STEROID DERIVATIVES. LXIX.*

PREPARATION OF HYDROXY ANALOGUES OF THE SUBSTANCES OF 16-METHYLENEPROGESTERONE SERIES

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On reduction of 17α-acetoxy-16-methyleneprogesterone derivatives with sodium boro-hydride corresponding 3β-hydroxy analogues of these compounds were obtained. If instead of the bulky 17α-acetoxy group only the 17α-hydroxy group was in the neighborhood of the $C_{(20)}$-oxo group 3β,17α,20β-triol was obtained as the main product which was then converted with manganese dioxide to the corresponding 17α,20β-dihydroxy-3-oxo derivative.

In our laboratory a series of derivatives of 16-methyleneprogesterone *I*–*IV* possessing gestagenic activity has been described[1–4]. The papers published in recent years in the literature[5–7] show, however, that the presence of an oxo group in position 3 or 20 is not indispensable for this activity, and that even the reduction of the oxo group to the hydroxy group sometimes brings about a useful modification of the biological activity. Therefore, we decided to change the compounds prepared by us by reducing the one or the other or both oxo groups. In order to compare the reactivity of the oxo groups in positions 3 and 20 we always carried out the reductions under the same conditions, *i.e.* with sodium boro-hydride in anhydrous methanol[8] and under cooling.

If 17α-acetoxy-16-methyleneprogesterone[1] (*I*), 17α-acetoxy-16-methylene-4,6-pregnadiene-3,20-dione[2] (*II*), 17α-acetoxy-6-chloro-16-methylene-4,6-pregnadiene-3,20-dione[3] (*III*), and 17α-acetoxy-6-bromo-16-methylene-4,6-pregnadiene-3,20-dione[4] (*IV*) were used as starting components, corresponding 3β-hydroxy derivatives *VII*, *IX*, *XI*, and *XIV* were always obtained in good yield. In contrast to this, when 17α-acetoxy 6-chloro-16-methylene-1,4,6-pregnatriene-3,20-dione[6] (*V*) and 17α-acetoxy-6-bromo-16-methylene-1,4,6-pregnatriene-3,20-dione[7] (*VI*) were reduced with sodium boro-hydride under such conditions, 3β-hydroxy derivatives *XI* and *XIV* saturated at the

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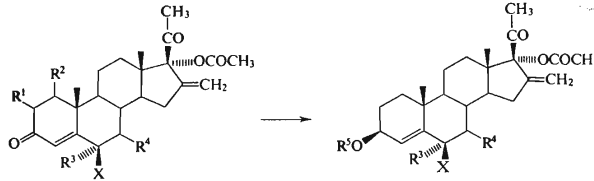
1,2-position were obtained exclusively. An analogous reduction of the 1,2-double bond with sodium boro-hydride was also observed by Sondheimer and coworkers[8] who reduced 1,4,6-androstatrien-3-one derivatives under similar conditions, giving rise to 3β-hydroxy-4,6-androstadienes. In all instances the $C_{(20)}$-oxo group remained unattacked, because it was sufficiently sterically hindered by the bulky acetoxy group in the position 17α, although the oxo group at $C_{(20)}$ is usually reduced more easily with sodium boro-hydride than the conjugated oxo group at $C_{(3)}$ (ref.[9]).

The obtained 3β-hydroxy derivatives *VII*, *IX*, *XI*, and *XIV* were acetylated with acetic anhydride in pyridine to corresponding 3-acetates *VIII*, *X*, *XII*, and *XV*; in addition to this, hydroxy derivative *XI* was converted by the same means to 3β-propionate *XIII*. 3β-Hydroxy derivative *XI* was hydrolyzed by sodium hydrogen carbonate in aqueous methanol to 3β,17α-diol *XVI* which was partially acetylated first in position 3 with acetic anhydride in pyridine (to 3β-monoacetate *XVII*), and in a subsequent step, with acetic anhydride in the presence of sulfosalicylic acid as catalyst, to diacetate *XII*, identical with the compound prepared by direct acetylation of the 3β-hydroxy derivative *XI*.

