STRATEGY IN DRUG RESEARCH. SYNTHESIS AND STUDY OF THE PROGESTATIONAL AND OVULATION INHIBITORY ACTIVITY OF A SERIES OF 11β-SUBSTITUTED-17α-ETHYNYL-4-ESTREN-17β-OLS.

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ABSTRACT

Using the strategy based on the Hansch method which analyses effects of substituents on biological activity in terms of their hydrophobic, electronic and steric effects we selectively synthesised a series of 11β-substituted-17α-ethynyl-4-estren-17β-ols that combine ease of synthesis with good discrimination between these factors aiming at finding the compounds with optimum biological activity in that series. The compounds were tested quantitatively in the Clauberg test (rabbit) and the ovulation inhibition test (rat). The differences in biological activity could reasonably be correlated with two steric effects introduced by the 11β-substituent. These were a change in the overall shape of the 11β-substituent and the angular methyl group, and direct steric hindrance of the steroid-receptor protein binding. Some exceptions were found possibly due to metabolic conversion of these compounds to the corresponding 11β-substituted-17α-ethynyl-1,3,5(10)-estratriene-3,17β-diols.

INTRODUCTION

In pharmaceutical research the aim of the primary biological investigations is to find the optimum activity in a series of related structures, for example a group of compounds only differing in the substituent at one position and with the same configuration. If that activity meets the desired standards the compound with that activity is considered a potential candidate for clinical trials and it will be evaluated further in animal experiments to confirm its activity and to prove the absence of unwanted side effects.

This approach is successful provided the biological activities of the compounds submitted by the chemists cover, in the biological test, a range of potencies, if possible some powers of ten. By plotting the activities found against structural parameters, leads for the synthesis of other promising compounds may be derived. Even with the limited precision of the biological screening tests the most active compound(s) are easily identified.

It breaks down however when the series of compounds, which are submitted for testing, are too closely related, then no significant differences in biological activities are found. Discrimination on the basis of the pharmacological profile can then be attempted after more extensive biological testing but usually within a closely related chemical series similar profiles are found. Only then common sense prevails and one compound is selected on grounds of being the cheapest or the first compound synthesised and thus tested **most** extensively thereby admitting that most of the work done and money spent on the synthesis and testing of the other compounds was wasted.

The proper strategy thus is, that the chemists aim at synthesising a diverse, limited series of compounds and submit these for quantitative biological testing. The crucial question then is: what substituents give the best discrimination? Hansch and others (1) have shown that the influence of a substituent on biological activity can often be correlated with its lipophilicity, steric size and electronic influence.

So both Craig (2) and Topliss (3) suggested to select a series of compounds with substituents that combine ease of synthesis

with good discrimination between these effects. We illustrate this approach by discussing our work in a series of 11β-substituted steroids.

PILOT INVESTIGATIONS

The basic structure selected was 17α-ethynyl-4-estren-17β-ol (lynestrenol) a widely used active progestational compound (4, 5). The choice for substitution at the 11β-position was based on the high progestational activity reported for some 11β-methyl- (6, 7) and 11β-chloro-steroids (8). The first series synthesised and tested for oral progestational (9) and ovulation inhibitory activity (10), consisted of the 11β-methyl-, 11β-chloro- and 11β-fluoro-derivative. This series of substituents gives a good discrimination as illustrated in table 1, where the Hansch parameter π (11) is used as a measure for lipophilicity and the Taft parameters E_S and σ (12) to quantify the steric and electronic factors respectively (13).

TABLE 1

	H	CH_3	Cl	F
π	0.00	0.50	0.39	-0.17
E_S	1.24	0.00	0.27	0.78
σ	0.00	-0.10	1.05	1.10

High progestational and ovulation inhibitory activities were found on testing (table 2). For this small series the results also suggest a good correlation between the Clauberg activity (rabbit) and the ovulation inhibitory activity (rat).

TABLE 2

Relative oral activities on a molar basis of 11β-substituted-17α-ethynyl-4-estren-17β-ols.

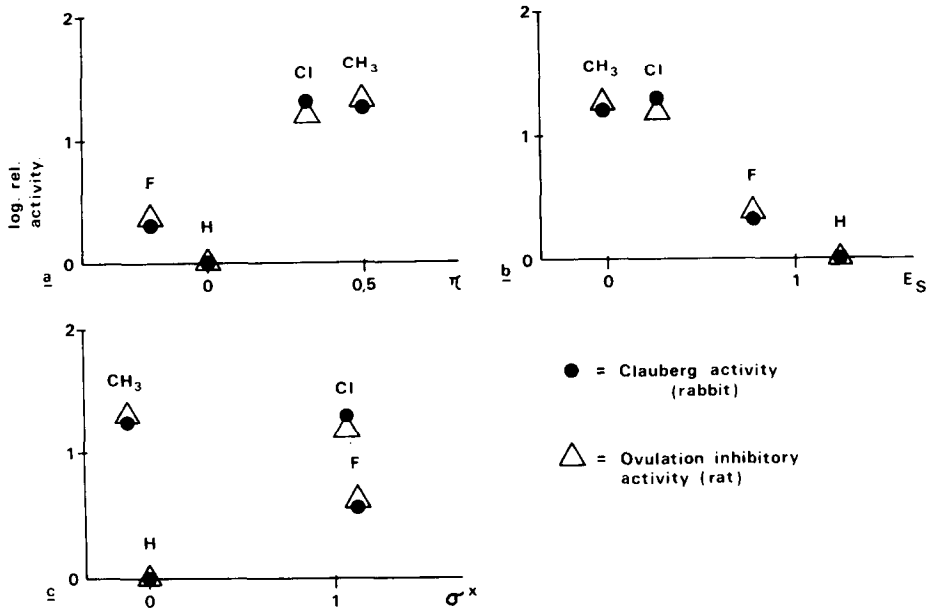
Substituent	Ovulation inhibition test	Clauberg test
H	1	1
CH_3	20.6	17.6
Cl	14.9	18.7
F	2.3	2.1

By making semilogarithmic plots of the relative activities found versus lipophilicity, steric size and electronic influence (Fig. 1), the data from this limited series of compounds suggest a good correlation between both progestational and ovulation inhibitory activity and the bulk of the substituent (Fig. 1b), while for both activities no correlation exists with the Taft electronic parameter σ (Fig. 1c). The series is too small to decide whether or not a correlation exists with the lipophilicity of the substituent (Fig. 1a).

It could be concluded after these pilot investigations that 11β-substitution in this series can lead to interesting compounds with enhanced activity, justifying the continuation of these investigations. To find the optimum compound we have to aim at the introduction of more bulky substituents than those used in the pilot investigation and we have to answer the question whether the lipophilicity of the 11β-substituent is important.

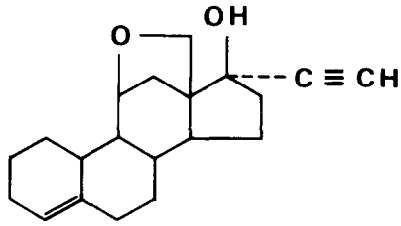
Fig. 1

Plot of the log.relative oral activity versus lipophilicity, steric and electronic parameters.



Definition of the steric effects

The important question in correlation analysis is: what type of interactions causes the biological effect and is responsible for the correlation found? In the case under discussion several explanations are possible. The more bulky 11β-substituents may directly hinder the binding to a degrading enzyme, thus explaining the enhanced activity, or it may promote binding to the receptor. In the latter, rare, case the lipohilicity will be of prime importance and one may expect an optimum in steric size. The effect of bulk can also be indirect, that is by distortion of the molecule due to interaction of the axial 11β-substituent with the axial angular methyl group. The 11β,18-epoxy-derivative serves to distinguish between a direct and an indirect steric effect.



