THE SYNTHESIS OF 5-METHYL-19-NOR-5β-PREGNA-9,16-DIENE--3,20-DIONE, 5-METHYL-19-NOR-5β-PREGNA-9,10-DIENE-3,6,20-TRIONE AND THEIR ANALOGUES WITH ANNELLATED E RING*

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Dedicated to Professor Alois Vystrčil on the occasion of his 70th birthday.

The synthesis of compounds *VII*, *XVII*, *XXXIV* and *XXXVII* is described, in which biological activity is assumed. The key steps of their preparation are the dehalogenation of compound *XVIII* and radicalic deoxygenation of the 6β-hydroxy group in compound *XXX*, which take place without skeletal rearrangements.

During the search for a new type of antigestagenic compounds we found[1] that an analogue of progesterone with a modified skeleton (5-methyl-19-nor-5β-pregn-9--ene-3,20-dione) displayed an abortion inducing activity. It could be expected that the biological activity of this compound might be modified by further changes of its skeleton. Such a modification could be represented by the introduction of a double bond into position 16, permitting both an access to analogues of the type of 17α--acetoxyprogesterone[2] and to the analogues with an annellated E ring, the positive effect of which on the gestagenic or antigestagenic activity has already been published in another type of compounds[3], or also this modification could consist in the introduction of a further keto group into position 6. The preparation of compounds *VII*, *XVII*, *XXXIV* and *XXXVII* is the subject of this study.

Compound *VII* was prepared (see Scheme 1) from 3β-acetoxypregna-5,16-dien--20-one (*I*) by epoxidation of the Δ^5-double bond with peracetic acid, acid hydrolysis of the mixture of 5α,6α- and 5β,6β-epoxides *II* and *III* formed in this way to a single diol *IV*, which was then submitted to Westphalen rearrangement in acetic aid and acetic anhydride, under formation of diacetate *V*. Its formation is evidenced both by the high positive value of specific rotation (+109°) and the shift of signals in the ^{1}H NMR spectrum, but especially by the change of the shape of the signal of the originally axial hydrogen in position 3α (δ 5·10), from a broad multiplet

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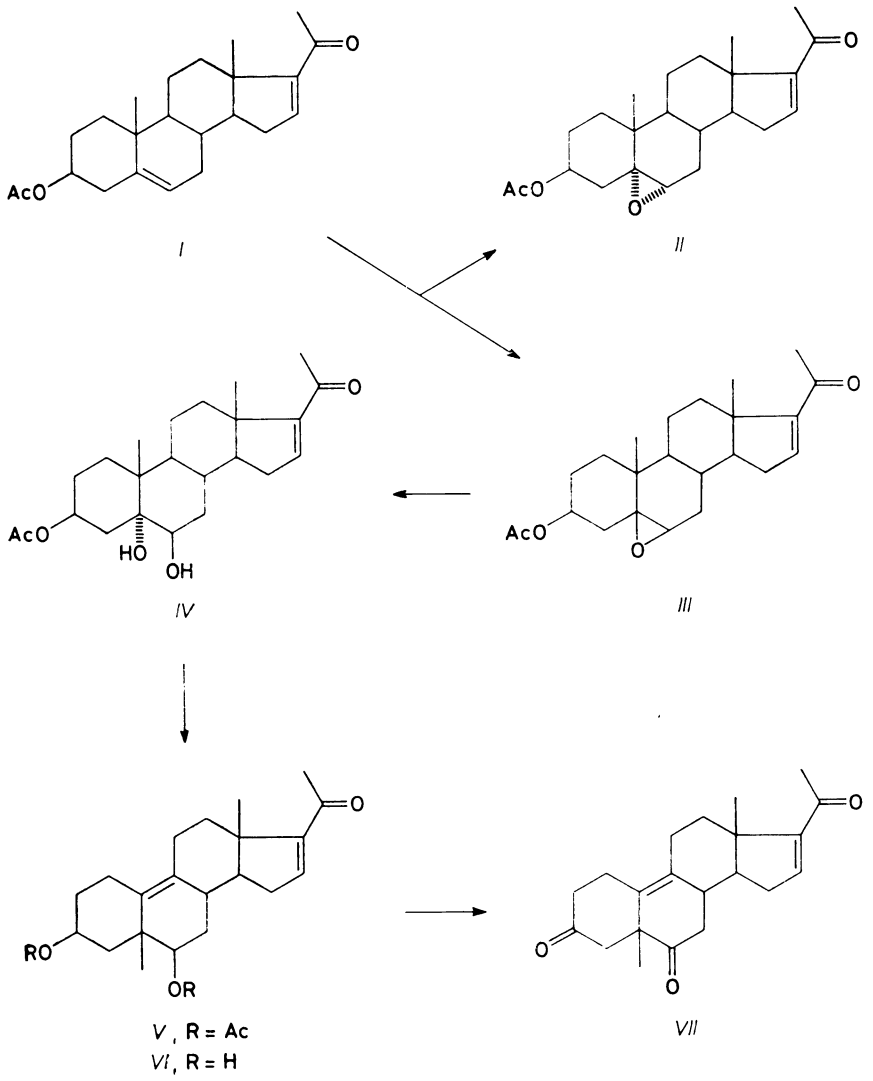
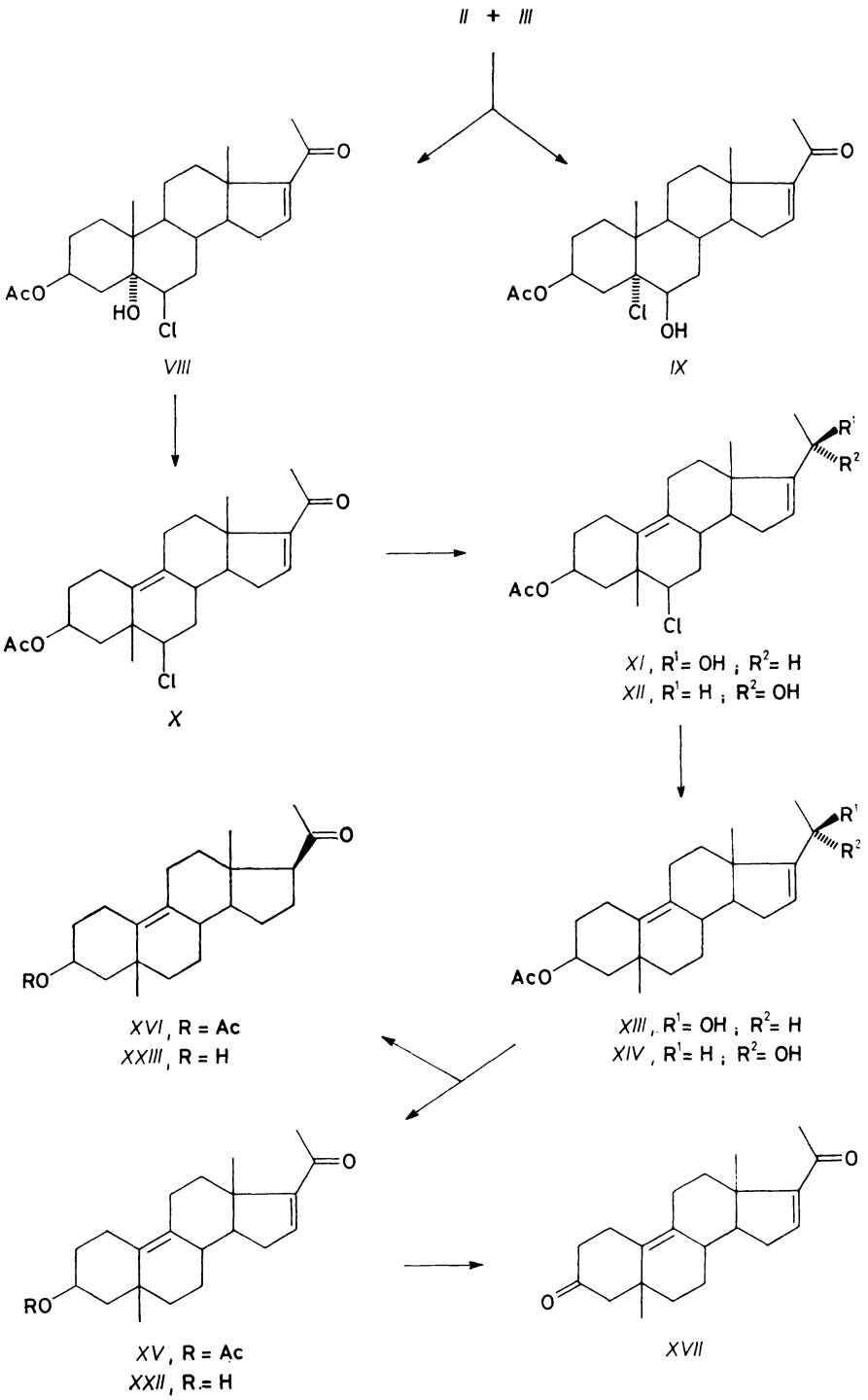
($W_{1/2}$ = 26 Hz) to a narrow multiplet of the equatorial 3α-proton (δ 5·05, $W_{1/2}$ = = 16 Hz). The diacetate *V* was submitted to acid hydrolysis in 2-methyl-2-propanol, affording diol *VI*, which was converted to the required trione *VII* on oxidation according to Jones.