From the obtained results it was clear that the $C_{(20)}$-oxo group cannot be reduced with sodium boro-hydride in the presence of 17α-acetoxy group. As most interesting for further transformations we chose 6-chloro derivative *III* which we converted under the influence of potassium hydrogen carbonate in aqueous methanol to 17α-hydroxy derivative *XVIII*. The latter was reduced under cooling with sodium boro-hydride in methanol. During the reaction both carbonyl groups, at $C_{(3)}$ and $3_{(20)}$, were attacked simultaneously and the sole isolated product was 3β,17α,20β-triol *XIX*.

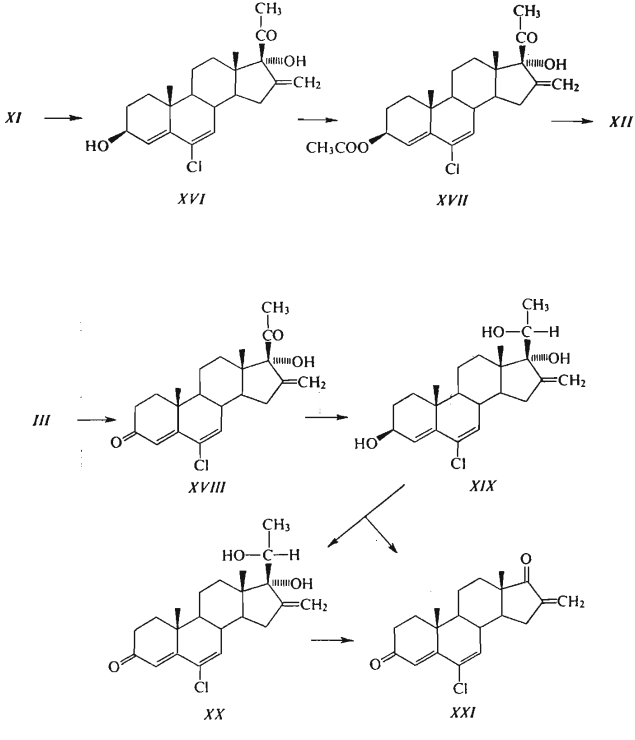


I, X = H; $R^1 = R^2 = R^3 = R^4 = H$
II, X = H; $R^1 = R^2 =$ H; $R^3 + R^4 = \Delta$
III, X = Cl; $R^1 = R^2 =$ H; $R^3 + R^4 = \Delta$
IV, X = Br; $R^1 = R^2 =$ H; $R^3 + R^4 = \Delta$
V, X = Cl; $R^1 + R^2 = \Delta$; $R^3 + R^4 = \Delta$
VI, X = Br; $R^1 + R^2 = \Delta$; $R^3 + R^4 = \Delta$

VII, X = H; $R^3 = R^4 =$ H; $R^5 = H$
VIII, X = H; $R^3 = R^4 =$ H; $R^5 = COCH_3$
IX, X = H; $R^3 + R^4 = \Delta$; $R^5 = H$
X, X = H; $R^3 + R^4 = \Delta$; $R^5 = COCH_3$
XI, X = Cl; $R^3 + R^4 = \Delta$; $R^5 = H$
XII, X = Cl; $R^3 + R^4 = \Delta$; $R^5 = COCH_3$
XIII, X = Cl; $R^3 + R^4 = \Delta$; $R^5 = COC_2H_5$
XIV, X = Br; $R^3 + R^4 = \Delta$; $R^5 = H$
XV, X = Br; $R^3 + R^4 = \Delta$; $R^5 = COCH_3$