In the case of a direct effect one would expect an activity comparable with that of the 11β-chloro- or 11β-methyl-derivatives, if the steric effect operates via distortion of the molecule a low activity would be expected, as the C-O distance will be about 1.47 Å (14,15), shorter than the combined v.d. Waals radii of a 11β-hydrogen and the axial methyl group, thus exerting strain in the skeleton of the molecule in a direction opposite to that induced by the 11β-substituents. The epoxide was found to have 1/8 x the activity of lynestrenol in the oral Clauberg and 1/4 x the activity in the oral ovulation inhibition test. It is to be concluded that both activities can be correlated with the overall shape of the molecule; its bending caused by the 1,3-diaxal interaction of the 11β-substituent and the angular methyl group being a major factor.

The importance of lipophilicity

The series was expanded by synthesising and testing the 11β-ethyl-, hydroxy- and methoxy-derivatives to answer this question. For the ovulation inhibition test the activities found (table 3) were in full agreement with expectations.

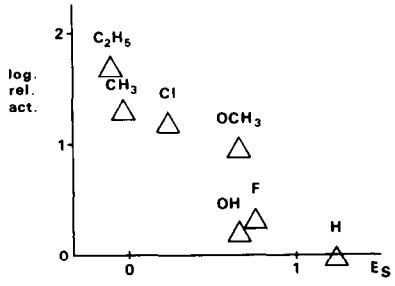
TABLE 3

Relative oral activities in ovulation inhibition test.	
11β-methyl	20.6
11β-ethyl	91.7
11β-methoxy	9.2
11β-hydroxy	1.5

Again a good correlation was found with the Taft parameter E_S (Fig. II), (16).

Fig. II

Relationship ovulation inhibitory activity and steric size.



A poor correlation is found between biological activity and lipophilicity (see Fig. III). Mathematically the correlation between the ovulation inhibitory activity and the steric size can be expressed in the form:

$$\log.\text{relative activity} = 1.36\ E_S + 1.55$$

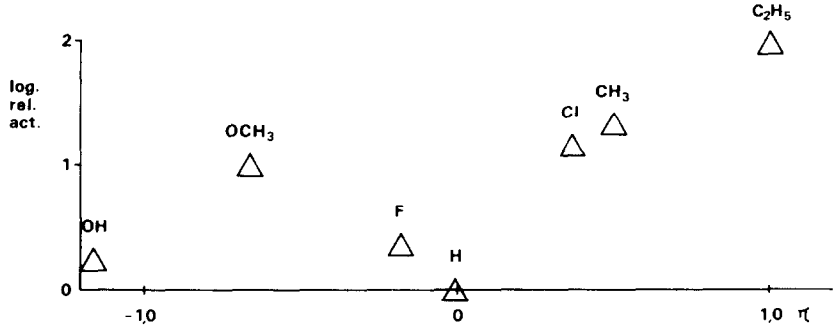
The correlation coefficient is 0.90; the standard error 0.33. No better correlation is found when it is tried to correlate the ovulation inhibitory activity with both steric and lipophilicity in a multiparameter equation. The equation then found is:

$$\log.\text{relative activity} = 1.07\ E_S + 0.31\pi + 1.40$$

with a correlation coefficient of 0.93 and a standard error of 0.31.

Fig. III

Relationship ovulation inhibitory activity and lipophilicity



The second steric parameter

It follows from the previous discussion that for the oral ovulation inhibition test (rat) the biological activity can be related to the steric parameter E_S. In the oral Clauberg assay (rabbit) however the same surprising low activity was found for the 11β-ethyl- as for the 11β-methoxy-derivative (table 4) indicating the existence of an effect that had been overlooked so far. It cannot be lipophilicity as both analogues have the same activity but strikingly different lipophilicity. A tentative explanation is that, in the Clauberg assay, groups that stick out too far at the 11β-position interfere with receptor binding; this could be tested with the 11β-propyl- and 11β-butyl-analogues. The 1,3-diaxial interaction with the angular methyl group will be the same for all the n-alkyl-derivatives but the suggested interference with the receptor should be stronger. The expected trend in ac-

TABLE 4

Relative activities in the oral Clauberg test.	
CH_3	17.6
C_2H_5	1.1
OCH_3	1.1
OH	0.03
$n\text{-}C_3H_7$	0.6
$n\text{-}C_4H_9$	0.15

tivities was indeed found (table 4). To describe the two steric factors in a quantitative manner we selected the Taft-Charton parameter E_S^x (17) as representing the 1,3 diaxal interaction. In view of the well-known flexibility of high molecular weight polypeptides the steric factor involved in the steroid-receptor protein interaction is best related with a factor representing the bulk of the hindering group. For this we selected, following the work of Hansch and coworkers (18), the molecular refractivity M_R. As expected for this series, with the exception of the hydroxy-derivative where metabolic instability might play a role, the structure-activity relationship can for the oral Clauberg test, be described by the equation:

$$\log \text{relative activity} = -1.46\ E_S^x - 0.14\ M_R + 1.97$$

Correlation coefficient 0.91; standard error 0.34.

So activity is enhanced by 11β-substituents that give rise to a strong 1,3-diaxial interaction with the angular methyl group, such as groups having a low Taft-Charton value E_S^x and is decreased by substituents that interfere by their total bulk (represented in the equation by the molecular refractivity) with receptor binding. Comparison of the structure-activity relationships for the two tests discussed shows that both relationships have the same dependence on the Taft-Charton E_S^x representing the 1,3-diaxial interaction but differ in the influence of direct steric hindrance. We do not know whether this dissociation of activities reflects a species difference between the rabbit used for the Clauberg test and the rat used for the ovulation inhibition test, or a difference between the endometrial and hypothalamic receptors.

The exceptional activity of the chloromethyl-analogue

Later work revealed the difference in the structure-activity relationship for the two tests to be a gradual one, when we found that the 11β-propyl- and 11β-butyl-derivatives mentioned above were also less active in the ovulation inhibition test than the 11β-ethyl-analogue. We did not quantify this any further but as an industrial research group and following the recommendations of the Humber committee (19) we focused our attention on those derivatives that based on the structure-activity relationships described should have the most interesting activities: the CH_2Cl-, CH_2OH-, $CH(CH_3)_2$- and probably the CH_2OCH_3-derivative.

TABLE 5

Oral ovulation inhibitory activity relative to lynestrenol.

Substituent	Predicted activity	Found
CH_2Cl	35	586
CH_2OH	35	< 2
$CH(CH_3)_2$	35	< 20
CH_2OCH_3	< 35	9

The activities found (table 5) were generally somewhat lower than expected, indicating that we have underestimated the influence of steric hindrance in binding, with one notable exception: the CH_2Cl-derivative, which in the ovulation inhibition test was 500-600x as active as the parent lynestrenol. Further pharmacological testing showed this compound to have a surprising high estrogenic activity. Its oral activity in the Allen-Doisy test (20,21) was twice even that of ethynylestradiol. It was less active after subcutaneous or intra vaginal administration suggesting that the compound owed its activity to metabolic activation. Therefore the 11β-chloromethyl-17α-ethynyl-1,3,5(10)-estratrien-3,17β-diol was also synthesised and found to be

a potent estrogen. In the ovulation inhibition test it was 1000x as active as lynestrenol after oral administration.

DISCUSSION

The results obtained clearly show how important it is when searching for the best compound in a series, to synthesise and test quantitatively derivatives with substituents as diverse as possible. Following the work of Hansch and others (1) substituents were selected that combined ease of synthesis with good discrimination between lipophilicity, electronic factors and steric size. These compounds showed an interesting range of activities.