SCHEME 1

In the preparation of compound *XVII* (see Scheme 2) the mixture of epimeric 5α,6α- and 5β-6β-epoxides *II* and *III* was opened by hydrolysis with hydrochloric


II + III
AcO
HO
Cl
O
VIII
AcO
Cl
OH
O
IX
AcO
Cl
O
X
R¹
R²
AcO
Cl
XI, R¹= OH ; R²= H
XII, R¹= H ; R²= OH
RO
O
XVI, R = Ac
XXIII, R = H
R¹
R²
AcO
XIII, R¹= OH ; R²= H
XIV, R¹= H ; R²= OH
RO
O
XV, R = Ac
XXII, R = H
O
O
XVII

SCHEME 2

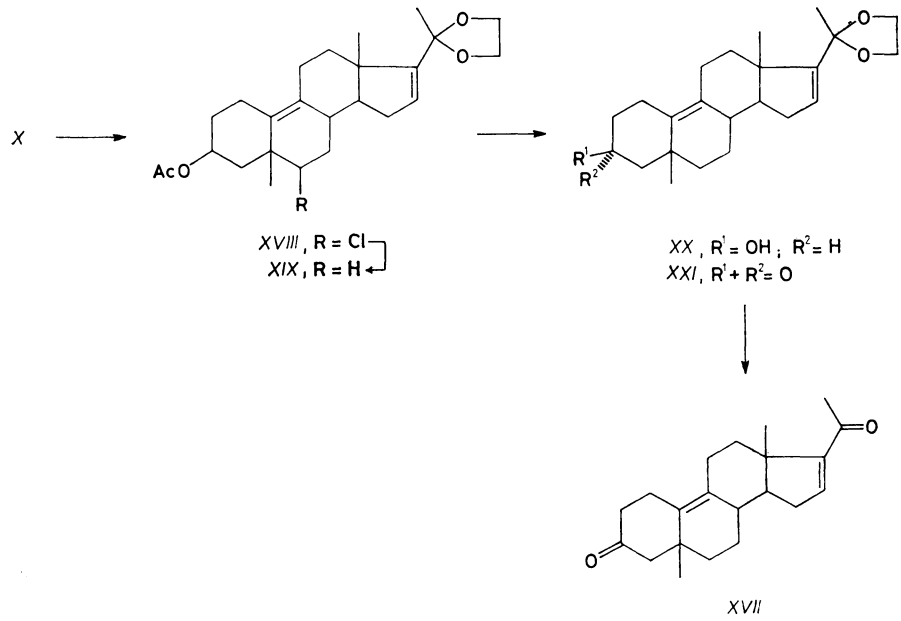
acid to a mixture of chlorohydrins *VIII* and *IX*, from which only[4] 5α-hydroxy-6β--chloro derivative *VIII* affords the rearranged product under the given conditions (acetic acid, acetic anhydride and sulfuric acid). However, we found that a mixture of both these substances may be used as starting substance for the rearrangement. In this manner ketone *X* was isolated from the reaction mixture, the structure of which was confirmed by spectral characteristic (see Experimental).

For the next step it was necessary to substitute the chlorine atom in compound *X* by a hydrogen atom. In view of the possibility of further skeletal rearrangements[5] during the reduction of the 6β-chlorosubstituent with complex hydrides, only the use of dehalogenation with a radicalic mechanism came into consideration, i.e. the use of tributyltin hydride as a reducing agent. Under these conditions the double bond of α,β-unsaturated ketones is also usually reduced[6]. The protection of this grouping by epoxidation of the double bond in position 16 and its deprotection after dehalogenation was not very successful[7], expecially owing to the difficulty of this deprotection. Therefore the reduction of α,β-unsaturated keto group in position 20 by converting it to a mixture of allylic alcohols *XI* and *XII* represented a further variant. Hence, ketone *X* was reduced with sodium borohydride in the presence of cerium(III) chloride[8] to a mixture of allylic alcohols *XI* and *XII*, which was submitted by radicalic dehalogenation to a mixture of alcohols *XIII* and *XIV*. After oxidation according to Jones its saturated analogue *XVI* was isolated in addition to the expected ketone *XV*. Thus it is evident that the allyl alcohols are not resistant to reductions with tributyltin hydride either. Compound *XV* was hydrolysed and oxidised to the required ketone *XVII*, but in view of considerable losses during the isolation of compound *XVI* the yield of this reaction sequence was very low.

