SYNTHESIS OF 6β,19-DIMETHOXY-3α,5-CYCLO-5α-PREGNAN-20-ONE*

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Preparation of the title compound *XVI* from 3β,20β-diacyloxy-5-pregnenes *VIIa–VIId* is described.

In the course of model experiments aimed at a synthesis of strophanthidin we needed 6β,19-dimethoxy-3α,5-cyclo-5α-pregnan-20-one (*XVI*). Preparation of a potential intermediate, 3β-acetoxy-19-hydroxy-5-pregnen-20-one, was described by other authors[1]. The procedure starts from pregnenolone acetate (*II*) and involves the addition of hypobromous acid to the 5,6-double bond followed by functionalization of $C_{(19)}$ with lead tetraacetate. In our hands, however, reproduction of this route gave unsatisfactory yields in the functionalization step where the desired product prevailed only slightly in a mixture of several compounds. Since this result is likely to be due to the presence of the keto group, we investigated an analogous route leading to the compound *XVI* and using 20-acyloxy derivatives. The necessity of protecting the 20-keto group by reduction and esterification makes this procedure somewhat lengthy but this disadvantage was expected to be counterbalanced by the elimination of the most by-products.

Starting from all four 3β- and 20β-acetates and benzoates of 3β,20β-diol *VI* (diesters *VIIa–VIId*) four series of intermediates *VIIIa–VIIId* to *XIa–XId* were prepared. Each of these compounds was eventually converted to the final products *XV* and *XVI*. The route is based on hypobromous acid addition to the 5,6-double bond (*VII* → *VIII*), lead tetraacetate functionalization (*VIII* → *IX* → *X*), methylation (*X* → *XI*), selective saponification of the 3-acyloxy group (*XI* → *XII*) and i-steroid rearrangement (*XIII* → *XIV*). This procedure not only gives a satisfactory yield in the crucial functionalization step (*VIII* → *IX*) but may even be modified to large-scale preparation without application of chromatography if the accompaying 20α-epimers are not separated in steps *VII–XII*. For this purpose, the variant with 3-acetoxy-20-benzoyloxy derivatives *VIIa–XIa* was most suitable because of the good crystallization ability of these compounds.

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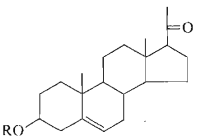
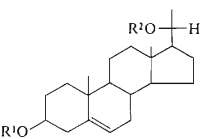
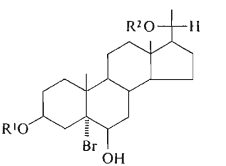


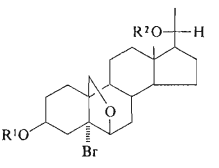
I, R = H
II, R = Ac
III, R = Bz



IV, R^1 = Ac, R^2 = H
V, R^1 = Bz, R^2 = H
VI, R^1 = H, R^2 = H
VIIa, R^1 = Ac, R^2 = Bz
VIIb, R^1 = Bz, R^2 = Bz
VIIc, R^1 = Ac, R^2 = Ac
VIId, R^1 = Bz, R^2 = Ac



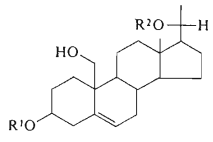
VIIIa, R^1 = Ac, R^2 = Bz
VIIIb, R^1 = Bz, R^2 = Bz
VIIIc, R^1 = Ac, R^2 = Ac
VIIId, R^1 = Bz, R^2 = Ac

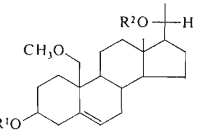


IXa, R^1 = Ac, R^2 = Bz
IXb, R^1 = Bz, R^2 = Bz
IXc, R^1 = Ac, R^2 = Ac
IXd, R^1 = Bz, R^2 = Ac

The reactions outlined above are conventional processes and their application needs no comment. However, hydrolysis of the 3β,20β-diacyloxy derivatives is of interest. It was anticipated that selective hydrolysis of the 3-benzoate 20-acetate *XId* would smoothly saponify the 20β-acetoxy group. Unexpectedly, the saponification experiment led to 3β-hydroxy-20β-acetoxy derivative *XIIc*. In line with this stability of the 20β-acyloxy group is also the behavior of the 20β-benzoyloxy compound *XIVa* toward alkaline hydrolysis in which the 20β-benzoyloxy group remained unaffected after boiling for 2 h with a 2% methanolic potassium hydroxide solution. This behavior is an interesting demonstration of the steric hindrance of 20β-acyloxy groups.