Two problems were encountered using this approach. The first one is an inherent problem of the Hansch approach: the use of only one steric parameter to describe the steric influence of a substituent (22). The present study clearly showed the need for at least two steric parameters to account for the steric effect of a substituent. This effect was not noted in our pilot series of derivatives as all substituents selected happened to be spherically shaped, for example illustrated by the high correlation (0.90) of the two steric parameters E_S and M_R used later. The second series brought more variation (correlation between E_S and M_R only 0.74) and it was there that we see the separate effects. The 11β,18-epoxy-derivative with its extreme separation of steric effects proves this point.

The second problem had to do with the biological test under investigation. The ovulation inhibition test measures in effect two activities: the progestational and the estrogenic activity. Most of the compounds studied had low estrogenic activity but those two compounds that showed a high estrogenic activity in the Allen Doisy

test (rat): the 11β-ethyl- and even more the 11β-chloromethyl-derivative also showed exceptionally high activity in the ovulation inhibition test. We should realise however that these unexpected results were so easily traced because we had been able to combine all other results in one logical scheme.

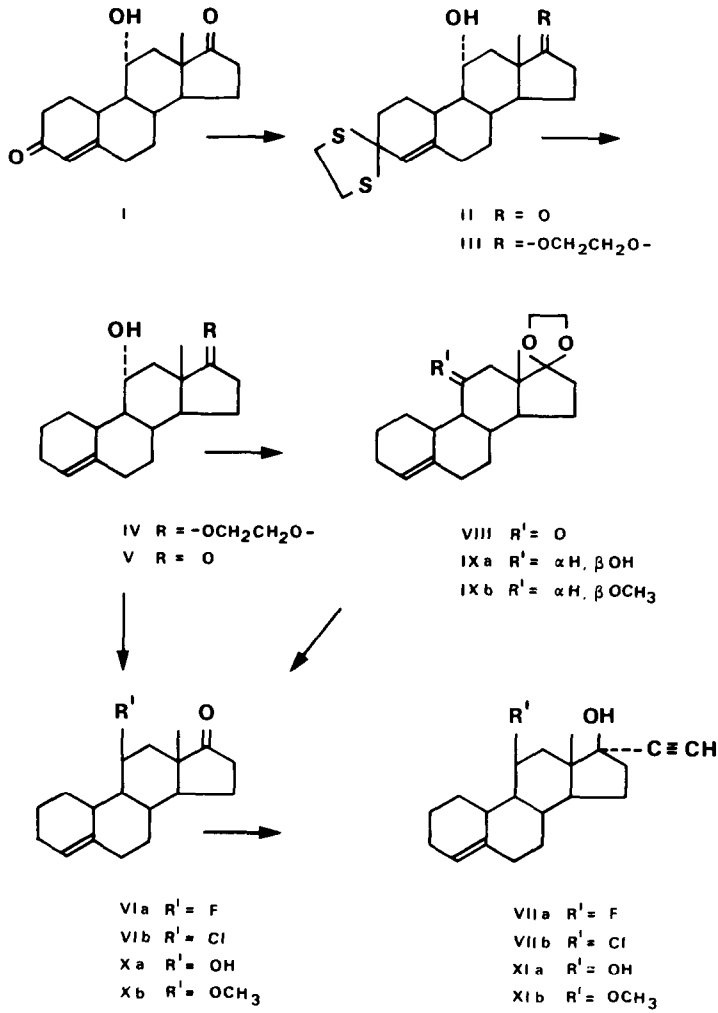
Consequently we feel that the approach followed is sound, although it can be argued, admittedly with hindsight, that we might have obtained the same results using an even smaller, more critically selected group of substituents.

Chemistry

Starting material for all syntheses was 11α-hydroxy-4-estrene-3,17-dione (I) easily obtainable by microbiological hydroxylation (23). For the syntheses of the 11β-chloro- and 11β-fluoro-derivatives (Scheme I) the diketone was selectively converted to the 3-ethylene dithioacetal II, which after protection of the 17-keto function as the ethylene acetal was reduced with Li/NH_3 to give, after removal of the protecting group, 11α-hydroxy-4-estren-17-one (V) (30). Treatment of this alcohol with N-(2-chloro-1,1,2-trifluoroethyl)diethylamine (8) gave with inversion 11β-fluoro-4-estren-17-one (VIa) in 45% yield. When 11α-hydroxy-4-estren-17-one was treated in tetrahydrofuran with the same reagent but in the presence of LiCl (8) 11β-chloro-4-estren-17-one (VIb) was obtained in 75% yield. A better yield of this compound (82%) was obtained using tripherylphosphine/N-chloro-succinimide in THF (24).

For the synthesis of the 11β-hydroxy-derivative (IXa) 11α-hydroxy-4-estren-17-one 17-ethylene acetal (IV) was oxidised with Jones reagent and then reduced with $NaBH_4$ to give the 11β-hydroxy-

Scheme 1


OH
O
O
I
OH
R
S
S
II R = O
III R = -OCH2CH2O-
OH
R
IV R = -OCH2CH2O-
V R = O
R'
O
O
VIII R' = O
IXa R' = αH, βOH
IXb R' = αH, βOCH3
R'
O
VIa R' = F
VIb R' = Cl
Xa R' = OH
Xb R' = OCH3
R'
OH
C≡CH
VIIa R' = F
VIIb R' = Cl
XIa R' = OH
XIb R' = OCH3

derivative (1Xa). The 11β-methoxy-derivative could be prepared by treatment of this alcohol with dimsyl sodium and CH_3I (25). Removal of the protecting group at C_{17} gave 11β-hydroxy-4-estren-17-one (Xa) and 11β-methoxy-4-estren-17-one (Xb) respectively. The ketones were converted to the 17α-ethynyl-17β-hydroxy-derivatives using potassium acetylide.

The assigned 11β-structures are supported by the ^{1}H-NMR spectra showing the characteristic quartet for the 11α-H, even doubled in the case of the 11β-fluoro derivative (table 4).

TABLE 4

Position of the 11α-H in the ^{1}H-NMR spectrum of 11β-substituted-17α-ethynyl-4-estren-17β-ols

R = OH	4.7 ppm	(J_q = 3Hz)
R = OCH_3	3.6 ppm	(J_q = 3Hz)
R = F	5.0 ppm	(J_d = 4.9Hz J_q = 3.5Hz)
R = Cl	4.6 ppm	(J_q = 3.5Hz)

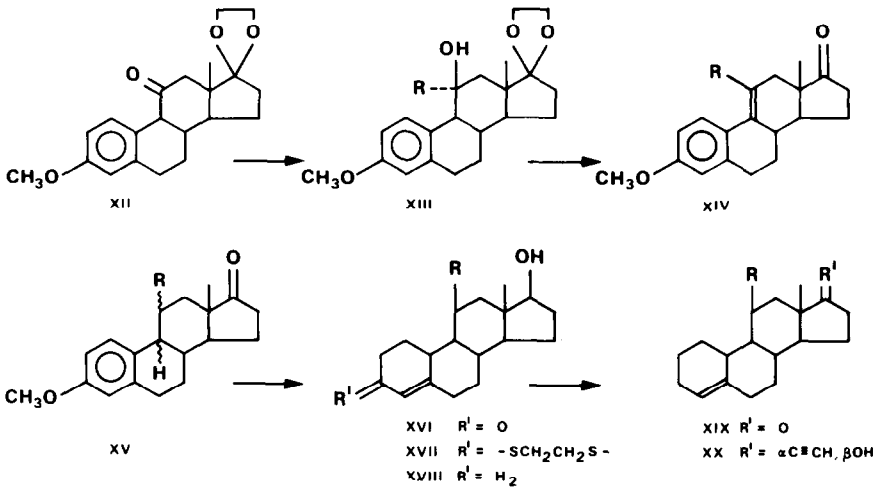
For the synthesis of the 11β-alkyl derivatives Baran's scheme (7) (Scheme II) was followed. The key step in this route, the catalytic hydrogenation of the 9(11)-double bond of 11-alkyl-3-methoxy-1,3,5(10),9(11)-estratetraen-17-one (XIV) proceeds with poor stereoselectivity giving under the most favourable conditions (10% Pd on carbon in methanol) for the 11-methyl a 3:1 mixture of the 9α-H,11β-CH_3- and 9β-H,11α-CH_3-isomers (XV) separable only by repeated fractional crystallisation. For the more bulky 11-substituents the ratio wanted/unwanted isomer is even worse (table 5).