An alternative protection of the Δ^{16}-20-keto grouping consists in its ketalisation (see Scheme 3). On reaction of 2,2-dimethyl-1,3-dioxolane with ketone *X* under catalysis with *p*-toluenesulfonic acid compound *X* was converted to ketal *XVIII* which was characterized by its ^{1}H NMR spectrum: the signal H-21 was shifted from its original value δ 2·26 in the ketone to the value δ 1·49, and a multiplet of four protons of the dioxolane ring appeared in the spectrum at δ 3·89. The disappearance of the distinct band of the ketone in the IR spectrum at 1 676 cm^{-1} and the presence of the band ν(C—O) at 1 190 and 1 027 cm^{-1} also indicate the structure *XVIII* of the ketal. Using these spectral characteristics it was possible to follow the stability of the protecting group during the reactions carried.

Reduction of ketal *XVIII* with tributyltin hydride afforded a product of hydrogenolysis, *XIX*. The yield (49%) was not decreased in this case by the undesirable reduction of the Δ^{16}-double bond. The splitting off of the acetyl group in compound *XIX* was achieved with lithium aluminum hydride and the 3β-hydroxy derivative *XX* formed was oxidized to the ketal of dione *XVII*, i.e. compound *XXI*. Elimination of the protecting ketal function led to the required analogue of progesterone

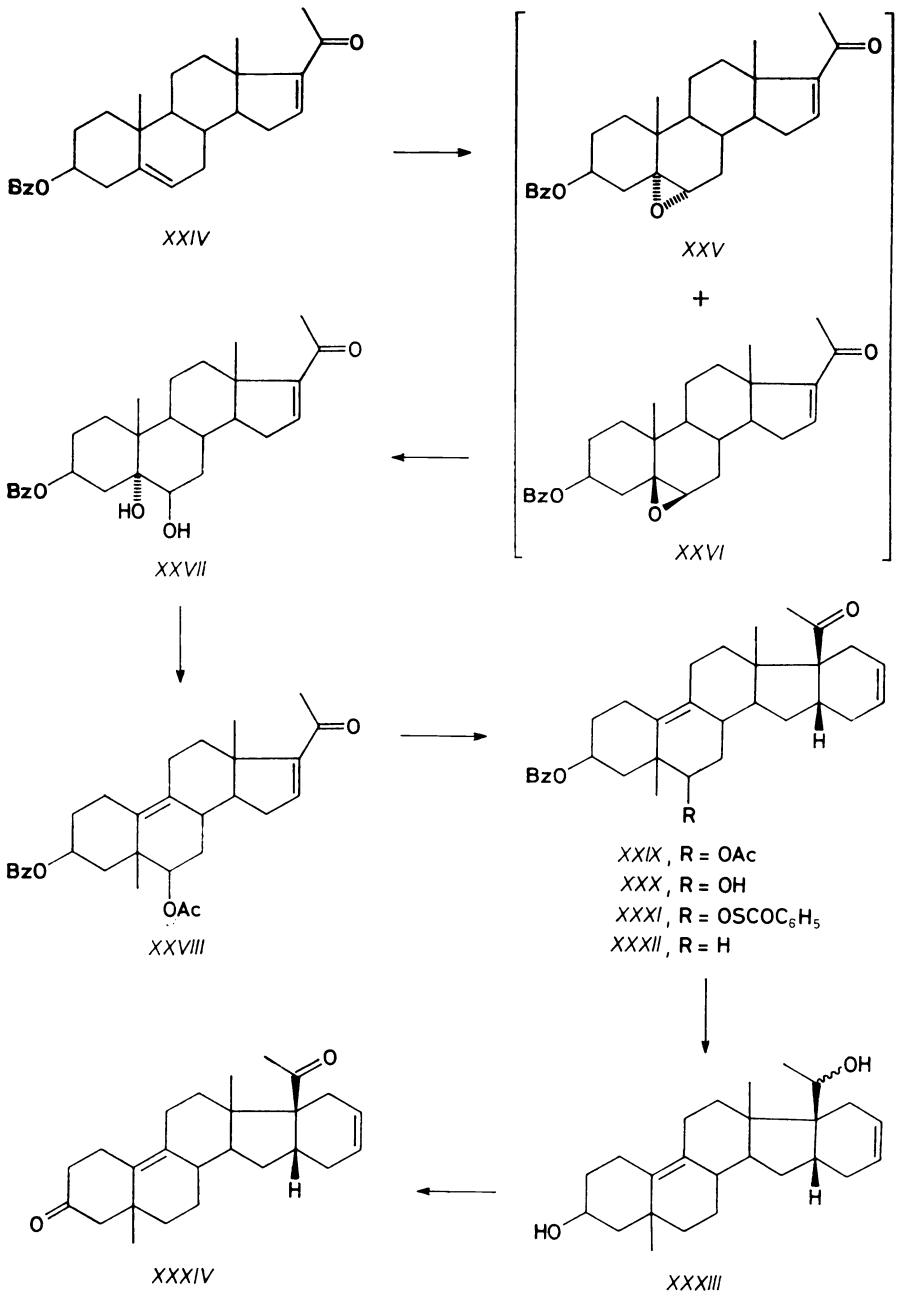
(*XVII*) in a 5·3% yield (with respect to compound *I*). Hydrolysis of the ketal group of compound *XIX* gave ketone *XV*.



SCHEME 3

From these results it follows that the best route to compound *XVII* is radicalic dehalogenation of the 6β-substituent after protection of the α,β-unsaturated ketonic grouping in the form of a ketal.

For the preparation of compound *XXXIV* (Scheme 4) 3β-benzoylpregna-5,16--dien-20-one (*XXIV*) was used which was chemoselectively epoxidated, as in the preceding syntheses, to a mixture of two 5,6-epoxides *XXV* and *XXVI*. Acid hydrolysis of this mixture gave a single 5,6-diol, *XXVII*. Using a mixture of acetic acid, acetic anhydride and sulfuric acid the latter compound was rearranged to 6β-acetate *XXVIII* which reacted with butadiene and aluminum chloride under the conditions of Diels–Alder diene synthesis to give the pentacyclic compound *XXIX*. The structure of the adduct is confirmed mainly by the presence of the molecular ion m/z 530 in its mass spectrum and the shift of the singlet of the hydrogen H-21 in its ^{1}H NMR spectrum, from a value δ 2·27, characteristic of steroidal Δ^{16}-20-ketone to the value δ 2·10, where the usual signal of a saturated 20 ketone is present, and the presence of the signal of two olefinic protons at δ 5·8. Acid hydrolysis of 6β-acetate *XXIX* gave the corresponding 6β-alcohol *XXX* which was further submitted to deoxygena-