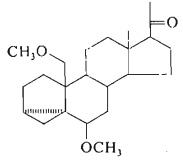
Conversion of the 20β-acyloxy group to hydroxyl function was achieved by reduction with lithium aluminum hydride. Finally, oxidation of the 20β-alcohol *XV* to the title compound *XVI* was performed with Corey's oxidant[5].



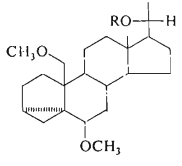


Xa, R^1 = Ac, R^2 = Bz
Xb, R^1 = Bz, R^2 = Bz
Xc, R^1 = Ac, R^2 = Ac
Xd, R^1 = Bz, R^2 = Ac

XIa, R^1 = Ac, R^2 = Bz
XIb, R^1 = Bz, R^2 = Bz
XIc, R^1 = Ac, R^2 = Ac
XId, R^1 = Bz, R^2 = Ac
XIIa, R^1 = H, R^2 = Bz
XIIc, R^1 = H, R^2 = Ac
XIIIa, R^1 = Mes, R^2 = Bz
XIIIc, R^1 = Mes, R^2 = Ac



XVI



XIVa, R = Bz
XIVc, R = Ac
XV, R = H

EXPERIMENTAL

Melting points were determined on a Kofler block. Analytical samples were dried at 50°C/0·2 Torr (26 Pa). Optical measurements were carried out in chloroform with an error of ±3°. The IR spectra were recorded on a Zeiss UR 20 spectrometer in tetrachloromethane. The ^{1}H-NMR spectra were recorded on a Tesla BS 467 instrument (60 MHz) in deuteriochloroform at 30° with tetramethylsilane as internal reference. Chemical shifts are given in ppm. Apparent coupling constants (in Hz) were obtained from a first order analysis. The identity of samples prepared by different routes was checked by mixture melting point determination, by thin layer chromatography (TLC) and by infrared and ^{1}H-NMR spectra. Usual work up of an ethereal solution means washing the solution with 5% aqueous hydrochloric acid solution, water, 5% aqueous potassium hydrogen carbonate solution, water, drying with sodium sulfate and evaporation of the solvent *in vacuo*.

5-Pregnene-3β,20β-diol 3-Monobenzoate (*V*)

The 20-ketone *III* (10 g) was dissolved in dimethylformamide (100 ml) at 70°C. Sodium borohydride (1 g) was introduced in four portions over a period of 30 min and the mixture was kept at the same temperature for 2 h with occasional stirring. The mixture was cooled with ice, the excess of reagent was decomposed with acetic acid and 5% aqueous hydrochloric acid, the mixture was diluted with water (300 ml) and the product was separated after 4 h by suction to yield the crude mixture of 20*R* and 20*S* epimeric alcohols in which the former prevailed. This mixture was chromatographed on a silica gel column (400 g) using a mixture of light petroleum and ether (93 : 7) as eluent. Corresponding fractions were collected and evaporated. The residue was crystallized from a mixture of acetone, methanol and water to yield the pure *V* (4·3 g), m.p. 190–191°C, $[\alpha]_D^{20}$ −41° (*c* 2·1). For $C_{28}H_{38}O_3$ (422·6) calculated: 79·58% C, 9·06% H found: 79·36% C, 9·12% H.

5-Pregnene-3β,20β-diol 3-Benzoate 20-Acetate (*VIId*)

The alcohol *V* (2·5 g) was dissolved in pyridine (10 ml) and refluxed with acetic anhydride (3 ml) for 1 h. The mixture was decomposed with ice and water, the product was taken up in ether and the ethereal solution was worked up as usual. The residue was crystallized from a mixture of chloroform and methanol to yield *VIId* (1·72 g), m.p. 194–196°C, $[\alpha]_D^{20}$ −13° (*c* 1·6). ^{1}H-NMR spectrum: 0·65 (3 H, s, 18-H), 1·02 (3 H, s, 19-H), 2·00 (3 H, s, CH_3CO_2), 4·85 (2 H, brd m, 3α-H, 20α-H), 5·42 (1 H, m, 6-H). For $C_{30}H_{40}O_4$ (464·7) calculated: 77·55% C, 8·68% H; found: 77·39% C, 8·54% H.