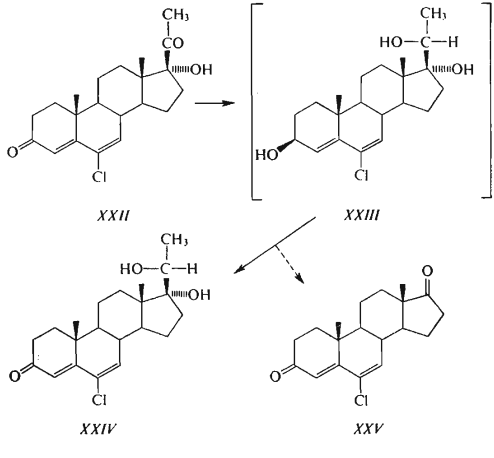
The configuration of the hydroxy group at $C_{(20)}$ was determined by analogy with other known alkali boro-hydride reductions of the $C_{(20)}$-oxo group (*cf.*[8-11]), leading always to 20β-hydroxy epimer. In our actual case a sole product was always isolated, and in no case, even when employing thin-layer chromatography, we were able to isolate a second product from the mixture, which would indicate the presence of a 20α-epimer or maybe a simultaneous reduction of some of the double bonds present in the molecule.

In order to convert the 3β,17α,20β-triol *XIX* to 3-oxo-17α, 20β-dihydroxy derivative we made use of the manganese dioxide oxidation according to Attemburrow[12],



already successfully applied by us several times. Manganese dioxide was prepared in alkaline medium by reacting potassium permanganate with manganese(*IV*)-sulfate at an elevated temperature. The washed and dried manganese dioxide was activated by stirring with acetic acid, washing, and drying. The reaction proper was carried out by 90 minutes boiling in chloroform freed from ethanol by shaking with silica gel. However, when we oxidized 3β,17α,20β-triol *XIX* the reaction mixture contained according to thin-layer chromatography another, less polar, substance in addition to the expected 3-oxo derivative *XX*. The reaction mixture was separated by column chromatography on silica gel, using benzene as eluent. The mentioned less polar component was eluted first (17% of the mixture). In subsequent fractions eluted with benzene the expected 17α,20β-dihydroxy-6-chloro-16-methylene-4,6-pregnadien-3-one (*XX*) (80·5%) was obtained, the IR and UV spectra of which were in good agreement with its structure. In another experiment the oxidation of triol *XVIII* with manganese dioxide was carried out at room temperature and a sole product was obtained again, *i.e.* the expected 3-oxopregnane derivative *XX*. However, the reaction time was excessively long, *i.e.* more than 5 days.

According to IR spectra the less polar product did not contain any hydroxy group, but only two different oxo groups, which was also confirmed by its UV spectrum which showed two maxima at 238 nm and 282 nm. This corresponds to a mono- and di-conjugated ketone. On the basis of these physical proterties and the elemental



XXII *XXIII*

XXIV *XXV*

analysis we assigned to this by-product the structure of 6-chloro-16-methylene-4,6-androstadiene-3,17-dione (*XXI*). This was also corroborated by the preparation of a sample for comparison, reacting pregnane-17α,20ξ-dihydroxy derivative with sodium periodate in methanol. This reaction was already applied in this laboratory[13,14] for the structure proof of 3β-acetoxy-17α-hydroxy-16-methylene-5-pregnen-20-one. During this reaction the side chain containing the vicinal glycol grouping at $C_{(17)}$ and $C_{(20)}$ was selectively attacked, and when excess reagent was used the reaction led to 16-methylene-17-oxo derivative. As starting material we took 17α,20β-diol *XX* from which on oxidation with periodate we obtained smoothly 3,17-dione *XXI*, identical with the product of the oxidation of 3β,17α,20β-triol *XVIII* with manganese dioxide. The degradation of the side chain in 17α,20-dihydroxypregnane derivatives with manganese dioxide was not yet observed. We supposed that in this actual case it would be possible because here the 17α-hydroxy group is in allylic position with respect to the 16-exomethylene group, although the reaction takes place with greater difficulty because a tertiary hydroxyl is involved. In order to verify this assumption we carried out the same reaction with 17α,3β,20β-trihydroxy-6-chloro-4,6-pregnadiene (*XXIII*) which differs from triol *XIX* only by the absence of the 16-exomethylene group. Triol *XXIII* was prepared again by reduction of diol *XXII* with sodium boro-hydride in methanol, under the same conditions and with the same results. From the reaction mixture after the oxidation of triol *XXIII* with manganese dioxide under the described conditions we isolated only 3-oxo derivative *XXIV*. Only after a twentyfold prolongation of the reaction time a little polar component was isolated from the mixture, which was identified on the basis of its IR spectrum and elemental analysis as 6-chloro-4,6-androstadiene-3,17-dione. Hence, in this case degradation takes place with incomparably greater difficulty.