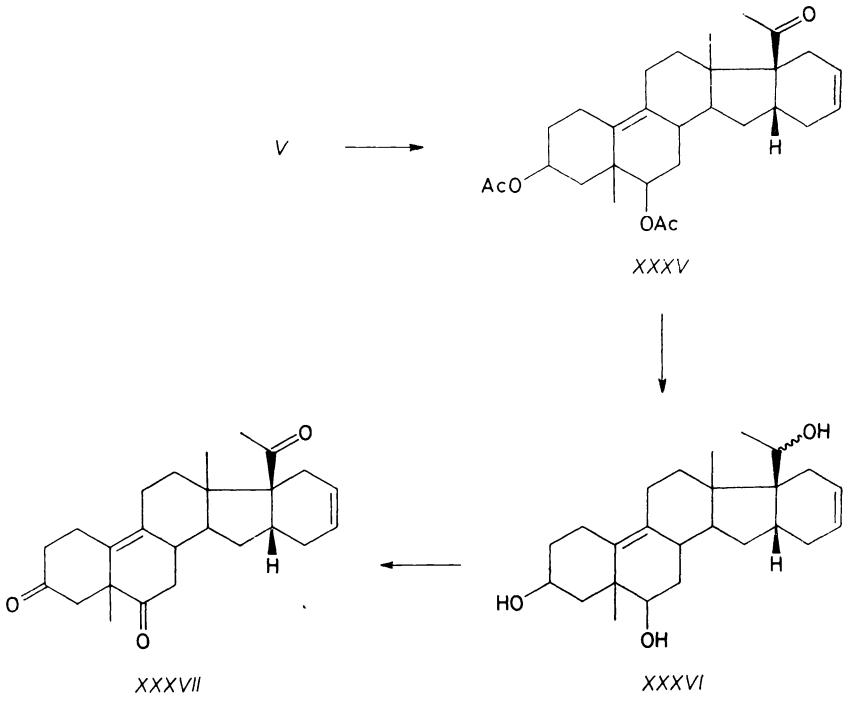


Bz benzoyl

SCHEME 4

tion. Derivatization of the 6β-alcohol with phenoxythiocarbonyl chloride[9] in the presence of 4-dimethylaminopyridine proved most suitable, giving rise to 6β-phenoxythiocarbonyloxy derivative *XXXI* which was deoxygenated to compound *XXXII* with tributyltin hydride. However, from the reaction mixture after deoxygenation the starting alcohol *XXX* was also isolated in addition to compound *XXXII*. Reaction of compound *XXXII* with lithium aluminum hydride gave diol *XXXIII* the oxidation of which according to Jones gave 3,20-dione *XXXIV*.

Similarly, when diacetate *V* was reacted with butadiene under pressure and in the presence of anhydrous aluminum chloride, the product of the Diels–Alder reaction was the pentacyclic diacetate *XXXV*. When boiled with a solution of lithium aluminum hydride in tetrahydrofuran this compound gave triol *XXXVI* which was oxidized according to Jones to the pentacyclic triketone *XXXVII* (Scheme 5) without previous characterization.



SCHEME 5

The optimal route to biologically interesting pentacyclic analogues of type *XXXIV*, lacking a substituent in position 6β, was the sequence in which the construction of the E ring was the first step, followed by radicalic deoxygenation of 6β-phenoxy-

thiocarbonyl derivative, which was no longer complicated by simultaneous reduction of the conjugated double bond.

The biological activities of compounds *VII*, *XVII*, *XXXIV* and *XXXVII* will be published later.

EXPERIMENTAL

The melting points were measured on a Kofler block and they were not corrected. The analytical samples were dried over phosphorus pentoxide at 50°C/100 Pa. Optical rotations were measured in chloroform at 23—25°C. The infrared spectra were measured on a UR-20 (Zeiss, Jena) instrument, in tetrachloromethane, the frequencies are in cm^{-1}. The ^1H NMR spectra were measured in deuteriochloroform with tetramethylsilane as internal standard on Tesla BS-497 (100 MHz; FT mode) and Varian XL-200 (200 MHz, FT mode) instruments. Chemical shifts are given in δ scale (ppm) and the coupling constants (J) and half-widths of multiplets ($W_{1/2}$) in Hz. The mass spectra were measured on a VG Analytical ZAB EQ instrument. The solutions were dried over sodium sulfate. For analytical and preparative thin-layer chromatography silica gel with 5% of gypsum (Woelm DC) was used, and for flash column chromatography the same silica gel without gypsum.

3β,6β-Diacetoxy-5-methyl-19-nor-5β-pregna-9,16-dien-20-one (*V*)

A solution of 3β-acetoxy-5,16-pregnadien-20-one (*I*, 100 g, 280 mmol) in chloroform (600 ml) was stirred with a solution of sodium hydrogen phosphate (100 g) in water (160 ml) and an aqueous solution of peracetic acid (134 ml, 34% 700 mmol) was added to it. After 2 h the mixture was diluted with chloroform, the aqueous phase separated, washed with chloroform and the combined organic phases were washed with a potassium hydrogen carbonate solution and water. The chloroform extract was concentrated in vacuo to dryness and the residue was dissolved in boiling dioxan (1 000 ml) and acetone (60 ml). The solution was cooled and acidified with aqueous perchloric acid (5%, 150 ml). After 3 h standing the solution was concentrated in a vacuum to half its volume and the product was precipitated with water. The precipitate was filtered off under suction, washed with water and used directly for the next reaction. Yield of compound *IV*, 94 g (86%). A sample (100 mg) was crystallized from a mixture of acetone and heptane, m.p. 257—258°C. The precipitate was dissolved in a mixture of acetic anhydride (800 ml), acetic acid (5 l) and sulfuric acid (3·2 ml) and stirred for 3 h at 25°C. The solution was then concentrated in a vacuum to about 1 litre volume and allowed to stand in methanol (1 l) and pyridine (10 ml) for 2 h. The solution was again concentrated, poured under stirring into a saturated aqueous solution of sodium chloride (2 l) and allowed to stand in a refrigerator for 18 h. The precipitated product was filtered off under suction, dissolved in ethyl acetate, washed with a solution of potassium carbonate and water. After drying the solvent was evaporated in a vacuum. The yield of compound *V* was 10·5 g (9%), m.p. 72—74°C (acetone–heptane, under decomposition), $[\alpha]_D$ +109° (*c* 1·7). IR spectrum: 1 742, 1 250 (AcO); 1 676, 1 590 (C=C—C=O). ^1H NMR spectrum: 1·02 s, 3 H (3 × H-18); 1·24 s, 3 H (CH_3-5β); 2·07 s, 3 H (AcO-β); 2·09 s, 3 H (AcO-6); 2·25 s, 3 H (3 × H-21); 4·71 dd, 1 H (H-6, J = 11·8; J' = 4·2); 5·05 p, 1 H (H-3, J = 3·6); 6·63 m, 1 H (H-16, $W_{1/2}$ = 6·4). For $C_{25}H_{34}O_5$ (414·5) calculated: 72·44% C, 8·27% H; found: 72·34% C, 8·30% H.