5-Bromo-5α-pregnane-3β,6β,20β-triol 3-Acetate 20-Benzoate (*VIIIa*)

The olefin[2] *VIIa* (4 g) was dissolved in a mixture of dioxane (200 ml) and water (8 ml). The solution was treated with 70% aqueous perchloric acid (1·2 ml) and N-bromoacetamide (1·6 g) at room temperature for 1 h. The mixture was diluted with water (130 ml), the precipitated product was collected by suction, washed with aqueous methanol and air-dried to yield the desired bromohydrin *VIIIa* of sufficient purity. The analytical sample obtained by crystallization from a mixture of chloroform and light petroleum had m.p. 154–156°C, $[\alpha]_D^{20}$ −47° (*c* 1·7). For $C_{30}H_{41}BrO_5$ (561·6) calculated: 64·16% C, 7·36% H, 14·23% Br; found: 63·98% C, 7·25% H, 14·06% Br.

5-Bromo-5α-pregnane-3β,6β,20β-triol 3,20-Dibenzoate (*VIIIb*)

The olefin[3] *VIIb* (4.2 g) was dissolved in dioxane (300 ml), water (10 ml) was added and the solution was treated with 70% aqueous perchloric acid (1·2 ml) and N-bromoacetamide (1·6 g) as in the previous experiment. The mixture was diluted with water, the product extracted with ether and the ethereal solution washed with water, 5% aqueous potassium hydrogen carbonate solution, 5% aqueous sodium thiosulfate solution, and water, then dried and the solvent was evaporated. The oily residue was crystallized from a mixture of chloroform and light petroleum to yield the bromohydrin *VIIIb* (3·5 g), m.p. 142–143°C, $[\alpha]_D^{20}$ −33° (*c* 2·6). ^{1}H-NMR spectrum: 0·68 (3 H, s, 18-H), 1·33 (3 H, s, 19-H), 1·25 (3 H, d, J = 6 Hz, 21-H), 4·20 (1 H, m, W = 8 Hz, 6α-H), 5·10 (1 H, brd m, 20α-H), 5·60 (1 H, brd m, 3α-H). For $C_{35}H_{43}BrO_5$ (623·6) calculated: 67·41% C, 6·95% H, 12·81% Br; found: 67·25% C, 6·81% H, 12·97% Br.

5-Bromo-5α-pregnane 3β,6β,20β-triol 3-Benzoate 20-Acetate (*VIIId*)

A solution of the olefin *VIId* (1·7 g) in dioxane (40 ml) and water (5 ml), was treated and worked up as given for *VIIIb*. The residue was chromatographed on a column of silica gel (100 g) using a mixture of light petroleum (95 : 5 and then 90 : 10) which eluted impurities. The mixture of the same solvents in a ratio of 85 : 15 eluted the desired bromohydrin. Corresponding fractions were collected and evaporated to yield the oily bromohydrin *VIIId* (1·1 g), $[\alpha]_D^{20}$ −26° (*c* 5·1). ^{1}H-NMR spectrum: 0·62 (3 H, s, 18-H), 1·37 (3 H, s, 19-H), 1·15 (3 H, d, $J = 6$ Hz, 21-H), 2·00 (3 H, s, CH_3CO_2), 4·22 (1 H, brd s, 6α-H), 4·85 (1 H, brd m, 20α-H), 5·70 (1 H, brd m, 3α-H). For $C_{30}H_{41}BrO_5$ (561·6) calculated: 64·16% C, 7·36% H, 14·36% Br; found: 64·08% C, 7·32% H, 14·36% Br.

