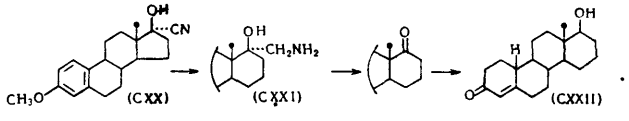


Ruscogenin (19-hydroxydiosgenin, a steroid sapogenin isolated from *Ruscus aculeatus*) (CXVII) undergoes Oppenauer oxidation to form the 4-en-3-one (CXVIII), which with alkali yields 19-nor-22α-spirost-4-en-3-one (CXIX), the first known 19-norsapogenin[269]:



6. 19-NOR-*D*-HOMOSTEROIDS

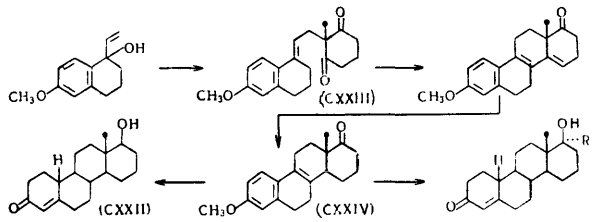
This class of compound includes 19-nor-*D*-homotestosterone, which has been prepared by total and partial synthesis, and certain of its derivatives. 19-Nor-*D*-homotestosterone (CXXII) has been obtained by partial synthesis from natural oestrone methyl ether cyanohydrin (CXX); lithium tetrahydroaluminate reduction of this produces the amine (CXXI), which on treatment with nitrous acid undergoes ring expansion to form the *D*-homosteroid. Successive reduction with sodium tetrahydroborate and lithium in liquid ammonia gives (CXXII), which has a ratio of anabolic to androgenic activity of 6 (testosterone = 1)[270]:



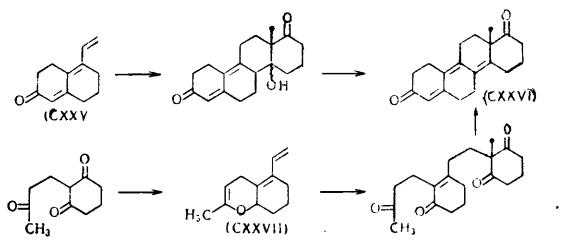
Racemic 19-nor-*D*-homotestosterone has been synthesised from 1,2,3,4-tetrahydro-6-methoxy-1-oxonaphthalene; the vinyl-substituted alcohol obtained from this was condensed with dihydro-2-methylresorcinol to give the diketone (CXXIII), which was cyclised to a chrysene derivative and the latter hydrogenated to the 14α-dihydro-compound (CXXIV). Reduction of the 17a-keto-group with lithium tetrahydroaluminate and of ring *A* with lithium in liquid ammonia produced (±)-19-nor-*D*-homotestosterone (CXXII), from which the 17aα-methyl and 17aα-ethyl derivatives

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were prepared. All these compounds have a high index of anabolic and androgenic activity, *e.g.* 3.7 for (CXXII), and 11.3 for its phenylpropionate[271-275].



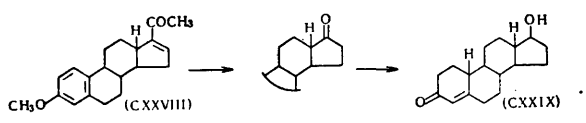
19-Nor-*D*-homosteroids have also been prepared by another procedure. The trienone (CXXV), obtained from methoxytetralone, was condensed with dihydro-2-methylresorcinol under the conditions of the Michael reaction to give 14ξ-hydroxy-19-nor-*D*-homoandrosta-3,9-diene--3,17a-dione. Dehydration of this with toluene-*p*-sulphonic acid produced the trienedione (CXXVI).[276,277] Compound (CXXVI) has been prepared also from the condensation product of dihydroresorcinol with methyl vinyl ketone, which was converted in three steps into the triene (CXXVII); condensation of this triene with dihydro-2-methylresorcinol gave a tetraketone, which under the influence of a pyridine–diethylamine mixture underwent double cyclisation to the trienedione (CXXVI).[278]



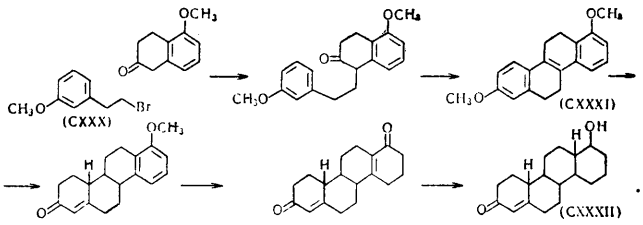
7. 18,19-DINORSTEROIDS

18,19-Dinorsteroids of the androstene, *D*-homoandrostane, and pregnane series have been prepared.