3β,6β-Dihydroxy-5-methyl-19-nor-5β-pregna-9,16-dien-20-one (*VI*)

Concentrated hydrochloric acid (9 ml) was added to a solution of diacetate *V* (850 mg,

2·05 mmol) in 2-methyl-2-propanol (27 ml) and the mixture was refluxed for 4 h. After cooling it was poured into a solution of potassium hydrogen carbonate and the organic compounds were extracted with ether. The ethereal layer was washed with water, dried and evaporated. The crude mixture was purified by flash chromatography on silica gel (50 g) with light petroleum–ethyl acetate (8 : 2). Yield of diol *VI*, 500 mg (74%), m.p. 137–138°C (acetone–heptane), $[\alpha]_D$ +210° (*c* 2·18). IR spectrum: 3 622, 3 611, 1 068, 1 033 (OH); 1 663, 1 588 (C=C—C=O). ^{1}H NMR spectrum: 1·02 s, 3 H (3 × H-18); 1·23 s, 3 H (CH_3-5β); 2·25 s, 3 H (3 × H-21); 3·51 dd, 1 H (H-6, J = 11; J' = 4); 4·09 p, 1 H (H-3, J = 3·5); 6·69 m, 1 H (H-16, $W_{1/2}$ = 6·2). For $C_{21}H_{30}O_3$ (330·5) calculated: 76·33% C, 9·15% H; found: 76·21% C, 9·10% H.

5-Methyl-19-nor-5β-pregna-9,16-diene-3,6,20-trione (*VII*)

Diol *VI* (450 mg, 1·36 mmol) was oxidized in acetone with Jones's reagent. After the conventional work-up trione *VII* was obtained (380 mg; 86%), m.p. 170–172°C (acetone–heptane), $[\alpha]_D$ −44° (*c* 1·26). IR spectrum: 1 719 (C=O); 1 671, 1 592 (C=C—C=O). ^{1}H NMR spectrum: 1·00 s, 3 H (3 × H-18); 1·22 s, 3 H (CH_3-5β); 2·29 s, 3 H (3 × H-21); 6·70 m, 1 H (H-16, $W_{1/2}$ = = 6). For $C_{21}H_{26}O_3$ (326·4) calculated: 77·27% C, 8·03% H; found: 77·19% C, 8·01% H.

3β-Acetoxy-6β-chloro-5-methyl-19-nor-5β-pregna-9,16-dien-20-one (*X*)

A solution of a mixture of epoxides *II* and *III* (6·6 g, 17·8 mmol) in chloroform (40 ml) was intensively shaken with concentrated hydrochloric acid (30 ml) at room temperature. After 20 min the aqueous phase was separated, washed with chloroform and the combined organic phases were washed with water, dried over sodium sulfate and evaporated in a vacuum. The residue was dissolved in acetic anhydride (160 ml) and 25 ml of volatiles were distilled off. Acetic acid (70 ml) was added to the hot solution and the mixture allowed to cool down. The mixture was acidified with concentrated sulfuric acid (0·5 ml) and the temperature kept at 30°C for 30 min and then at 20°C for 3 h. The mixture was then poured into a cooled and stirred saturated sodium chloride solution (1 l) and allowed to stand in a refrigerator for 18 h. The separated product was filtered off under suction, dissolved in ethyl acetate and washed with a potassium carbonate solution and water. After drying the solution was concentrated and the residue crystallized. Compound *X* (1·5 g, 22%), m.p. 151–157°C (acetone–heptane, under decomposition), $[\alpha]_D$ +233° (*c* 1·2). IR spectrum: 1 742, 1 250 (AcO); 1 676, 1 590 (C=C—C=O). ^{1}H NMR spectrum: 1·01 s, 3 H (3 × H-18); 1·24 s, 3 H (CH_3-5β); 2·06 s, 3 H (AcO); 2·25 s, 3 H (3 × H-21); 3·98 dd, 1 H (H-6, J = 12·8; J' = 3·8); 5·07 p, 1 H (H-3, J = 3·6); 6·68 m, 1 H (H-16, $W_{1/2}$ = 6·4). For $C_{23}H_{31}ClO_3$ (390·9) calculated: 70·66% C, 7·98% H; found: 70·63% C, 7·98% H.

3β-Acetoxy-5-methyl-19-nor-5β-pregna-9,16-dien-20-one (*XV*)

a) A solution of ceric chloride (70 ml of 0·4M $CeCl_3.6\,H_2O$ in methanol) and sodium borohydride (540 mg) was added under stirring to a solution of ketone *X* (5 g, 12·79 mmol) in ethyl acetate (70 ml) and allowed to stand for 5 min. Then the solution was poured into water, the precipitate was extracted with ether, the etheral phase was washed gradually with hydrochloric acid (5%), potassium hydrogen carbonate solution and water, and evaporated. A mixture was obtained consisting of (20*R*) and (20*S*) alcohols *XI* and *XII*, in a 2 : 1 ratio. IR spectrum: 3 620 (OH); 3 050, 1 671 (C=C); 1 740, 1 249 (AcO). ^{1}H NMR spectrum of the 1st compound: 0·96 s, 3 H (3 × H-18); 1·26 s, 3 H (CH_3-5β); 1·29 d, 3 H (3 × H-21, J = 7); 2·07 s, 3 H (AcO); 3·99 dd, 1 H (H-6, J = 13; J' = 3·5); 4·35 q, 1 H (H-20, J = 7); 5·08 p, 1 H (H-3, J = 3·5); 5·62 m, 1 H (H-16, $W_{1/2}$ = 6). ^{1}H NMR spectrum of the 2nd compound: 1·01 s, 3 H (3 × H-18); 1·26 s,

3 H (CH_3-5β); 1·36 d, 3 H (3 × H-21, J = 7); 2·07 s, 3 H (AcO); 3·99 dd, 1 H (H-6, J = 13; J' = 3·5); 4·35 q, 1 H (H-20, J = 7); 5·08 p, 1 H (H-3, J = 3·5); 5·62 m, 1 H (H-16, $W_{1/2}$ = 6). A solution of a mixture of alcohols *XI* and *XII* (5·0 g, 12·7 mmol) in benzene (70 ml) was added dropwise to a boiling solution of 1M tributyltin hydride in benzene (20 ml) and the mixture was refluxed for 8 h. After cooling the solvent was evaporated and the residue dissolved in ether and washed several times with an aqueous solution of potassium fluoride and water. The organic layer was dried over sodium sulfate and the solvent was evaporated. The residue was dissolved in acetone (30 ml) and oxidized according to Jones. The mixture was poured into water, the precipitate formed was extracted with ether and washed with dilute hydrochloric acid, potassium hydrogen carbonate and water. After evaporation of the solvent the mixture was chromatographed on silica gel (200 g). Elution with a light petroleum–ethyl acetate mixture (19 : 1) gave first 3β-acetoxy-5-methyl-19-nor-5β-pregn-9-en-20-one *XVI* (200 mg; identical with an authetic sample[10]), folowed by a mixture of compound *XVI* and dienone *XV* in an approximatively 2 : 3 ratio (1·86 g), from which a sample was withdrawn (50 mg), which was chromatographed on preparative thin-layer plates. Ketone *XV* (5 mg was thus) obtained, which was identical with the compound obtained under *b*).