5-Bromo-6β,19-epoxy-5α-pregnane-3β,20β-diol 3-Acetate 20-Benzoate (*IXa*)

A mixture of calcium carbonate (2 g) and lead tetraacetate (4 g) in benzene (50 ml) was refluxed and stirred for 2 h. The solution of bromohydrin *VIIIa* (3·5 g) in benzene (50 ml) was added, the mixture was refluxed and stirred for 15 min, crystalline iodine (1 g) was added and the mixture was refluxed for 3 h. The solid was filtered off, the solution washed with water, 5% aqueous potassium hydrogen carbonate solution, 5% aqueous sodium thiosulfate, and water, then dried and the solvent evaporated. The residue was chromatographed on a silica gel column (100 g) using a mixture of light petroleum and ether (90 : 10) as eluent. Corresponding fractions were collected and evaporated. The residue was crystallized from a mixture of acetone, methanol and water to yield the bromo epoxide *IXa* (1·5 g), m.p. 171–172°C, $[\alpha]_D^{20}$ +1° (*c* 1·8). ^{1}H-NMR spectrum: 0·67 (3 H, s, 18-H), 1·27 (3 H, d, $J = 6$ Hz, 21-H), 2·00 (3 H s, CH_3CO_2), 3·69 (1 H, d, $J_{gem} = 8$ Hz, 19-H), 3·93 (1 H, d, $J_{gem} = 8$ Hz, 19-H), 4·05 (1 H, brd s, 6α-H), 5·20 (2 H, brd m, 3α-H and 20α-H). For $C_{30}H_{39}BrO_5$ (559·6) calculated: 64·40% C, 7·03% H, 14·28% Br; found: 64·21% C, 6·99% H, 14·45% Br.

5-Bromo-6β,19-epoxy-5α-pregnane-3β,20β-diol 3,20-Dibenzoate (*IXb*)

The solution of bromohydrin *VIIIb* (3·5 g) in benzene (130 ml) was treated as in the previous experiment. The residue was crystallized from a mixture of chloroform and methanol to yield *IXb* (2·8 g), m.p. 248–249°C, $[\alpha]_D^{20}$ −3° (*c* 2·1). ^{1}H-NMR spectrum: 0·70 (3 H, s, 18-H), 1·25 (3 H, d, $J = 6$ Hz, 21-H), 3·68 (1 H, d, $J_{gem} = 8$ Hz, 19-H), 3·95 (1 H, d, $J_{gem} = 8$ Hz, 19-H), 4·06 (1 H, brd s, 6α-H), 5·10 (2 H, brd m, 3α-H and 20α-H). For $C_{35}H_{41}BrO_5$ (621·6) calculated: 67·63% C, 6·65% H, 12·85% Br; found: 67·46% C, 6·37% H, 13·01% Br.

5-Bromo-6β,19-epoxy-5α-pregnane-3β,20β-diol 3-Benzoate 20-Acetate (*IXd*)

The solution of bromohydrin *VIIId* (1 g) in benzene (15 ml) was treated as given for *IXa*. The residue was chromatographed on a silica gel column (100 g) using a mixture of light petroleum and ether (93 : 7) as eluent. Corresponding fractions were collected and evaporated. The residue was crystallized from a mixture of acetone, methanol and water to yield *IXd* (246 mg), m.p. 170–172°C, $[\alpha]_D^{20}$ +17° (*c* 1·8). ^{1}H-NMR spectrum: 0·65 (3 H, s, 18-H), 1·13 (3 H, d, $J = 6$ Hz, 21-H), 2·00 (3 H, s, CH_3CO_2), 3·82 (1 H, d, $J_{gem} = 8$ Hz, 19-H), 4·03 (1 H, d, $J_{gem} = 8$ Hz, 19-H), 4·10 (1 H, brd s, 6α-H), 4·85 (1 H, brd m, 20α-H), 5·45 (1 H, brd m, 3α-H). For $C_{30}H_{39}$. $.BrO_5$ (559·6) calculated: 64·40% C, 7·03% H, 14·28% Br; found: 64·26% C, 6·82% H, 14·41% Br.