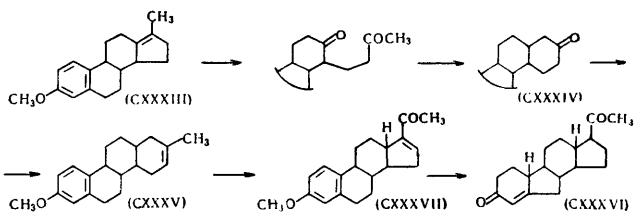
18,19-Dinortestosterone (CXXIX) has been obtained from the compound (CXXVIII), which is an intermediate in the synthesis of 18,19-dinorprogesterone (see below). Removal of the side-chain of this compound gave the 17-ketone, which on successive reduction with lithium tetrahydroaluminate and lithium in liquid ammonia formed (CXXIX); this has no androgenic or anti-oestrogenic activity[221].



A procedure has been developed for the total synthesis of 18,19-dinor-*D*-homotestosterone. Alkylation of methoxytetralone with the bromide (CXXX) produces a dimethoxy--ketone, which can be cyclised to the dimethoxychrysene derivative (CXXXI). Reduction of the central double bond with sodium in butanol and of ring *A* by the Birch method gave the compound with an aromatic *D* ring; this was converted into its ethylene ketal, ring *D* also reduced by the Birch method, the reduction product hydrolysed, and the resulting diketone reduced at the double bond and the keto--group in ring *D* to give 18,19-dinor-*D*-homotestosterone (CXXXII); this has neither androgenic nor anabolic activity[279-282]. The 11α-hydroxy-analogue of (CXXXII) has also been prepared by total synthesis; it has weak androgenic activity[283].



18,19-Dinorprogesterone (CXXXVI) has been prepared by heating oestradiol with boric acid to give (CXXXIII), which is ozonised to the diketone, and the *D*-homo-ketone (CXXXIV) obtained from this in three stages. Reaction of (CXXXIV) with methylmagnesium iodide and subsequent dehydration produces (CXXXV), which on ozonolysis to the corresponding dialdehyde followed by cyclisation gives the pregnane derivative (CXXXVIII); this on Birch reduction and oxidation of the resulting 20ξ -hydroxy-compound with chromium(VI) oxide yields (+)-18,19-dinorprogesterone (CXXXVI), which has no gestagenic activity[284-287]. Racemic 18,19-dinorprogesterone (CXXXVI) and its 14α-hydroxy--analogue have been prepared by total synthesis using a modified Sarett procedure; these compounds have less than 2% of the gestagenic activity of progesterone[288].



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2,4,6-TRICHLORO-1,3,5-TRIAZINE (CYANURYL CHLORIDE) AND ITS FUTURE APPLICATIONS

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I. INTRODUCTION

The chemistry of 2,4,6-trichloro-1,3,5-triazine† (cyanuryl chloride)[1-5] formed the subject of a section in the comprehensive monograph "s-Triazines and Derivatives"[6], which reviewed work, published up to 1954, on the preparation, reactions, and applications of the compound. The problem of the reactivity of cyanuryl chloride and other halogenated derivatives of triazine was not discussed in the monograph.

Although the chemistry of cyanuryl chloride has been intensively developed since then, only one review paper in Japanese, covering the literature up to 1956, has dealt with this question[7]. It describes the synthesis of triazine derivatives from cyanuryl chloride, and examines some relations between the nature of the reactants and their reactivity. This review does not cover the practical application of cyanuryl chloride and the products obtained from it.

The chemistry of cyanuryl chloride has not been reviewed in the Soviet literature, and it is therefore opportune and useful to report progress in this field.

A great achievement is the production of a new type of dyes — the reactive dyes[8-28] — based on cyanuryl chloride. Their molecules contain active chlorine atoms combined with the triazine ring, and during dyeing react with the hydroxy- or amino-groups of the fibre. This results in the formation of a chemical compound between the fibre and the dye, which is of ether type in the case of cellulose and of amide type with wool and other fibres containing primary or secondary amino-groups. The resulting dyeings are distinguished by their brightness and purity of colour and by exceptionally high fastness to wet treatments, and the dyes themselves by simplicity of application and relative cheapness, which gives them an advantage over other groups of dyes.

Cyanuryl chloride is of great value for agricultural needs: especially during recent years numerous derivatives have been synthesised which act as insecticides, fungicides, and week-killers[29-37], some of which have already been used in agriculture. The most effective are compounds containing active chlorine atoms combined with triazine, in particular 2-chloro-4,6-bisdimethylaminotriazine, and also dichloro-derivatives of triazine.

Recently compounds have been obtained from cyanuryl chloride which inhibit the growth of tumors, and this may prove invaluable in the treatment of cancer[38-41]. Other drugs required in medicine are synthesised on the same basis, for example antitubercular[42,43] and trypanocidal[44-49] preparations.

Cyanuryl chloride is of equal value for the synthesis of many other substances required in various branches of the economy. Thus certain sulphur-containing triazine derivatives obtained from cyanuryl chloride act as antioxidants[50], plasticisers[51], and vulcanisation accelerators[53] in the rubber industry. Other preparations have great importance as textile auxiliaries, especially as finishing[54] and brightening[55,56] agents. In the synthetic dye industry cyanuryl chloride is employed not only for the synthesis of reactive dyes, on which more than a hundred patents have been taken

† Since the present review is concerned only with derivatives of 1,3,5-triazine, the numerical locants will be omitted, and the molecule referred to simply as "triazine".