TABLE 5

Ratio 9α-H, 11β-alkyl- and 9β-H, 11α-alkyl-isomers formed upon hydrogenation of 11-alkyl-3-methoxy-1,3,5(10),9(11)-estretraen-17-one (Estimated using gas chromatography).

11-methyl	76 : 24
11-ethyl	68 : 32
11- n-propyl	64 : 36
11- n-butyl	64 : 36
11- i-propyl	60 : 40

Scheme II



a R=CH_3 ; b R=C_2H_5 ; c R=nC_3H_7 ; d R=iC_3H_7 ; e R=nC_4H_9.

It was found that after the mixture had been reduced with $NaBH_4$, subjected to Birch reduction and treated with acid the 11β-alkyl steroid can easily be separated by chromatography from the more polar isomeric 11α-alkyl-9β-H, 10α-H-steroids formed from the 9β-H,11α-alkyl isomers present in the original mixture (26, 27). The structures of the isomers were assigned on the basis of their optical rotations, the 11α-alkyl-9β-H, 10α-H-steroids having a molecular rotation about 450° lower than the corresponding 11β-alkyl substituted normal steroids (TABLE 6).

TABLE 6

Molecular rotations ($CHCl_3$) of 11-alkyl-17β-hydroxy-4-estren-3-ones

11-alkyl	9α-H,10β-H,11β-alkyl	9β-H,10α-H,11α-alkyl
methyl	+233°	-288°
ethyl	+196°	-266°
n-propyl	+273°	
n-butyl	+270°	
i-propyl	+229°	
For comparison (28)		
19-nor-4-pregnen-3,20-dione	+448°	+ 42° (29)
17α-hydroxy-19-nor-4-pregnen-3,20-dione	+130°	-316°

The ^{1}H-NMR spectra show small but consistent differences (TABLE 7).

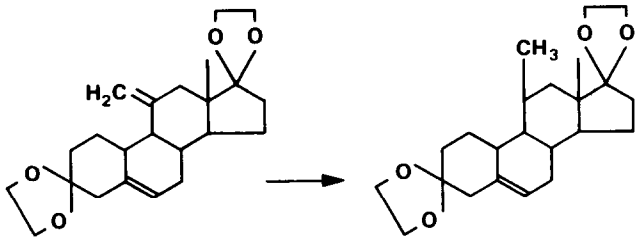
TABLE 7

^{1}H NMR spectra of 11-alkyl-17β-hydroxy-4-estren-3-ones

11-alkyl	9α-H,10β-H,11β-alkyl			9β-H,10α-H,11α-alkyl		
	13-CH_3	17α-H	4-H	13-CH_3	17α-H	4-H
methyl	0.89	3.62	5.83	0.85	3.77	5.87
ethyl	0.89	3.64	5.87	0.86	3.80	5.90
n-propyl	0.89	3.64	5.88			
n-butyl	0.89	3.62	5.85	0.86	3.77	5.86
i-propyl	0.89	3.62	5.85			

For the important 11β-methyl derivatives a much better route (Scheme III) was found via selective hydrogenation of 11-methylene-5-estrene-3,17-dione 3,17-diethylene acetal (XXI) to give 11β-methyl-5-estrene-3,17-dione 3,17-diethylene acetal (XXII). As we have described earlier (30) 11-alkylidene-19-norsteroids can be prepared in high yields.

Scheme III

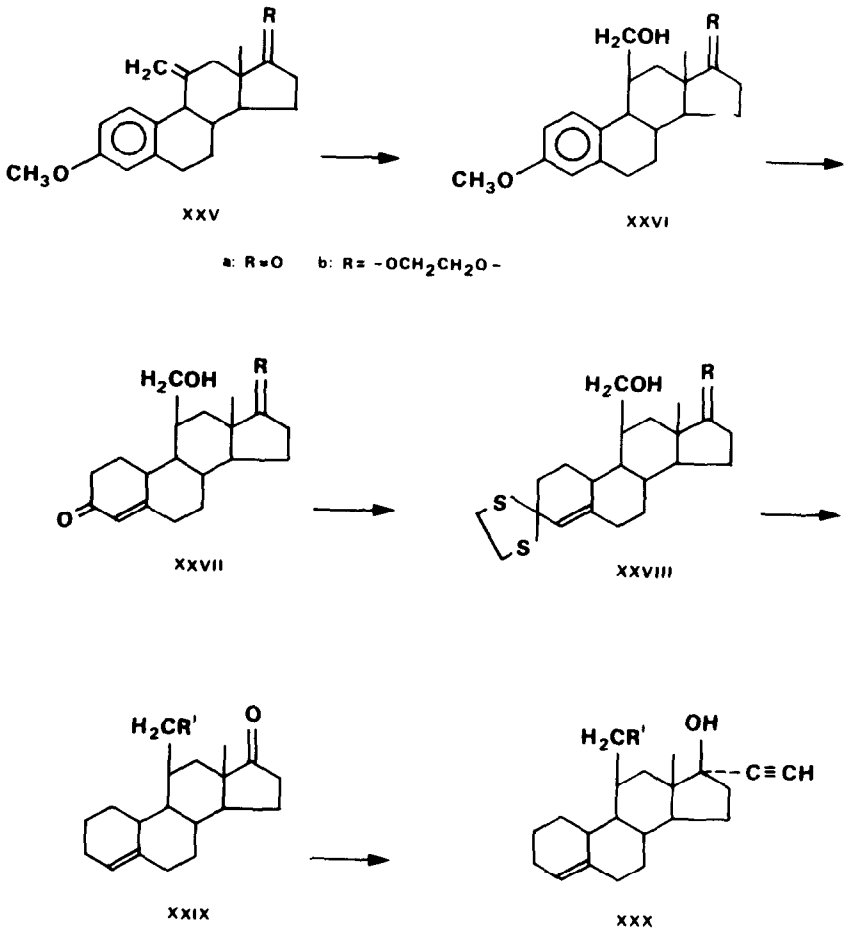


XXI XXII

The 11-methylene steroids also served as starting material for the synthesis of the 11β-hydroxymethyl-,11β-methoxymethyl- and the 11β-chloromethyl-steroids (scheme IV). For this 3-methoxy-11-methylene-1,3,5(10)-estratrien-17-one 17-ethylene acetal (XXVb) was hydroborated to give the 11β-hydroxymethyl-derivative (XXVIb). Birch reduction followed by acid treatment gave 11β-hydroxymethyl-4-estrene-3,17-dione (XXVIIa) in a yield of only 40%. Better yields were obtained by protecting the free hydroxyl group as tetrahydropyranylether during the Birch reduction.

For this compound the 11β-hydroxymethyl structure was proven by ^{1}H-NMR using the INDOR technique. The CH_2 multiplet at 3.81 ppm (J_{AB} = 11Hz, J_{AX} = 7Hz, J_{BX} = 7Hz) of the CH_2OH group was used to reveal the 11-H at 2.31 ppm as a sharp signal, representative for the equatorial 11α-H thus confirming the assigned structure. The positive molecular optical rotation (M_D = +431°) found for this compound also supports the assigned structure.