5-Pregnene-3β,19,20β-triol 3-Acetate 20-Benzoate (*Xa*)

The epoxide *IXa* (1·4 g) was dissolved in a mixture of acetic acid (20 ml) and methanol (5 ml) by heating up to 90—100°C, zinc powder (2 g) was added in four portions while stirring, the mixture was heated at 90—100°C and stirred for 5 min, the inorganic material was filtered off, hot water was added to the hot filtrate and the solution was set aside overnight to yield *Xa* (1·1 g), m.p. 143—145°C, $[\alpha]_D^{20}$ −67° (*c* 1·9). ^{1}H-NMR spectrum: 0·72 (3 H, s, 18-H), 1·26 (3 H, d, J = 6 Hz, 21-H), 2·00 (3 H, s, C$\underline{H}_3$CO$_2$), 3·52 (1 H, d, J_{gem} = 12 Hz, 19-H), 3·81 (1 H, d, J_{gem} = = 12 Hz, 19-H), 4·65 (1 H, brd m, 3α-H), 5·15 (1 H, brd m, 20α-H), 6·37 (1 H, m, 6-H). For $C_{30}H_{40}O_5$ (480·7) calculated: 74·97% C, 8·39% H; found: 74·72% C, 8·41% H.

5-Pregnene-3β,19,20β-triol 3,20-Dibenzoate (*Xb*)

A solution of the epoxide *IXb* (2·8 g) in acetic acid (30 ml), dioxane (20 ml) and methanol (5 ml) was treated as given for *Xa*, water was added and the mixture was set aside overnight to yield the alcohol *Xb* (1·9 g), m.p. 227—229°C, $[\alpha]_D^{20}$ −39° (*c* 1·6). ^{1}H-NMR spectrum: 0·72 (3 H, s, 18-H), 1·25 (3 H, d, J = 6 Hz, 21-H), 3·70 (2 H, brd m, 19-H), 5·00 (2 H, m, W = 40 Hz, 3α-H and 20α-H), 5·77 (1 H, m, W = 13 Hz, 6-H), For $C_{35}H_{42}O_5$ (542·7) calculated: 77·46% C, 7·80% H; found: 77·38% C, 7·39% H.

5-Pregnane-3β,19,20β-triol 3-Benzoate 20-Acetate (*Xd*)

A solution of the epoxide *IXd* (200 mg) in acetic acid (5 ml) and methanol (0·5 ml) was treated as given for *Xa* to yield the alcohol *Xd* (140 mg), m.p. 239—241°C, (subl.), $[\alpha]_D^{20}$ +7° (*c* 1·5). ^{1}H-NMR spectrum: 0·70 (3 H, s, 18-H), 1·13 (3 H, d, J = 6 Hz, 21-H), 2·00 (3 H, s, C$\underline{H}_3$CO$_2$), 3·81 (2 H, brd m, 19-H), 4·80 (2 H, m, W = 30 Hz, 3α-H and 20α-H), 5·80 (1 H, m, W = 12 Hz, 6-H). For $C_{30}H_{40}O_5$ (480·7) calculated: 74·97% C, 8·39% H; found: 74·72% C, 8·41% H.

19-Methoxy-5-pregnene-3β,20β-diol 3-Acetate 20-Benzoate (*XIa*)

A mixture of the alcohol *Xa* (500 mg), sodium hydride (200 mg), and methyl iodide (0·5 ml) in dimethylformamide (5 ml) was stirred at room temperature for 2 h. The excess reagent was decomposed with acetic acid and 5% aqueous hydrochloric acid, the mixture diluted with water, the product taken up in ether and the ethereal solution worked up as usual. The residue was chromatographed on a silica gel column (30 g) using a mixture of light petroleum and ether (93 : 7) as eluent. The lipophilic fractions were collected and evaporated. The residue was crystallized from a mixture of acetone, methanol and water to yield *XIa* (175 mg), m.p. 129—131°C, $[\alpha]_D^{20}$ −84° (*c* 1·5). ^{1}H-NMR spectrum: 0·70 (3 H, s, 18-H), 1·26 (3 H, d, J = 6 Hz, 21-H), 2·00 (3 H, s, C$\underline{H}_3$CO$_2$), 3·22 (3 H, s, CH$_3$O), 3·20 (1 H, d, J_{gem} = 10 Hz, 19-H), 3·56 (1 H, d, J_{gem} = 10 Hz, 19-H), 4·61 (1 H, brd m, 3α-H), 5·15 (1 H, brd m, 20α-H), 5·61 (1 H, m, 6-H). For $C_{31}H_{42}O_5$ (494·7) calculated: 75·27% C, 8·56% H; found: 75·09% C, 8·32% H.