b) A solution of ketal *XIX* (116 mg, 0·29 mmol) and *p*-toluenesulfonic acid (35 mg, 0·18 mmol) in acetone (2 ml) was allowed to stand at room temperature for 2 h. It was then poured into a potasium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and dried. After evaporation of the solvent ketone *XV* (90 mg, 87%) was obtained, m.p. 123°C (methanol), $[\alpha]_D$ +110° (*c* 1·0). IR spectrum: 1 736, 1 238, 1 018 (AcO); 1 670, 1 590, (C=C—C=O). ^{1}H NMR spectrum: 1·00 s, 3 H (3 × H-18); 1·18 s, 3 H (CH_3-5β); 2·06 s, 3 H (AcO); 2·25 s, 3 H (3 × H-21); 5·07 p, 1 H (H-3, J = 3·5); 6·69 m, 1 H (H-16, $W_{1/2}$ = 6·2). For $C_{23}H_{32}O_3$ (356·5) calculated: 77·49% C, 9·05% H; found: 77·51% C, 9·10% H.

5-Methyl-19-nor-5β-pregna-9,16-diene-3,20-dione (*XVII*)

a) From the obtained mixture of compounds *XV* and *XVI*. A mixture of saturated and unsaturated ketone, *XVI* and *XV* (880 mg), obtained in the preparation of compound *XV*, was dissolved in 2-methyl-2-propanol (29 ml) and conc. hydrochloric acid (1·3 ml) and the solution was refluxed for 5 h. After cooling the residues of the acid were neutralized with a sodium hydrogen carbonate solution and the solution was then concentrated in a vacuum, extracted with ether and the extract evaporated to dryness. The residue was chromatographed on silica gel (80 g) with a light petroleum–ethyl acetate (8 : 2) solution. Elution gave first acetate *XV* (260 mg) followed by compound *XXIII* with an admixture of compound *XXII* (in about 3 : 1 ratio, determined by ^{1}H NMR spectrometry). Fraction 1 was dissolved in 2-methyl-2-propanol and conc. hydrochloric acid (3 ml) and refluxed for 24 h. After an identical working up, alcohol *XXII* was isolated, which was dissolved in acetone and oxidized according to Jones under cooling with ice. The mixture was poured into water, the precipitate was extracted with ether and the organic extract washed with hydrochloric acid, potassium hydrogen carbonate and water. After evaporation of the solvent diketone *XVII* (36 mg) was obtained, m.p. 116–118°C (ether), $[\alpha]_D$ +85° (*c* 2·0). IR spectrum: 1 714 (C=O); 1 670, 1 590 (C=C—C=O). ^{1}H NMR spectrum: 1·02 s, 3 H (3 × H-18); 1·52 s, 3 H (CH_3-5β); 2·27 s, 3 H (3 × H-21); 6·71 m, 1 H (H-16, $W_{1/2}$ = = 6·4). For $C_{21}H_{28}O_2$ (312·5) calculated: 80·73% C, 9·03% H; found: 80·91% C, 9·01% H.

b) From ketal *XIX*. Lithium aluminum hydride (150 mg, 4·05 mmol) was added to a solution of ketal *XIX* (250 mg, 0·62 mmol) in dioxane (8 ml) and the suspension was refluxed for 8 h. After cooling the reaction mixture was poured into water, the organic material was extracted with ether and the organic layer was washed twice with water. After evaporation of the solvent

the crude residue was dissolved in acetone (6 ml) and the compound was oxidized according to Jones. The reaction mixture was poured into water, the organic material was extracted with ether and the extract was washed with water. After evaporation of the solvent the crude product was dissolved in acetone (4 ml) and *p*-toluenesulfonic acid (70 mg) was added to the solution. It was then stirred for 4 h and poured into an aqueous solution of sodium hydrogen carbonate and extracted with ether. The organic layer was washed with water, dried and evaporated. Diketone *XVII* was obtained (120 mg, 62%), identical with a compound prepared as under *a*).

6β-Chloro-20,20-ethylenedioxy-5-methyl-19-nor-5β-pregna-
-9,16-dien-3β-ol 3-Acetate (*XVIII*)

p-Toluenesulfonic acid (100 mg, 0·52 mmol) was added to a solution of ketone *X* (1 g, 2·56 mmol) in 2,2-dimethyl-1,3-dioxolane (30 ml) and the solution was refluxed for 1·5 h under slow distilling off of the solvent. After cooling the solution was poured into a two-phase mixture of aqueous potassium hydrogen carbonate and ethyl acetate, shaken and separated. The organic phase was washed with water (2×). Afer drying the solvent was evaporated. The crude residue was chromatographed on a column of alumina (250 g) with benzene–light petroleum (1 : 1) as eluent. Ketal *XVIII* (890 mg, 80%) was obtained, m.p. 139—140°C (methanol), $[\alpha]_D$ +85° (*c* 1·2). IR spectrum: 3 059, 1 617 (C=C); 1 739, 1 244 (AcO); 1 190, 1 027, 948 (dioxolane ring). ^{1}H-NMR spectrum: 1·05 s, 3 H (3 × H-18); 1·26 s, 3 H (CH_3-5β); 1·49 s, 3 H (3× H-21); 2·06 s, 3 H (AcO); 3·89 m, 5 H (H-6 + dioxolane, $W_{1/2}$ = 6). For $C_{25}H_{35}ClO_4$ (435·0) calculated: 69·03% C, 8·11% H; 8·15% Cl; found: 69·13% C, 8·11% H, 8·15% Cl.

20,20-Ethylenedioxy-5-methyl-19-nor-5β-pregna-9,16-dien-3β-ol 3-Acetate (*XIX*)

A 1M solution of tributyltin hydride in benzene (4 ml) was added to a solution of ketal *XVIII* (850 mg, 1·95 mmol) and azo-bis-isobutyronitrile (5 mg) in benzene (12 ml), and the mixture was refluxed under argon for 8 h. After cooling the solution was evaporated under reduced pressure and the residue was chromatographed on alumina (160 g) and gradually eluted with light petroleum (1 l), a mixture of light petroleum and benzene (1 : 1, 1 l) and finally with benzene (2 l). Compound *XIX* was obtained (380 mg, 49%), m.p. 66—67°C (methanol), $[\alpha]_D$ +42, (*c* 1·6). IR spectrum: 3 056, 1 620 (C=C); 1 736, 1 239, 1 048, 1 023 (AcO); 1 263, 1 184, 1 117 948 (dioxolane ring). ^{1}H NMR spectrum: 1·04 s, 3 H (3 × H-18); 1·18 s, 3 H (CH_3-5β); 1·50 s, 3 H (3 × H-21); 2·06 s, 3 H (AcO); 3·89 m, 4 H (dioxolane, $W_{1/2}$ = 16); 5·07 p, 1 H (H-3, J = 3·5); 5·77 m, 1 H (H-16, $W_{1/2}$ = 6). For $C_{25}H_{36}O_4$ (400·6) calculated: 74·96% C, 9·06% H; found: 74·89% C, 9·10% H.