Scheme IV



The conversion of the 11β-hydroxymethyl- to the 11β-chloromethyl group using either N-(2-chloro-1,1,2-trifluoroethyl)diethylamine/LiCl or triphenylphosphine/N-chlorosuccinimide in THF was always accompanied by formation of the 11-methylene derivative as side product. A good method for the separation of the two compounds was found in chromatography on silicagel impregnated with silver

nitrate.

The 11β,18-epoxide in this series was (preferably) synthesised from 11β-hydroxy-4-estrene-3,17-dione 3,17-diethylene acetal obtained from its 11α-epimer via oxidation (30) and sodiumborohydride reduction. The key-step in the synthesis was treatment of the 11β-ol with lead tetraacetate and iodine to give the 11β-hydroxy-18 iodo-derivative, converted with base to the 11β,18-epoxide (sequence XXXI - XXXVIII in Experimental part).

Experimental part

In collaboration with C. Bos, F. Brands, F.G. Damhuis, H. Polderdijk, miss J. Vinke.

Elemental analyses were performed by Dr. W. McMeekin, Analytical Department, Organon Labs, Newhouse, Scotland. Melting points were taken in open capillaries on a Büchi-Tottoli apparatus and are uncorrected. Optical rotations were measured at concentrations of about 1% in chloroform at 20° with a Perkin Elmer polarimeter 141. All temperatures are given in degrees centigrade. NMR spectra were obtained with a Varian A-60 or Bruker HX-90E spectrometer. Chemical shifts are reported in ppm relative to TMS as the internal standard and coupling constants in Hz.

11β-Fluoro-4-estren-17-one VI a

To a solution of 11α-hydroxy-4-estren-17-one (30) (5.0 g, 18 mmol) in methylene chloride (100 ml) was added at -15° N-(2-chloro-1,1,2-trifluoroethyl)diethylamine (4.2 ml, 26 mmol). After 65 hours at -15° the reaction mixture was filtered through alumina (250 g). Elution with methylene chloride gave 4,9(11)-estradien-17-one (1.25 g, 5 mmol, 27%) as an oil, then 11β-fluoro-4-estren-17-one (2.25 g, 8 mmol, 45%) after crystallisation from ether/hexane, melting range 150-152°, $[\alpha]_D$ = +142°.

Analysis: Calc. for $C_{18}H_{25}OF$: C 78.22% H 9.12% O 5.79% F 6.87%
Found : C 78.5 % H 9.0 % O 6.0 % F 6.4 %

11β-Chloro-4-estren-17-one VI b
Using N-(2-chloro-1,1,2-trifluoroethyl)diethylamine/LiCl

Anhydrous lithium chloride (33.0 g, 0.78 mol) was added to a solution of 11α-hydroxy-4-estren-17-one (50.0 g, 0.18 mol) in dry tetrahydrofuran (500 ml) at -5° in a nitrogen atmosphere. After stirring for 10 minutes N-(2-chloro-1,1,2-trifluoroethyl)diethylamine (42 ml, 0.26 mol) was added and stirring continued for 30 minutes at -5°. The reaction mixture was then poured into ice-water (4000 ml), neutralised with sodium hydrogen carbonate solution and after stirring for 1 hour the solid product was filtered and crystallised from ether-hexane. Yield 37 g (0.13 mol, 72%) with melting range 159-161°, $[\alpha]_D$ = +174°.

Analysis: Calc. for $C_{18}H_{25}OCl$: C 73.82% H 8.60% O 5.46% Cl 12.11%
Found : C 74.0 % H 8.7 % O 5.4 % Cl 12.1 %

From the mother liquors were isolated by chromatography on silicagel (200 g) and crystallisation 11β-chloro-4-estren-17-one (2 g, 6 mmol, 3%), melting range 157-159° and 4,9(11)-estradien-17-one (2.5 g, 9 mmol, 4.5%), melting range 104-107°.

Using triphenylphosphine/N-chlorosuccinimide.

A solution of triphenylphosphine (2.62 g, 10 mmol) in tetrahydrofuran (30 ml) was added dropwise, within 15 minutes at room temperature, to a solution of N-chlorosuccinimide (1.33 g,10 mmol) in tetrahydrofuran (50 ml). To the suspension formed was added dropwise, within 15 minutes, a solution of 11α-hydroxy-4-estren-17-one (1.37 g, 5 mmol) in tetrahydrofuran (10 ml). Stirring was continued for 2 hours at room temperature and the then clear solution concentrated at reduced pressure. The residue was crystallised from 70% methanol (50 ml) to yield 11β-chloro-4-estren-17-one (1.20 g, 4.1 mmol, 82%), melting range 156-158°.

General prescription for the synthesis of 17α-ethynyl-17β-hydroxysteroids from the corresponding 17-ketones.

A solution of potassium acetylide in tetrahydrofuran is prepared by dissolving potassium t-butylate (1.12 g, 10 mmol) in tetrahydrofuran (10 ml) and saturating this solution at 0° with acetylene. At the same temperature and while passing through acetylene a solution of the 17-ketone (2.5 mmol) in tetrahydrofuran (5 ml) is added while stirring. Stirring is continued for 3 hours at 0° while passing through acetylene. The reaction mixture is acidified with dilute sulphuric acid (2N) and worked up in the usual manner. When necessary the product is purified by chromatography.

4-Estren-11,17-dione 17-ethylene acetal VIII

To a stirred solution of 11α-hydroxy-4-estren-17-one 17-ethylene acetal (12.4 g, 39 mmol) in acetone (500 ml) at -10°C was added within 30 minutes 8N Jones reagent (13.0 ml, 104 mmol). The reaction mixture was poured into ice-water (800 ml) + methanol (40 ml). After evaporation of acetone under reduced pressure the

product was extracted into methylene chloride, washed with water, dried and the solvent removed by evaporation to yield 11.3 g (36 mmol, 92%) of crude product. This was used without purification in the next reaction step.

11β-Hydroxy-4-estren-17-one 17-ethylene acetal IXa

To a stirred solution of 4-estren-11,17-dione 17-ethylene acetal (11.3 g, 36 mmol) in tetrahydrofuran (300 ml) and water (45 ml) was added at 20° under nitrogen, a solution of sodium borohydride (8.60 g, 225 mmol) in water (60 ml). After stirring for 5 hours at 20°C the reaction mixture was neutralised with 50% acetic acid. Tetrahydrofuran was evaporated under reduced pressure and after the addition of water (200 ml) the solid product was filtered and dried to give 12.0 g (37 mmol, 100%) of crude product. It was used in further reaction steps without purification.

11β-Hydroxy-4-estren-17-one Xa

11β-Hydroxy-4-estren-17-one 17-ethylene acetal (12.0 g,37 mmol) was dissolved in acetone (150 ml) and after adding 4N hydrochloric acid (20 ml) the reaction mixture was stirred at 20° for 2½ hours. Acetone was evaporated under reduced pressure and the solid product was filtered after adding water (200 ml). After crystallisation 8.0 g (29 mmol, 78%) of crystalline product was obtained with melting range 138-140°.

11β-Methoxy-4-estren-17-one 17-ethylene acetal IXb

A suspension of sodium hydride (28.0 g, 50% in mineral oil, 583 mmol) in DMSO (670 ml) was stirred at 60-70° for one hour. After the addition of a solution of 11β-hydroxy-4-estren-17-one 17-ethylene acetal (14.0 g , 44 mmol) in DMSO (300 ml) the reaction mixture was stirred for another hour at 60-70°C.
Please note that solutions of dimsyl sodium in DMSO may decompose exothermally when overheated or stored for prolonged periods of time! Never use concentrations > 10% dimsyl sodium in DMSO.

After cooling with ice-water methyl iodide (140 ml, 2250 mmol) was added and the mixture was stirred for 3 hours at room temperature. The mixture was then poured into ice-water and extracted with ether. The ether layers were washed neutral, dried and concentrated, giving 27.7 g of an oil, which was chromatographed over silicagel (150 g) and eluted with hexane-acetone 98:2 to give 13.4 g (40 mmol, 90%) of nearly pure 11β-methoxy-4-estren-17-one 17-ethylene acetal with melting range 81-82°.