19-Methoxy-5-pregnene-3β,20β-diol 3,20-Dibenzoate (*XIb*)

The alcohol *Xb* (1·8 g) in dimethylformamide (16 ml) was treated and chromatographed as given for *XIa* to yield after crystallization from a mixture of acetone, methanol, and water *XIb* (1·2 g), m.p. 186—187°C, $[\alpha]_D^{20}$ −68° (*c* 1·6). ^{1}H-NMR spectrum: 0·72 (3 H, s, 18-H), 1·26 (3 H, d, J = 6 Hz, 21-H), 3·25 (3 H, s, CH$_3$O), 3·24 (1 H, d, J_{gem} = 9 Hz, 19-H), 3·85 (1 H, d, J_{gem} = = 9 Hz, 19-H), 5·00 (2 H, brd m, 3α-H and 20α-H), 5·64 (1 H, m, W = 13 Hz, 6-H). For $C_{36}H_{44}O_5$ (556·7) calculated: 77·67% C, 7·97% H; found: 77·54% C, 8·03% H.

19-Methoxy-5-pregnen-3β,20β-diol 3,20-Diacetate (*XIc*)

The alcohol[4] *Xc* (2·3 g) in dimethylformamide (17 ml) was treated and chromatographed as given for *XIa* to yield after crystallization from a mixture of acetone, methanol and water *XIc* (630 mg), m.p. 121–123°C, $[\alpha]_D^{20}$ −47° (*c* 2·4). For $C_{26}H_{40}O_5$ (432·6) calculated: 72·19% C, 9·32% H; found: 71·96% C, 9·11% H.

19-Methoxy-5-pregnen-3β,20β-diol 3-Benzoate 20-Acetate (*XId*)

The alcohol *Xd* (120 mg) in dimethylformamide (2·5 ml) was treated as given for *XIa*. The residue was crystallized from a mixture of chloroform and methanol to yield *XId* (80 mg), m.p., 172–173°C, $[\alpha]_D^{20}$ −18° (*c* 1·9). ^{1}H-NMR spectrum: 0·68 (3 H, s, 18-H), 1·15 (3 H, d, J = 6 Hz 21-H), 2·00 (3 H, s, $C\underline{H}_3CO_2$), 3·30 (3 H, s, CH_3O), 3·32 (1 H, d, J_{gem} = 10 Hz, 19-H), 3·64 (1 H, d, J_{gem} = 10 Hz, 19-H), 4·81 (2 H, m, W = 30 Hz, 3α-H and 20α-H), 5·63 (1 H, m, W = = 12 Hz, 6-H). For $C_{31}H_{42}O_5$ (494·7) calculated: 75·27% C, 8·56% H; found: 75·18% C, 8·47% H.

19-Methoxy-5-pregnene-3β,20β-diol 20-Monobenzoate (*XIIa*)

a) The diester *XIa* (150 mg) in chloroform (1·5 ml) and methanol (6 ml) was treated with concentrated hydrochloric acid (0·2 ml) at room temperature for 2 days. Solvents were distilled off under reduced pressure, the residue was treated with ether and water, the ethereal layer washed with wather, 5% aqueous potassium hydrogen carbonate, and water, then dried and the solvent was evaporated to yield the oily alcohol *XIIa*, (110 mg), $[\alpha]_D^{20}$ −76° (*c* 2·0). ^{1}H-NMR spectrum: 0·70 (3 H, s, 18-H), 1·25 (3 H, d, J = 6 Hz, 21-H), 3·20 (3 H, s, CH_3O), 3·18 (1 H, d, J_{gem} = = 10 Hz, 19-H), 3·54 (1 H, d, J_{gem} = 10 Hz, 19-H), 3·50 (1 H, brd m, 3α-H), 5·10 (1 H, brd m, 20α-H), 5·64 (1 H, m, 6-H). For $C_{29}H_{40}O_4$ (452·6) calculated: 76·95% C, 8·91% H; found: 76·79% 8·83% H.

b) A mixture of the diester *XIb* (1·2 g), methanol (70 ml), dioxane (30 ml), water (10 ml) and potassium hydroxide (0·5 g) was allowed to stand at room temperature for 8 h, water was added, the product extracted with ether, the ethereal solution washed with water, dried and the solvent evaporated to yield the oily alcohol *XIIa* (1 g), $[\alpha]_D^{20}$ −79 (*c* 2·6).