Certain 3β-hydroxy derivatives and their esters *VII*–*XV* were tested for their gestagenic activity using Mac-Phail's test. It was found that their activity is in between the activities of progesterone and megestrol acetate. These results will be published elsewhere.

EXPERIMENTAL

Melting points were determined on a Kofler block. Optical rotations, unless stated otherwise, were measured in chloroform with an error of ±3°. Samples for analysis were dried over phosphorus pentoxide at 0.1 Torr and 76°C for 8 hours. UV spectra were measured on a Zeiss model VSU spectrophotometer (NaCl prisms, quartz cell 1 cm), in methanol. IR spectra were measured on a double-beam spectrophotometer (Zeiss, model UR 10) using 6% solution in chloroform or suspensions in nujol.

17α-Acetoxy-3β-hydroxy-16-methylene-4-pregnen-20-one (*VII*)

A suspension of 17α-acetoxy-16-methyleneprogesterone (*I*) (1 g) in methanol (50 ml) was reduced with sodium boro-hydride (900 mg), added gradually over one minute, at −5°C. After 6 minutes, when according to thin-layer chromatography the starting compound disappeared from the mixture, the reaction was stopped by addition of 0·2 ml of acetic acid. The reaction mixture was

diluted with 70 ml water and the precipitated material was extracted into ether. The extract was washed with water, dried over magnesium sulfate and evaporated to dryness under reduced pressure. The solid residue (1·029 g) was crystallised from acetone–light petroleum, affording 0·802 g of hydroxy derivative *XII*, m.p. 199–205°C. A sample for analysis was crystallised from the same solvent mixture, its m.p. was 219·5–221°C, $[\alpha]_D^{20}$ −78°; IR spectrum: 3450 (assoc. OH), 3590 (free OH), 1730, 1260, 1020 (—$OCOCH_3$), 1710, 1354 (methyl keto group), 1650, 895 (exomethylene). For $C_{24}H_{34}O_4$ (386·5) calculated: 74·57% C, 8·87% H; found: 74·35% C, 8·60% H,

17α-Acetoxy-3β-hydroxy-16-methylene-4,6-pregnadien-20-one (*IX*)

Reduction of 4,6-dien-3-one *II* (4 g) with sodium boro-hydride (3·6 g) and crystallisation of the crude product from acetone–light petroleum gave 3·46 g of hydroxy derivative *IX*, m.p. 184 to 186°C. The analytical sample was crystallised from the same solvent mixture, m.p. 185·5–188°C, $[\alpha]_D^{20}$ −193°, λ_{max} 231·5 nm (log ε 4·45), 238·5 nm (log ε 4·52). IR spectrum: 3450 (assoc. OH), 3590 (free OH), 1730, 1260, 1020 ($OCOCH_3$), 1720 ($C_{(20)}$ = O), 1351 (methyl keto group), 1645, 1608, 870 (4,6-diene), 895 (exomethylene) cm^{-1}. For $C_{24}H_{32}O_4$ (384·5) calculated: 74·97% C, 8·39% H; found: 74·64% C, 8·11% H.

17α-Acetoxy-6-chloro-3β-hydroxy-16-methylene-4,6-pregnadien-20-one (*XI*)

a) *Reduction of* 6-*chloro*-4,6-*dien*-3-*one* III: A suspension of 3 g of ketone *III* was reduced in the described manner. Crystallisation of 2·82 g of crude product from acetone–light petroleum gave 2·28 g of hydroxy derivative *XI*, m.p. 221–227°C. The sample for analysis was crystallised from the same solvent, m.p. 233–235°C, $[\alpha]_D^{20}$ −180°C, λ_{max} = 237 nm (log ε 4·265), 244 nm (4·33). IR spectrum: 3450 (assoc. OH), 3590 (free OH), 1731. 1260, 1020 ($OCOCH_3$), 1710 ($C_{(20)}$ = O), 1354 (methyl keto group), 1650, 895 (exomethylene) cm^{-1}. For $C_{24}H_{31}ClO_4$ (418·5) calculated: 68·88% C, 7·47% H, 8·48% Cl; found: 68·61% C, 7·27% H, 8·48% Cl.

b) *Reduction of* 6-*chloro*-1,4,6-*trien*-3-*one* V: Taking 3 g of ketone *V* and applying the same procedure as above 2·21 g of hydroxy derivative *XI* were obtained, m.p. 230–235°C, which according to its IR spectrum and mixture melting point was identical with the sample obtained under *a*).