3β-Benzoyloxy-5,6β-dihydroxy-5α-pregn-16-en-20-one (*XXVII*)

A solution of 3β-benzoyloxy-5,16-pregnadien-20-one (*XXIV*, 20 g, 47·8 mmol) in chloroform (200 ml) was stirred with a solution of disodium hydrogen phosphate (120 g) in water (160 ml) and an aqueous solution of peracetic acid (34%, 150 ml) was poured into this mixture. After 2 h standing the mixture was diluted with chloroform, the aqueous phase was separated, washed with chloroform and the combined organic phases were then washed with a potassium hydrogen carbonate solution and water. The chloroform extract was concentrated in a vacuum to dryness and the residue was dissolved in a boiling mixture of dioxane (260 ml) and acetone (130 ml). The solution was cooled and acidified with perchloric acid (5%, 64 ml). After 3 h the reaction mixture was concentrated in vacuo to half its volume and the product was precipitated with water. The precipitate was filtered off under suction, washed with water and used in the next

step without purification. Yield, 20·2 g (93%). A sample (100 mg) was crystallized from acetone–heptane, m.p. 231–233°C, $[\alpha]_D$ −1° (*c* 1·0). IR spectrum: 3 625 (OH); 1 711, 1 285 (COO); 1 665, 1 586 (C=C—C=O). ^{1}H NMR spectrum: 0·92 s, 3 H (3 × H-18); 1·28 s, 3 H (CH_3-5β); 2·25 s, 3 H (3 × H-21); 3·62 m, 1 H (H-6, $W_{1/2}$ = 6); 5·42 m, 1 H (H-3, $W_{1/2}$ = 24); 6·68 m, 1 H (H-16, $W_{1/2}$ = 6); 7·50 m and 8·06 m, 5 H (H-arom.). For $C_{28}H_{36}O_5$ (452·6) calculated: 74·31% C, 8·02% H; found: 74·22% C, 8·00% H.

3β-Benzoyloxy-6β-acetoxy-5-methyl-19-nor-5β-pregna-9,16-dien-20-one (*XXVIII*)

From a solution of diol *XXVII* (20 g, 44·2 mmol) in acetic anhydride (750 ml) about 80 ml of distillate were distilled off and concentrated sulfuric acid (1·2 ml) was added dropwise over 30 min to the stirred mixture kept at 30°C. The mixture was kept at this temperature for another 30 min and then at room temperature for 3 h. The mixture was then poured into a cooled and stirred saturated sodium chloride solution in water (3 l) and then allowed to stand in a refrigerator. After 18 h standing the precipitate was filtered off under suction, dissolved in ethyl acetate and the solution was washed with a potassium carbonate solution and water and dried. After evaporation of the solvent the residue was chromatographed on silica gel (320 g) with a mixture of toluene and ether (98 : 2). The obtained compound *XXVIII* (7·3 g, 35%) had m.p. 132–136°C (acetone–heptane), $[\alpha]_D$ +152° (*c* 1·1). IR spectrum: 1 730, 1 376, 1 261 (AcO); 1 720, 1 282 (benzoate); 1 682, 1 671, 1 615 (C=C—C=O). ^{1}H NMR spectrum: 1·03 s, 3 H (3 × H-18); 1·33 s, 3 H (CH_3-5β); 2·04 s, 1 H (AcO); 2·27 s, 3 H (3 × H-21); 4·77 m, 1 H (H-6, J = 4·5; J' = 10); 5·35 m, 1 H (H-3, $W_{1/2}$ = 10); 6·71 m, 1 H (H-16, $W_{1/2}$ = 6·2); 7·5 and 8·06 m, 5 H (H-arom.). For $C_{30}H_{36}O_5$ (476·6) calculated: 75·60% C, 7·61% H; found: 75·87% C, 7·88% H.

3β-Benzoyloxy-6β-acetoxy-5-methyl-19-nor-16β*H*-cyclohexa-[16,17]5β-pregna-4′,9-dien-20-one (*XXIX*)

Compound *XXVIII* (850 mg, 1·78 mmol) was dissolved in dichloromethane (10 ml) and anhydrous aluminum chloride (50 mg) was added to it under stirring. After 40 minutes' stirring the mixture was cooled to −60°C and liquid butadiene (about 2 ml) was added to it. The reaction mixture was heated in an autoclave at 80°C for 6 h, allowed to cool, diluted with dichloromethane (30 ml) and washed with brine. The organic layer was evaporated and the residue chromatographed on silica gel (50 g). Compound *XXIX* (650 mg, 69%) was eluted with a mixture of benzene and ether (19 : 1), and it had m.p. 86–88°C (from ether–heptane), $[\alpha]_D$ +102° (*c* 1·06). IR spectrum: 1 740, 1 250 (AcO); 1 723, 1 278 (benzoate); 1 710, 1 355 (CH_3C=O). ^{1}H NMR spectrum: 0·86 s, 3 H (3 × H-18); 1·33 s, 3 H (CH_3-5β); 2·04 s, 3 H (AcO); 2·10 s, 3 H (3 × H-21); 4·77 dd, 1 H (H-6, J = 4·5; J' = 10); 5·38 p, 1 H (H-3, J = 3·5); 5·80 m, 2 H (H-4′ and H-5′); 7·5 m and 8·06 m, 5 H (H-arom.). For $C_{34}H_{42}O_5$ (530·7) calculated: 76·95% C, 7·98% H; found: 76·89% C, 7·99% H. On further elution the starting compound *XXVIII* (50 mg) was recovered.

3β-Benzoyloxy-6β-hydroxy-5-methyl-19-nor-16β*H*-cyclohexa-[16,17]5β-pregna-4′,9-dien-20-one (*XXX*)

Concentrated hydrochloric acid (1·2 ml) was added to a solution of acetate *XXIX* (650 mg, 1·22 mmol) in methanol (30 ml) and chloroform (10 ml), and the mixture was allowed to stand at 40°C overnight. It was poured into an aqueous solution of potassium hydrogen carbonate, extracted with ethyl acetate and the organic layer was washed with a potassium hydrogen carbonate solution and water, and then evaporated. The product *XXX* (595 mg, 99%) had m.p. 84 to

86°C (acetone–heptane), $[\alpha]_D$ +104° (*c* 2·0). IR spectrum: 3 612, 3 526 (OH); 1 075, 1 352 (C═O); 1 705, 1 279, 712 (benzoate); 1 653, 663 (C═C). ^{1}H NMR spectrum: 0·84 s, 3 H (3 × H-18); 1·26 s, 3 H (CH_3-5β); 2·1 s, 3 H (3 × H-21); 3·54 dd, 1 H (H-6, J = 4·5; J' = 10); 5·38 p, 1 H (H-3, J = 3·5); 5·79 m, 2 H (H-4′ and H-5′); 7·5 m and 8·06 m, 5 H (H-arom.). For $C_{32}H_{40}O_4$ (488·7) calculated: 78·65% C, 8·25% H; found: 78·76% C, 8·14% H.