19-Methoxy-5-pregnene-3β,20β-diol 20-Monoacetate (*XIIc*)

a) A mixture of the diacetate *XIc* (1·4 g), methanol (50 ml) and potassium hydroxide (0·5 g) was allowed to stand at 0°C for 24 h and worked up as given for saponification of *XIb*. The residue was chromatographed on a silica gel column (70 g) with a mixture of light petroleum and ether (85 : 15), then with a mixture of light petroleum, ether and acetone (80 : 15 : 5), which eluted small amounts of impurities, and finally with a mixture of light petroleum, ether and acetone (75 : 15 : 10) which eluted the desired compound. Corresponding fraction were collected and evaporated. The residue was crystallized from a mixture of acetone and n-heptane to yield *XIIc* (600 mg), m.p. 142–143°C, $[\alpha]_D^{20}$ −33° (*c* 2·0). ^{1}H-NMR spectrum: 0·66 (3 H, s, 18-H), 1·12 (3 H, d, J = 6 Hz, 21-H), 1·99 (3 H, s, $C\underline{H}_3CO_2$), 3·22 (1 H, d, J_{gem} = 10 Hz, 19-H), 3·56 (1 H, d, J_{gem} = 10 Hz, 19-H), 3·25 (3 H, s, CH_3O), 3·50 (1 H, brd m, overlapped by signal of 19-H and CH_3O; 3α-H), 4·78 (1 H, m, W = 25 Hz, 20α-H), 5·56 (1 H, m, W = 12 Hz, 6-H). For $C_{24}H_{38}O_4$ (390·6) calculated: 73·81% C, 9·81% H; found: 73·69% C, 9·75% H.

b) A solution of the diester *XId* (50 mg) in a mixture of methanol (8 ml) and dioxane (2 ml) was treated with potassium hydroxide (100 mg) at room temperature for 2 h. The mixture was

worked up as given in the previous experiment to yield the alcohol *XIIc* (32 mg), m.p. 141 to 142°C.

6β,19-Dimethoxy-3α,5-cyclo-5α-pregnan-20β-ol 20-Benzoate (*XIVa*)

A solution of the alcohol *XIIa* (700 mg) in pyridine (5 ml) was treated with methanesulfonyl chloride (1 ml) at 0°C for 1 h. The mixture was decomposed with ice and water, the product was taken up in ether and the ethereal solution was worked up as usual to yield the oily mesylate *XIIIa* (*c.* 750 mg), which was dissolved in a mixture of methanol (10 ml) and dioxane (3 ml), anhydrous potassium acetate (300 mg) was added and the mixture was refluxed for 1 h. The mixture was diluted with ether and water, the ethereal solution was washed with water, dried and evaporated. The residue was chromatographed on a silica gel column using a mixture of light petroleum and ether (97 : 3) as eluent. Corresponding fractions were collected and evaporated to yield the pure oily cyclo derivative *XIVa* (530 m), $[\alpha]_D^{20}$ +9° (*c* 1·8). ^{1}H-NMR spectrum: 0·75 (3 H, s, 18-H), 1·25 (3 H, d, J = 6 Hz, 21-H), 3·34 (1 H, d, J_{gem} = 10 Hz, 19-H), 3·61 (1 H, d, J = 10 Hz, 19-H), 3·20 (3 H, s, $CH_3O—C_{19}$), 3·30 (3 H, s, $CH_3O—C_6$), 2·70 (1 H, m, W = 9 Hz, 6α-H), 5·10 (1 H, m, W = 30 Hz, 20α-H). For $C_{30}H_{42}O_4$ (466·7) calculated: 77·21% C 9·07% H; found: 77·06% C, 9·13% H.