17α-Acetoxy-6-bromo-3β-hydroxy-16-methylene-4,6-pregnadien-20-one (*XIV*)

a) *Reduction of* 6-*bromo*-4,6-*dien*-3-*one* IV: From 3 g of *IV* 2·65 g of hydroxy derivative *XIV* were obtained, m.p. 210–220°C. The analytical sample was crystallised from acetone–light petroleum, m.p. 217·5–221°C, $[\alpha]_D^{20}$ −168°; λ_{max} 235·5 nm (log ε 4·13), 243 nm (4·09). IR spectrum: 3450 (assoc. OH), 3590 (free OH), 1730, 1260, 1020 ($OCOCH_3$), 1710 ($C_{(20)}$ = O), 1354 (methyl keto group), 1600, 1610, 870 (4,6-diene), 895 (exomethylene) cm^{-1}. For $C_{24}H_{31}$·BrO_4 (463·4) calculated: 62·19% C, 6·74% H, 17·25% Br; found: 62·29% C, 6·54% H, 17·47% Br.

b) *Reduction of* 6-*bromo*-1,4,6-*trien*-3-*one* VI: Using the same procedure as above 3 g of compound *VI* gave 2·652 g of hydroxy derivative *XIV*, m.p. 218–220°C, identical in all respects with the sample obtained under *a*).

Acetylation of 3β-hydroxy derivatives *VII*, *IX*, *XI*, and *XIV*

3β,17α-*Diacetoxy*-16-*methylene*-4-*pregnen*-20-*one* (VIII): A solution of 0·547 g of hydroxy derivative *VII* in 5 ml of pyridine was acetylated with 0·5 ml of acetic anhydride at room temperature for 16 hours. The reaction product was isolated by pouring the reaction mixture into 50 ml

of icy water and filtering off the precipitated product. Crystallisation from methanol gave 0·456 g of diacetate *VIII*, m.p. 160—164°E. The analytical sample was crystallised from the same solvent, m.p. 163—164°C, $[\alpha]_D^{20}$ −102°. IR spectrum: 1721, 1250, 1021 ($OCOCH_3$), 1708 ($C_{(20)}$=O), 1353 (methyl keto group), 1651 (trisubstituted C=C), 898 (exomethylene) cm^{-1}. For $C_{26}H_{36}O_5$ (428·55) calculated: 72·86% C, 8·47% H; found: 72·52% C, 8·39% H.

3β,17α-*Diacetoxy-16-methylene-4,6-pregnadien-20-one* (X): Melting point 195—200°C, $[\alpha]_D^{20}$ −207·5°; λ_{max} = 234·5 nm (log ε 4·47). IR spectrum: 1721, 1250, 1021 ($OCOCH_3$), 1708 ($C_{(20)}$=O), 1356 (methyl keto group), 1615, 1648 (4,6-diene), 898 (exomethylene) cm^{-1}. For $C_{26}H_{34}O_5$ (426·5) calculated: 73·19% C, 8·04% H; found: 73·29% C, 7·87% H.

3β,17α-*Diacetoxy-6-chloro-16-methylene-4,6-pregnadien-20-one* (XII): M.p. 209—211°C, $[\alpha]_D^{20}$ −197°, λ_{max} 244 nm (log ε 4·34). IR spectrum: 1725 ($OCOCH_3$), 1710 ($C_{(20)}$=O), 1356 (methyl keto group), 1605 (conjugated C=C), 898 (exomethylene) cm^{-1}. For $C_{26}H_{33}ClO_5$ (461·0) calculated: 67·74% C, 7·22% H, 7·69% Cl; found: 67·88% C, 7·25% H, 7·86% Cl.