11β-Methoxy-4-estren-17-one Xb

The above acetal (13.0 g, 39 mmol) was dissolved in methanol (200 ml), THF (50 ml) and concentrated hydrochloric acid (15 ml). After stirring for two hours at room temperature the mixture was neutralised with sodium hydrogen carbonate solution, evaporated to small volume, diluted with water and extracted with ether. The ether layers were washed neutral, dried and concentrated to give 11.0 g of an oil. Crystallisation from methanol gave 8.5 g (29 mmol, 74% of pure 11β-methoxy-4-estren-17-one, melting range 68-68.5°, $[\alpha]_D = +132°$.

Analysis: Calc. for $C_{19}H_{28}O_2$: C 79.12% H 9.79% O 11.10%
Found : C 79.3 % H 9.8 % O 11.4 %

11β-Methyl-5-estrene-3,17-dione 3,17-diethylene acetal XXII

Adams catalyst (5.0 g, 20 mmol) was activated by shaking under hydrogen in a mixture of isopropanol (500 ml) and acetic acid (12.5 ml). When no more hydrogen was consumed a solution of 11-methylene-5-estrene-3,17-dione 3,17-diethylene acetal (30) (50.0 g, 134 mmol) in a mixture of tetrahydrofuran (1000 ml), isopropanol (500 ml) and acetic acid (38 ml) was added. After an equimolar amount of hydrogen had been consumed the mixture was filtered, concentrated and the residue crystallised from isopropanol to yield 38.0 g (102 mmol, 76%) with melting range 160-162°.

11β-Methyl-4-estrene-3,17-dione XXIII

A solution of 11β-methyl-5-estrene-3,17-dione 3,17-diethylene acetal (77 g, 206 mmol) in acetone (500 ml) was treated with aqueous 14% hydrogen chloride (25 ml, 105 mmol) at 40° for 1 hour. The reaction mixture was neutralised with an aqueous solution of sodium hydrogen carbonate, diluted with water and the precipitate formed collected. Crystallisation from acetone-hexane gave 42.0 g of pure dione (147 mmol, 71%) with melting range 149-151°, $[\alpha]_D$ = +145°.
Analysis: Calc. for $C_{19}H_{26}O_2$: C 79.68% H 9.15% O 11.17%
Found : C 79.9 % H 9.0 % O 11.4 %

11β-Methyl-4-estrene-3,17-dione 3-ethylene dithioacetal XXIV

A solution of 11β-methyl-4-estrene-3,17-dione (5.0 g, 17.5 mmol) in methanol (55 ml) was treated with ethane dithiol (5.3 ml, 63 mmol) and boron trifluoride etherate (5.3 ml, 43 mmol) at 0° for 1 hour. The precipitate formed was filtered, washed with cold methanol and dried to yield 4.7 g of the dithioacetal (13 mmol, 73%) with melting range 158-160°, $[\alpha]_D$ = +177°.
Analysis: Calc. for $C_{21}H_{30}OS_2$: C 69.58% H 8.34%
Found : C 69.7 % H 8.3 %

11β-Methyl-4-estren-17-one XIX a

A suspension of 11β-methyl-4-estrene-3,17-dione 3-ethylene dithio acetal (5.0 g, 14 mmol) in ethanol (100 ml) was stirred with sodium borohydride (1.2 g, 32 mmol) at ambient temperature for 2 hours. After decomposition of the excess of sodium borohydride with 50% acetic acid the reaction mixture was diluted with water and the precipitate filtered off. The crude 17β-hydroxy compound (5.0 g, 14 mmol, 100%) was dissolved in tetrahydrofuran (26 ml) and added to a solution of sodium (2.9 g, 126 mmol) in liquid ammonia (110 ml) at -40°. Stirring was continued for another 30 minutes at this temperature and the excess of sodium was destroyed by adding ethanol (19 ml) with caution. After evaporation of the ammonia, the residue was diluted with water and the precipitate filtered off giving crude 11β-methyl-4-estren-17β-ol XVIII a (3.6 g, 13 mmol, 92%). This was dissolved in acetone (280 ml) and 8N Jones reagent (4.4 ml, 11.7 mmol) was added dropwise at -10° over a period of 10 minutes. After stirring for 15 minutes at this temperature the

excess of chromic acid was decomposed with methanol, the reaction mixture diluted with water and the acetone evaporated in vacuo. The crystals were collected by filtration and chromatographed over silica (12.5 g). Elution with toluene-ethyl acetate 9:1 and crystallisation from acetone gave 11β-methyl-4-estren-17-one (2.3 g, 8 mmol, 65%) with melting range 92-93°, $[\alpha]_D$ = +153°.
Analysis: Calc. for $C_{19}H_{28}O$: C 83.77% H 10.36% O 5.87%
Found : C 83.7 % H 10.3 % O 6.0 %

3-Methoxy-11-methylene-1,3,5(10)estratrien-17-one 17-ethylene acetal XXV b.

A solution of 3-methoxy-11-methylene-1,3,5(10)-estratrien-17-one (30) (40.4 g, 137 mmol) in methylene chloride (400 ml) was refluxed for 4 hours under nitrogen with ethylene glycol (806 ml 14.3 mmol), triethylorthoformate (124 ml) and p-toluenesulphonic acid (1.24 g). The solution was cooled, neutralised with pyridine (1.5 ml) and poured into water (2 L). The organic layer was separated, washed with water, dried over sodium sulphate and concentrated to give the oily acetal (46.5 g, 136 mmol, 100%).

11β-Hydroxymethyl-3-methoxy-1,3,5(10)-estratrien-17-one 17-ethylene acetal XXVI b.

Diborane (39 mmol) in tetrahydrofuran (48.5 ml) was added to a solution of above acetal (5.25 g, 15.4 mmol) in tetrahydrofuran (165 ml) and stirred for 3 hours at room temperature. After cooling to 0° sodium hydroxide (113 ml 10% in water) was added carefully over 45 minutes. Then hydrogen peroxide (27 ml of a 30% solution) was added and stirring was continued for 1½ hour at 0°, and for 16 hours at room temperature. The mixture was then poured into ice-water (2 L) and extracted with methylene chloride. The extract was washed with a $NaHSO_3$ solution, with water until neutral, dried over sodium sulphate and concentrated to give the crude product (4.9 g). Crystallisation from methylene chloride-ether gave the pure product (3.9 g, 11 mmol, 71%), with melting range 153-154°, $[\alpha]_D$ = +123°.

11β-Hydroxymethyl-3-methoxy-1,3,5(10)-estratrien-17-one 17-ethylene acetal, 11β-hydroxymethyl tetrahydropyranyl ether.

The above acetal (2.3 g, 6.5 mmol) dissolved in tetrahydrofuran (39 ml) was reacted for 1 hour at room temperature with dihydropyran (7.5 ml) and p-toluene sulphonic acid (0.12 g). The reaction mixture was poured into water and extracted with methylene chloride. After drying over sodium sulphate and evaporation the compound (2.9 g, 6.5 mmol, 100%) was obtained as an oily product.

11β-Hydroxymethyl-4-estrene-3,17-dione XXVII a.