6β,19-Dimethoxy-3α,5-cyclo-5α-pregnan-20β-ol 20-Acetate (*XIVc*)

A solution of the alcohol *XIIc* (500 mg) in pyridine (5 ml) was treated with methanesulfonyl chloride (0·7 ml) at 0°C for 30 min. The mixture was decomposed with ice and water, and worked up as usual to yield the mesylate *XIIIc* (*c.* 550 mg) which was dissolved in a mixture of methanol (10 ml) and dioxane (3 ml), anhydrous potassium acetate (500 mg) was added and the mixture refluxed for 2 h. The mixture was diluted with ether and water, the ethereal layer washed with water, dried and the solvent evaporated. The residue was chromatographed on a silica gel column (30 g) using a mixture of light petroleum and ether (95 : 5) as eluent. Corresponding fractions were collected and evaporated to yield the pure oily 3α,5α-cyclo derivative *XIVc* (410mg), $[\alpha]_D^{20}$ +57° (*c* 3·1). ^{1}H-NMR spectrum: 0·68 (3 H, s, 18-H), 1·14 (3 H, d, J = 6 Hz), 2·00 (3 H, s, CH_3CO_2), 2·70 (1 H, m, W = 9 Hz, 6α-H), 3·16 (1 H, d, J_{gem} = 9 Hz, 19-H), 3·64 (1 H, d, J_{gem} = 9 Hz, 19-H), 3·91 (3 H, s, CH_3O), 3·98 (3 H, s, CH_3O), 4·80 (1 H, m, W = 30 Hz, 20α-H). For $C_{25}H_{40}O_4$ (404·6) calculated: 74·22% C, 9·97% H; found: 74·01% C, 10·09% H.

6β,19-Dimethoxy-3α,5-cyclo-5α-pregnan-20β-ol (*XV*)

a) A solution of the benzoate *XIVa* (500 mg) in ether (10 ml) was treated with lithium aluminum hydride (200 mg) at room temperature for 2 h. The mixture was decomposed with a saturated aqueous solution of sodium sulfate, the inorganic material was removed by suction, washed with ether and the filtrate evaporated. The residue was chromatographed on a silica gel pretreated with ammonia (20 g) using a mixture of light petroleum and ether (90 : 10) as eluent. Corresponding fractions were collected and evaporated to yield the oily alcohol *XV* (340 mg), $[\alpha]_D^{20}$ +30° (*c* 2·0). For $C_{23}H_{38}O_3$ (362·6) calculated: 76·20% C, 10·56% H; found: 76·36% C, 10·44% H.

b) A solution of the acetate *XIVc* (400 mg) in ether (10 ml) was treated with lithium aluminum hydride (100 mg) at room temperature for 1 h. The mixture was worked up and chromatographed as in the previous experiment to yield the oily alcohol *XV* (320 mg), $[\alpha]_D^{20}$ +29° (*c* 2·1).

6β,19-Dimethoxy-3α,5-cyclo-5α-pregnan-20-one (*XVI*)

The alcohol *XV* (500 mg) was dissolved in dichloromethane (10 ml) and oxidized with Corey's oxidant[5] (700 mg) at room temperature for 2 h. The mixture was filtered through a column of aluminum oxide and the filtrate was evaporated. The residue was chromatographed on silica gel (30 g) pretreated with ammonia and using a mixture of light petroleum and ether (95 : 5) as eluent. Corresponding fractions were collected and evaporated to yield the crude product, which on crystallization from a mixture of acetone, methanol and water afforded the ketone *XVI* (290 mg), m.p. 94–96°C, $[\alpha]_D^{20}$ +113° (*c* 2·5). ^{1}H-NMR spectrum: 0·65 (3 H, s, 18-H), 2·08 (3 H, s, 21-H), 2·70 (1 H, m, W = 13 Hz, 6α-H), 3·23 (3 H, s, CH_3O), 3·28 (3 H, s, CH_3O), 3·33 (1 H, d, J_{gem} = 10 Hz, 19-H), 3·61 (1 H, d, J_{gem} = 10 Hz, 19-H). For $C_{23}H_{36}O_3$ (360·5) calculated: 76·62% C, 10·06% H; found: 76·38% C, 10·29% H.

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