3β,17α-*Diacetoxy-6-bromo-16-methylene-4,6-pregnadien-20-one* (XIV): M.p. 210—212°C, $[\alpha]_D^{20}$ −166°, λ_{max} = 238 nm (log ε = 4·38). IR spectrum: 1725, 1245, 1021 ($OCOCH_3$), 1708 ($C_{(20)}$=O), 1356 (methyl keto group), 1600, 1648 (4,6-diene), 898 (exomethylene) cm^{-1}. For $C_{26}H_{33}BrO_5$ (505·44) calculated: 61·79% C, 6·58% H, 15·81% Br; found: 61·90% C, 6·84% H, 16·01% Br.

17α-Acetoxy-6-chloro-16-methylene-3β-propionyloxy-4,6-pregnadien-20-one (*XIII*)

A solution of hydroxy derivative *XI* (1 g) in pyridine (10 ml) was esterified with 1 ml propionic anhydride at room temperature for 16 hours. The product was isolated in the same manner as after acetylation. Crystallisation from ether gave 0·786 g of 3β-propionate *XIII*, m.p. 153 to 157°C. The analytical sample was crystallised from the same solvent: m.p. 156—159°C, $[\alpha]_D^{20}$ −202°, λ_{max} 245 nm (log ε 4·42). IR spectrum: 1728, 1190—1260 (ester and acetate), 1710 ($C_{(20)}$=O), 1605 (conjugated C=C), 1355 (methyl keto group), 898 (exomethylene) cm^{-1}. For $C_{27}H_{35}ClO_5$ (475·0) calculated: 68·28% C, 7·43% H, 7·47% Cl; found: 68·37% C, 7·18% H, 7·53% Cl.

3β,17α-Dihydroxy-6-chloro-16-methylene-4,6-pregnadien-20-one (*XVI*)

A solution of 3β-hydroxy derivative *XI* (2 g) in methanol (250 ml) was hydrolysed under reflux in 10% aqueous potassium hydrogen carbonate solution (25 ml) for two hours. The solution was evaporated under normal pressure and the residue diluted with 50 ml of water. The precipitated product was filtered off under suction, washed with water, and dried. The product (1·79g) was crystallised from methanol (decolorisation with a small amount of charcoal). The obtained diol *XVI* had m.p. 166—182°C. The analytical sample was crystallised from the same solvent, m.p. 180—182°C, $[\alpha]_D^{20}$ −107° (dioxan), λ_{max} 242 nm (log ε 4·38). IR spectrum (nujol): 3400, 3510 (OH), 1696 ($C_{(20)}$=O), 1602—1545 (conjugated C=C) cm^{-1}. For $C_{22}H_{29}ClO_3$ (376·9) calculated: 70·10% C, 7·76% H, 9·41% Cl; found: 69·55% C, 7·39% H, 9·10% Cl.

3β-Acetoxy-17α-hydroxy-6-chloro-16-methylene-4,6-pregnadien-20-one (*XVII*)

A solution of 3β,17α-diol *XVI* (200 mg) in pyridine (5 ml) was acetylated with 0·5 ml of acetic anhydride at room temperature for 16 hours. The reaction product was worked up in the above described manner. Crystallisation of the crude product from methanol gave 180 mg of 3-monoacetate *XVII*, m.p. 156—159°C. The analytical sample was obtained by crystallisation from the same solvent, m.p. 158—160°C, $[\alpha]_D^{20}$ −164°, λ_{max} 242 nm (log ε 4·36). IR spectrum: 3405,

3515 (OH), 1730 ($OCOCH_3$), 1700 ($C_{(20)}$=O), 1602 (conjugated C=C) cm^{-1}. For $C_{24}H_{31}ClO_4$ (418·5) calculated: 68·88% C, 7·47% H, 8·48% Cl; found: 68·52% C, 7·31% H, 8·22% Cl.