3β-Benzoyloxy-5-methyl-19-nor-16β*H*-cyclohexa[16,17]-5β-pregna-4′,9-dien-20-one (*XXXII*)

A solution of alcohol *XXX* (158 mg, 0·32 mmol), phenoxythiocarbonyl chloride (130 mg, 0·9 mmol) and 4-dimethylaminopyridine (125 mg, 0·97 mmol) in pyridine (7 ml) was stirred at room temperature for 48 h and then poured into water and extracted with ether. The ethereal layer was washed with a solution of sodium hydrogen carbonate and water and dried. The solvent was evaporated and the residue (crude compound *XXXI*) was dissolved in toluene (8 ml), of which one half was distilled off. A 1M solution of tributyltin hydride in toluene (1·5 ml) and azo-bis-isobutyronitrile (3 mg) were then added to the solution and the mixture was refluxed for 6 h under argon. After cooling the solvent was evaporated and the residue chromatographed on silica gel (20 g) with light petroleum–ethyl acetate (19 : 1); Compound *XXXII* (24 mg, 16%) was eluted first, m.p. 132°C (methanol), $[\alpha]_D$ +48° (*c* 2·5). IR spectrum: 3 035, 1 718, 1 603, 1 585, 1 277 (benzoate); 1 700, 1 351 (CH_3CO). ^{1}H NMR spectrum: 0·89 s, 3 H (3 × H-18); 1·29 s, 3 H (CH_3-5β); 2·10 s, 3 H (3 × H-21); 5·38 p, 1 H (H-3, J = 3·5); 5·78 m, 2 H (H-4′ and H-5′); 7·3—7·66 and 7·97—8·24 (H-arom.). Mass spectrum, *m/z*: 472 (M^+, 6); 350 (M − C_6H_5COOH, 26); 307 (M − C_6H_5COOH—CH_3CO, 30); 269 (100); 213 (18). For $C_{32}H_{40}O_3$ (472·7) calculated: 81·32% C, 8·53% H; found: 81·54% C, 8·51% H. On further elution a mixture of compounds *XXXII* and *XXX* (14 mg, 9%) and compound *XXX* (21 mg, 14%) were gradually eluted.

5-Methyl-19-nor-16β*H*-cyclohexa[16,17]5β-pregna-4′,9-diene-3,20-dione (*XXXIV*)

Lithium aluminum hydride (30 mg) was added to a solution of benzoate (24 mg, 0·05 mmol) in tetrahydrofuran (1 ml) and the mixture was refluxed for 2 h. After cooling it was poured into water and the organic compounds were extracted with ether. The organic phases were washed with a sodium hydrogen carbonate solution and water, and the solvent was evaporated under reduced pressure. The residue was dissolved in acetone (1·5 ml) and oxidized according to Jones. After the conventional work-up the mixture was separated on a preparative thin-layer plate with benzene–ether (8 : 2). The result of the elution was compound *XXXIV* (15 mg, 81%), m.p. 114°C (ethyl acetate). IR spectrum: 3 037, 1 636, 675 (C═C); 1 712, 1 700 (C═O); 1 700, 1 351 ($COCH_3$). ^{1}H NMR spectrum (200 MHz): 0·83 s, 3 H (3 × H-18); 1·01 s, 3 H (CH_3-5β); 2·12 s, 3 H (3 × H-21); 5·78 m, 2 H (H-4′ and H-5′). Mass spectrum (high resolution): 366, 2550201 ($C_{25}H_{34}O_2$, M^+, 27); 323 (31); 244 (100); 217 (23); 123 (78). For $C_{25}H_{34}O_2$ (366·5) calculated: 81·92% C, 9·35% H; found: 81·90% C, 9·36% H.

3β,6β-Diacetoxy-5-methyl-19-nor-16β*H*-cyclohexa[16,17]-5β-pregna-4′,9-dien-20-one (*XXXV*)

A solution of ketone *V* (2·0 g, 4·82 mmol) in dichloromethane (3·5 ml) was stirred for 45 min with anhydrous aluminum chloride (150 mg) and condensed butadiene (3 g) with a trace of hydroquinone was added to the mixture, which was then heated at 80°C in an autoclave for 1 h. After cooling the solvent was evaporated and the residue separated by flash chromatography

on silica gel (50 g) with light petroleum–ethyl acetate (85 : 15). Elution gave compound *XXXV* (197 mg, 9%), m.p. 116–117°C (acetone–heptane), $[\alpha]_D$ +85° (*c* 1·0). IR spectrum: 3 039, 1 668 (C=C); 1 739, 1 241 (AcO); 1 700, 1 352 (CH_3CO). ^{1}H NMR spectrum: 0·83 s, 3 H (3 × H-18); 1·24 s, 3 H (CH_3-5β); 2·02 s, 3 H (AcO); 2·06 s, 3 H (AcO); 2·09 s, 3 H (3 × H-21); 4·71 dd 1 H (H-6, J = 4·5; J' = 10·5); 5·09 p, 1 H (H-3, J = 3); 5·79 m, 2 H (H-4′ and H-5′). Mass spectrum, *m/z*: 468 (M^+, 42), 408 (100), 365 (67), 348 (42), 333 (29), 305 (25). For $C_{29}H_{40}O_5$ (468·6) calculated: 74·33% C, 8·60% H; found: 74·29% C, 8·49% H. Further elution gave compound *XXXV* and *V* (530 mg, 23%) and compound *V* (554 mg, 24%).

5-Methyl-19-nor-16β*H*-cyclohexa[16,17]5β-pregna-4′,9-diene-3,6,20-trione (*XXXVII*)

Diacetate *XXXV* (190 mg, 0·41 mmol) was dried by azeotropic distillation with toluene (5 ml), dissolved in tetrahydrofuran (8 ml) and lithium aluminum hydride (250 mg) was added to the mixture which was then refluxed for 2 h. After cooling the unreacted reagent was decomposed with water and the organic substances were extracted with ether. The extract was washed gradually with 5% hydrochloric acid, sodium hydrogen carbonate and water and the solvent was evaporated under reduced pressure. The residue (crude substance *XXXVI*) was dissolved in acetone (3 ml) and oxidized according to Jones. After a conventional work-up 150 mg (97%) of compound *XXXVII* were obtained, m.p. 185–186°C (ethyl acetate), $[\alpha]_D$ −86° (*c* 1·0). IR spectrum: 3 037, 1 635 (C=C); 1 720, 1 702 (C=O); 1 702, 1 352 (CH_3CO). ^{1}H NMR spectrum: 0·83 s, 3 H (3 × H-18); 1·21 s, 3 H (CH_3-5β); 2·13 s, 3 H (3 × H-21); 5·78 m, 2 H (H-4′ and H-5′). For $C_{25}H_{32}O_3$ (380·5) calculated: 78·91% C, 8·48% H; found: 78·89% C, 8·51% H.

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