A solution of the above tetrahydropyranyl ether (2.9 g, 6.5 mmol) in tetrahydrofuran (30 ml) was added at -50° to a stirred solution of lithium (0.7 g, 100 mmol) in ammonia (50 ml) and stirring at this temperature continued for 1½ hour. The excess of lithium was destroyed with ethanol, the ammonia evaporated and the resulting mixture poured into water and extracted with methylene chloride. The extract was washed with water until neutral, dried over sodium sulphate and concentrated. The residue was dissolved

in methanol (98 ml) containing diluted hydrochloric acid (30 ml, 10%), boiled under reflux for 20 minutes and after cooling poured into water and extracted with methylene chloride. The extract was washed with water until neutral and concentrated to yield the crude dione (1.6 g, 5.3 mmol, 81%). Crystallisation from acetonitrile gave the pure dione (0.9 g, 3 mmol, 46%) with melting range 191-193°, $[\alpha]_D$ = +143°. Ultra violet absorbtion spectrum λ_{max} 239 nm, ε 15000.

Analysis: Calc. for $C_{19}H_{26}O_3$: C 75.5% H 8.7% O 15.8%
Found : C 74.9% H 8.9% O 15.8%

11β-Hydroxymethyl-4-estrene-3,17-dione 3-ethylene dithioacetal XXVIII a.

A solution of 11β-hydroxymethyl-4-estrene-3,17-dione (1 g, 3.3 mmol) in methanol (11 ml) was treated for 1 hour at 0° with ethanedithiol (1 ml, 10 mmol) and BF_3-etherate (1 ml) then poured into water and extracted into methylene chloride. The extract was washed with 2N sodium hydroxide, dried over sodium sulphate and evaporated to give the crude thioacetal (1.25 g, 3.3 mmol, 100%).

11β-Hydroxymethyl-4-estrene-3,17-dione 3-ethylene dithioacetal 17-ethylene acetal XXVIII b.

A solution of the above thioacetal (1.25 g, 3.3 mmol) in methylene chloride (13 ml) was refluxed for 4 hours with ethylene glycol (26 ml, 460 mmol), triethyl orthoformate (4 ml) and p-toluenesulphonic acid (40 mg). The solution was cooled, neutralised with pyridine (0.2 ml) and poured into water. The organic layer was separated, washed with water, dried and evaporated to give the acetal (1.4 g, 3.3 mmol, 100%) as an oil.

11β-Hydroxymethyl-4-estren-17-one 17-ethylene acetal

A solution of the above acetal (21 g, 49.7 mmol) in dry tetrahydrofuran (105 ml) was added over a period of 30 minutes to a solution of sodium (10.8 g, 0.47 mmol) in liquid ammonia (415 ml) and stirring continued for 30 minutes at -40°. The excess of sodium was destroyed with ethanol, the ammonia evaporated and the residue diluted with water. Extraction with methylene chloride gave after removal of the solvent the crude acetal (23 g), which was dissolved in toluene-ethyl acetate (6:4) and carefully chromatographed on silicagel. The fractions containing the 11β-hydroxymethyl-4-estren-17-one 17-ethylene acetal were combined and evaporated to dryness to give the product (14.2 g, 42.7 mmol, 86%) as an oil.

11β-Hydroxymethyl-4-estren-17-one XXIX a.

A solution of the above acetal (8.8 g, 26.6 mmol) in acetone (175 ml) was treated for 1½ hour at room temperature with conc. hydrochloric acid (0.9 ml). The reaction mixture was poured into water and the solid collected (6.92 g, 24 mmol, 90%). The analytical sample was obtained by crystallisation from ether, melting range 122½-125°, $[\alpha]_D$ = +146°.

Analysis: Calc. for $C_{19}H_{28}O_2$: C 78.9% H 9.8% O 11.2%
Found : C 79.1% H 9.8% O 11.1%

11β-Methoxymethyl-4-estren-17-one XXIX b.

A mixture of sodium hydride (6.8 g 50% oil dispersion, 130 mmol) and dimethylsulphoxide (124 ml) was heated at 60° in a nitrogen atmosphere until evolution of hydrogen ceased. (See note on safety precautions under IX b). A solution of 11β-hydroxymethyl-4-estren-17-one 17-ethylene acetal (3.1 g, 9.3 mmol) in dimethylsulphoxide (37 ml) was added and stirring continued at 60° for 1 hour. Then the reaction mixture was cooled to room temperature, methyl iodide (33 ml, 530 mmol) added and the reaction mixture stirred another 2 hours at room temperature. Working-up by extraction and evaporation of the extract gave a residue of the 11β-methoxymethyl-17-acetal which was dissolved in acetone (62 ml) and treated with 36% hydrochloric acid (0.3 ml) at room temperature for 1½ hour. Working-up by extraction, chromatography over silicagel (160 g), elution with the solvent system toluene-ethyl acetate (7:3) and crystallisation from methylene chloride-hexane gave the 17-ketone (2.0 g, 6.6 mmol, 71%) with melting range 128½-130½°, $[\alpha]_D$ = +134°.

Analysis: Calc. for $C_{20}H_{30}O_2$: C 79.42% H 10.00% O 10.58%
Found : C 79.6%% H 10.1 % O 10.5 %

11β-Chloromethyl-4-estren-17-one XXIX c.

To a solution of 11β-hydroxymethyl-4-estren-17-one (2.6 g, 9 mmol) and LiCl (3.4 g, 81 mmol), was added N-(2-chloro-1,1,2-trifluoroethyl) diethylamine (4.4 g, 23 mmol). Stirring was continued for 1 hour at room temperature then a second portion of LiCl (3.4 g) was added and stirring was continued for another hour. The reaction mixture was poured into water, extracted with methylene chloride and after drying over sodium sulphate the solvent was evaporated and the residue dissolved in methanol (70 ml). In order to saponify the 11β-chlorofluoroacetate formed as a side product it was treated with NaOH (0.72 g, 18 mmol) in water (0.7 ml) for 1 hour at 0°. The reaction mixture was neutralised with acetic acid, poured into water and the solid precipitate (2.4 g) filtered off. The crude product, a mixture of the 11,11-methylene- and the 11β-chloromethylcompound in a ratio of 3:2, was chromatographed on a column of silicagel impregnated with $AgNO_3$ (17% w/w). Elution was carried out with hexane-acetone 9:1. Crystallisation from methylene chloride-ether gave the pure compound (0.69 g, 2.2 mmol, 25%) with melting range 131½-133½°, $[\alpha]_D$ = +139°.

Analysis: Calc. for $C_{19}H_{27}OCl$: C 74.2% H 8.9% O 5.2%
Found : C 74.3% H 8.7% O 5.5%

11β-Hydroxy-5-estrene-3,17-dione 3,17-diethylene acetal XXXI

Sodium borohydride (13.0 g, 345 mmol) was carefully added under nitrogen at 20° to a stirred solution of 5-estrene-3,11,17-trione 3,17-diethylene acetal (30) (52.6 g, 140 mmol) in tetrahydrofuran (400 ml) and methanol (400 ml). Stirring was continued for half an hour, then acetic acid (20 ml) and water (100 ml) were slowly added. The mixture was concentrated under reduced pressure, the precipate collected, washed with a small amount of methanol and dried to give the crude acetal (41.4 g, 110 mmol, 78%) with melting range 244-245°.

11β-Hydroxy-18-iodo-5-estrene-3,17-dione 3,17-diethylene acetal XXXII

A mixture of cyclohexane (900 ml), lead tetraacetate (52.0 g, 117 mmol) and iodine (10.4 g, 41 mmol) was refluxed for ten minutes, then 11β-hydroxy-5-estrene-3,17-dione 3,17-diethylene acetal (26.0 g, 69 mmol) and azodiisobutyronitrile (1.82 g) were added. After refluxing for 20 minutes the mixture, which was almost colourless, was cooled, filtered over hyflo and the residue washed with cyclohexane. The combined filtrates were washed with thiosulphate, sodium hydrogencarbonate and water until neutral, dried over sodium sulphate and pyridine (5 ml) was added. Concentration in vacuo yield 43.0 g of crude product which was triturated with methanol to give crystals. These were recrystallised from methylene chloride-methanol to give almost pure iodohydrin (1.0 g, 38 mmol, 55%).