Acetylation: 100 mg of monoacetate *XVII* were acetylated with 4 ml acetic anhydride in the presence of sulfosalicylic acid (50 mg) at room temperature for 20 hours. The reaction mixture was poured onto crushed ice and after approx. two hours standing, necessary for the decomposition of acetic anhydride, the formed precipitate was extracted with ether. The ethereal solution was washed with water, 5% potassium hydrogen carbonate, and water, and after drying over magnesium sulfate it was evaporated to dryness. On crystallisation of the residue (87 mg) from acetone–light petroleum 62 mg of diacetate *XII* were obtained, which was identical in all respects with an authentic sample.

17α-Hydroxy-6-chloro-16-methylene-4,6-pregnadiene-3,20-dione (*XVIII*)

A solution of 17α-acetate *III* (6 g) in methanol (360 ml) was boiled with a solution of 4 g potassium hydrogen carbonate in 100 ml of water for 16 hours. The reaction mixture was worked up as described above. The crude product (5·12 g, m.p. 100–112°C) was crystallised from methanol, giving 4·98 g of 17α-hydroxy derivative *XVIII*, m.p. 176–178°C. The sample for analysis was crystallised from the same solvent, m.p. 178·5–180·5°C, $[\alpha]_D^{20}$ −57°, λ_{max} 285 nm (log ε 4·835). IR spectrum: 3480, 3590 (OH), 1709 ($C_{(20)}$=O), 1690 (—CO···HO), 1588, 1603, 1658, 882 (6-chloro-4,6-dien-3-one and exomethylene) cm^{-1}. For $C_{22}H_{27}ClO_3$ (374·9) calculated: 70·47% C, 7·23% H, 9·46% Cl; found: 70·71% C, 7·13% H, 9·26% Cl.

6-Chloro-16-methylene-4,6-pregnadiene-3β,17α,20β-triol (*XIX*)

A solution of 17α-hydroxy derivative *XVIII* (2·6 g) in methanol (266 ml) was reduced with sodium boro-hydride (2·6 g) at 0–5°C by the method described above. The excess reagent was decomposed with 1·8 ml of acetic acid, and the solution was diluted with 1500 ml of water. The separated material was filtered off, washed, and dried. Yield 2·32 g of the crude product. Crystallisation from methanol gave triol, *XIX* (1·82 g), m.p. 168–175°C (change of crystalline modification at 118 to 128°C). The sample for analysis, crystallised from the same solvent, m.p. 178–180°C, $[\alpha]_D^{20}$ −104°, λ_{max} 236 nm (log ε 4·23), 244 nm (4·30). For $C_{22}H_{31}ClO_3$ (378·9) calculated: 69·73% C, 8·25% H, 9·36% Cl; found: 69·48% C, 7·93% H, 9·19% Cl.

Preparation of manganese dioxide: Manganese(II)-sulfate (66·6 g) was dissolved under stirring in 240 ml of water of 95°C. The insoluble material was filtered off and the clear filtrate was heated again, to 95°C. At this temperature 70·2 ml of 40% potassium hydroxide solution and 95°C hot solution of 57·6 g of potassium permanganate in 360 ml of water were added simultaneously and dropwise, over 50 minutes, to the above hot filtrate. The reaction mixture is stirred for another 60 minutes at the same temperature. Finally it is cooled and the separated manganese dioxide is filtered off, washed with distilled water until neutral, and dried at 120°C for 16 hours. The dry oxide is then suspended with stirring in a treble amount (by weight) of acetic acid and stirred for 8 hours. It is then filtered off, washed with distilled water until neutral, and dried at 120°C.

Oxidation in boiling chloroform: A solution of triol *XIX* (0·793 g) in boiling chloroform (80 ml) was oxidized with activated manganese dioxide (2·4 g) under reflux for 100 minutes. The inorganic material was filtered off using kieselguhr as filter-aid, and the filtrate was washed with 5% hydrochloric acid, water, 5% aqueous potassium hydrogen carbonate, and again with water. It was then dried over calcium chloride and evaporated to dryness. The residue (0·705 g) was chromatographed on 6 g of silica gel, using benzene for elution. The first fraction contained 125 mg (17·7%) of 6-chloro-16-methylene-4,6-androstadiene-3,17-dione (*XXI*), m.p. 213–217°C, $[\alpha]_D^{20}$ +31°, λ_{max} 238 nm (log ε 4·1), 282 nm (4·42). IR spectrum: OH absent, 1725 (unconjugated CO), 1660,

1603, 1588 (conjugated CO) cm^{-1}. For $C_{20}H_{23}ClO_2$ (330·8) calculated: 72·61% C, 7·00% H, 10·72% Cl; found: 72·60% C, 6·90% H, 10·77% Cl. Further elution with benzene gave 558 mg (80·5%) of diol *XX*, m.p. 168–170°C. Crystallisation from acetone–pentane gave an analytically pure sample, m.p. 169–170°C, $[\alpha]_D^{20}$ −54°, λ_{max} 285 nm (log ε 4·395). IR spectrum: 3450, 3590 (OH), 1588, 1603, 1658 (6-chloro-4,6-dien-3-one) cm^{-1}). For $C_{22}H_{29}ClO_3$ (376·91) calculated: 70·10% C, 7·76% H, 9·41% Cl; found: 70·28% C, 7·71% H, 9·20% Cl.

Oxidation at room temperature: 100 mg of triol *XIX* were oxidized with manganese dioxide in chloroform at room temperature for 6 days. Diol *XX* only was obtained.

Reduction and Oxidation of Derivative *XXII*

A solution of hydroxy derivative *XXII* (0·9053 g) in 54 ml of methanol was reduced with sodium boro-hydride (0·9 g) under the above conditions. The obtained triol *XXIII* weighed 0·7647 g, m.p. 218–221°C. It was oxidized with 2·3 g of manganese dioxide in boiling chloroform. After 90 minutes boiling no less polar fraction could be detected on a thin-layer chromatogram. After 30 hours boiling the reaction was interrupted and the residue (0·74 g) was chromatographed on a column of silica gel (20 g) with benzene. Diketone *XXV* (0·027 g) was eluted first, m.p. 186 to 189°C. The sample for analysis was crystallised from methanol, m.p. 189–192°C, $[\alpha]_D^{20}$ +124°, λ_{max} 284 nm (log ε 4·26). IR spectrum: OH absent, 1735 (five-membered CO), 1408 (CH_2 in α-position to the five-membered CO), 1588, 1604, 1660 (4,6-dien-3-one), 1418 (CH_2 on C_2) cm^{-1}. For $C_{19}H_{23}ClO_2$ (318·83) calculated: 71·58% C, 7·27% H, 11·12% Cl; found: 71·44% C, 7·03% H, 11·16% Cl. In subsequent fractions diol *XXIV* (0·7 g) was present, m.p. 157–166°C. The sample for analysis was obtained on crystallisation from acetone–light petroleum: m.p. 164–166°C, λ_{max} 284 nm (log ε 4·29). IR spectrum: 3500, 3610 (assoc. and free OH), 1588, 1604, 1660 (4,6-dien-3-one) cm^{-1}. For $C_{21}H_{29}ClO_3$ (364·9) calculated: 69·12% C, 8·01% H, 9·72% Cl; found: 68·95% C, 7·82% H, 9·54% Cl.

Degradation of 17α,20β-Dihydroxy-6-chloro-16-methylene-4,6-pregnadien-3-one (*XX*) with Sodium Periodate

To a solution of diol *XX* (105 mg) in methanol (20 ml) sodium periodate solution in 5 ml of water was added and the reaction mixture was allowed to stand at room temperature for 16 hours. The crystals of the separated iodate were filtered off under suction, washed with ethyl acetate, and the filtrate was concentrated under reduced pressure to half its volume and then diluted with 30 ml of water. The precipitate formed was filtered off under suction, washed with water and dried. Diketone *XXI* (0·095 g) was obtained, m.p. 182–196°C. Crystallisation from methanol gave a product melting at 212–218°C; λ_{max} 239 nm (log ε 4·09), 282 (4·365), the IR spectrum of which was identical with the by-product of the oxidation of triol *XIX* with manganese dioxide.

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