11β,18-Epoxy-5-estrene-3,17-dione 3,17-diethylene acetal XXXIII

The above iodohydrin (13.8 g, 27.5 mmol) was dissolved in methanol (350 ml), potassium hydroxide (7.5 g, 134 mmol) was added and the solution refluxed for half an hour. After cooling the reaction mixture was neutralised with acetic acid (15 ml), diluted with water and concentrated to small volume. The crystals of the almost pure diacetal (9.9 g, 26.5 mmol, 96%) were collected, dried and used in the next reaction step.

11β,18-Epoxy-4-estrene-3,17-dione XXXIV

The above diacetal (9.9 g, 26 mmol) was dissolved in acetone (100 ml), concentrated hydrochloric acid (1.0 ml) was added and the mixture refluxed for 1 hour. After neutralising with sodium hydrogen carbonate, water was added and the mixture concentrated to a small volume. After standing for 2 days at 0° the crystals were collected and dried to give the dione (6.9 g, 24 mmol, 93%) with melting range 158-161°. The analytical sample crystallised from methylene chloride-methanol melted 163-164°, $[\alpha]_D = +225°$.

Analysis: Calc. for $C_{18}H_{22}O_3$: C 75.49% H 7.7% O 16.76%
Found: C 75.2 % H 7.6% O 16.8 %

11β,18-Epoxy-4-estrene-3,17-dione 3-ethylene dithioacetal XXXV

The above dione (18.6 g, 65 mmol) was dissolved under reflux in methanol (150 ml), the BF_3-etherate (2.75 ml) and ethanedithiol (8.5 ml, 98 mmol) were added and the mixture refluxed for another 15 minutes. After cooling the crystals were collected and dried to give the pure dithioacetal (22.3 g, 62 mmol, 95%) with melting range 234½-236½°.

11β,18-Epoxy-4-estrene-3,17-dione 3-ethylene dithioacetal 17-ethylene acetal XXXVI

The dithioacetal (22.3 g, 62 mmol) in toluene (220 ml) was refluxed under nitrogen for 3 hours 15 minutes with ethylene glycol (22 ml, 392 mmol), ethyl orthoformate (16 ml) and p-toluenesulphonic acid (0.4 g). After cooling sodium hydrogen carbonate solution was added, the precipitate filtered and dried (14.2 g). The organic layers were washed, dried and evaporated to give the

crude product (25.1 g, 62 mmol, 100%) with melting range 254-256°.

11β,18-Epoxy-4-estren-17-one 17-ethylene acetal XXXVII

Sodium (15.0 g, 0.65 mmol) was dissolved in liquid ammonia (750 ml) with stirring over ½ hour. The dithioacetal XXXVI (25.0 g, 61 mmol) suspended in tetrahydrofuran (1500 ml) was then added and stirring continued for 1 hour. The mixture was quenched with ethyl-alcohol (30 ml, 96%), the ammonia evaporated and most of the tetra-hydrofuran distilled in vacuo. Water was then added and extraction with ether yielded the crude acetal (17.0 g, 53 mmol, 88%) as an oil.

11β,18-Epoxy-4-estren-17-one XXXVIII

The above acetal (17.0 g, 53 mmol) was dissolved in acetone (200 ml), concentrated hydrochloric acid (2 ml) was added and the mixture refluxed for ½ hour. After neutralisation with sodium hydrogen carbonate solution and evaporation to small volume the crystalline precipitate was collected and dried to give the ketone (14.3 g, 52 mmol, 99%) with melting range 132-134°. The analytical sample crystallised from methanol melted 140-141° $[\alpha]_D = +219°$.

Analysis: Calc. for $C_{18}H_{42}O_2$: C 79.3% H 8.88% O 11.75%
Found : C 79.6% H 9.0 % O 11.7 %

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Physical constants of compounds prepared by general methods.

	Name:	M.p.:	$[\alpha]_D$
VIIa	17α-ethynyl-11β-fluoro-4-estren-17β-ol	143-145°	+16°
VIIb	11β-chloro-17α-ethynyl-4-estren-17β-ol	158-160°	+63°
XIa	17α-ethynyl-4-estren-11β,17β-diol	152-155°	+15°
XIb	17α-ethynyl-11β-methoxy-4-estren-17β-ol	84- 85°	+12°
XXa	17α-ethynyl-11β-methyl-4-estren-17β-ol	106-107°	+26°
XXb	17α-ethynyl-11β-ethyl-4-estren-17β-ol	54- 57°	+12°
XXc	17α-ethynyl-11β-n-propyl-4-estren-17β-ol	oil	+15°
XXd	17α-ethynyl-11β-i-propyl-4-estren-17β-ol	oil	+ 5.5°
XXe	11β-n-butyl-17α-ethynyl-4-estren-17β-ol	44- 48°	+13°
XXXa	17α-ethynyl-11β-hydroxymethyl-4-estren-17β-ol	165-167°	+18°
XXXb	17α-ethynyl-11β-methoxymethyl-4-estren-17β-ol	86- 88°	+20°
XXXc	11β-chloromethyl-17α-ethynyl-4-estren-17β-ol complex with 1/3 mole CH_3OH	69- 89°	+17°
XXXVIII	11β,18-epoxy-17α-ethynyl-4-estren-17β-ol	201-202½°	+39°
XIIIb	11α-ethyl-11β-hydroxy-3-methoxy-1,3,5(10)-estratrien-17-one 17-ethylen acetal	115-116°	-48°
XIIIc	11β-hydroxy-3-methoxy-11α-n-propyl-1,3,5(10)-estratrien-17-one 17-ethylene acetal	168-170°	-52°
XIIId	11β-hydroxy-3-methoxy-11α-i-propyl-1,3,5(10)-estratrien-17-one 17-ethylene acetal	158-159°	-74°
XIIIe	11α-n-butyl-11β-hydroxy-3-methoxy-1,3,5(10)-estratrien-17-one 17-ethylene acetal	oil	-48°
XIVb	11-ethyl-3-methoxy-1,3,5(10),9(11)-estratetraen-17-one	81- 82°	+370°
XIVc	3-methoxy-11-n-propyl-1,3,5(10),9(11)-estratetraen-17-one	101-102°	+318°
XIVd	3-methoxy-11-i-propyl-1,3,5(10),9(11)-estratetraen-17-one	143-143½°	+322°
XIVe	11β-n-butyl-3-methoxy-1,3,5(10),9(11)-estratetraen-17-one	100-101°	+322°
XVIb	11β-ethyl-17β-hydroxy-4-estren-3-one	146½-147°	+ 65°
XVIc	17β-hydroxy-11β-n-propyl-4-estren-3-one	144½-145°	+ 86½°
XVId	17β-hydroxy-11β-i-propyl-4-estren-3-one	141-142°	+ 72½°
XVIe	11β-n-butyl-17β-hydroxy-4-estren-3-one	148½-149½°	+ 82°

XVIIb	11β-ethyl-17β-hydroxy-4-estren-3-one 3-ethylene dithioacetal	171-172	+113½°
XVIIe	11β-n-butyl-17β-hydroxy-4-estren-3-one 3-ethylene-dithioacetal	120-121°	+112°
XVIIIb	11β-ethyl-4-estren-17β-ol	149-151°	+ 75°
XVIIId	11β-i-propyl-4-estren-17β-ol	88- 89°	+ 58°
XVIIIe	11β-n-butyl-4-estren-17β-ol	oil	+ 78°
XIXb	11β-ethyl-4-estren-17-one	84-84½°	+141°
XIXc	11β-n-propyl-4-estren-17-one	62½-63½°	+137°
XIXd	11β-i-propyl-4-estren-17-one	oil	+119°
XIXe	11β-n-butyl-4-estren-17-one	oil	+126°