SYNTHESIS OF 19-NOR-10β-VINYL-5α-CHOLESTANE AND ITS 5β-EPIMER*

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The title compound *IX* was synthesized from the monoacetate *I* in seven steps. The key point of the synthesis is selective hydrolysis of the diacetate *II* to *III* and removal of the substitutent from the position 3 (*IV* → *V*). The 5β-isomeric olefin *XX* was prepared from the monoester *XI* in a similar manner. Conformational factors leading to differences in the reactivity of the ester groups in positions 3 and 19 in relation to the annelation of the A and B rings are discussed.

For our studies on some aspects of electrophilic additions to 10β-vinyl steroids[1-3], we needed 10β-vinyl derivatives with *trans* (*IX*) and *cis*-annellation (*XX*) of the rings A and B of the steroid skeleton and the mesylates *VII* and *XVIII*.

As starting compounds we utilized 5-epimeric monoacetates *I* and *XI* which can be obtained by hydrogenation of 19-hydroxycholesteryl acetate[4]. The diacetate *II* prepared from the monoacetate *I* was saponified selectively in position 3 by treatment with potassium hydrogen carbonate in methanol to yield the monoester *III*. This alcohol was converted to the corresponding mesylate *IV* which on reduction with zinc in the presence of sodium iodide[5,6] gave the 3-deoxy derivative *V* in a neat reaction. Saponification of the acetoxy group in position 19 provided the alcohol *VI* which was converted to the desired mesylate *VII*. The alcohol *VI* was also prepared by hydrogenation of the 2,3-unsaturated alcohol[7] *X*. The aldehyde *VIII* was obtained by a mild oxidation of the alcohol *VI* with chromium trioxide in acetone (Jones' reagent) and converted to the required 10β-vinyl derivative *IX* by Wittig reaction.

A similar procedure was applied to the 5β-series. However, the diacetate *XII* could not be saponified selectively under the same conditions to give the desired 3,19-diol 19-monoacetate. In compound *XII* the acetoxy group in position 19 is saponified preferentially. A TLC analysis reveals that the product resulting from saponification at position 19 predominates over the product of saponification at position 3 in about 3 : 2 ratio. Moreover, both monoesters are accompanied by the corresponding diol. This pronounced difference in reactivities of the acetoxy groups in positions 3 and 19 in both the diacetates *II* and *XII* can be explained in the fol-

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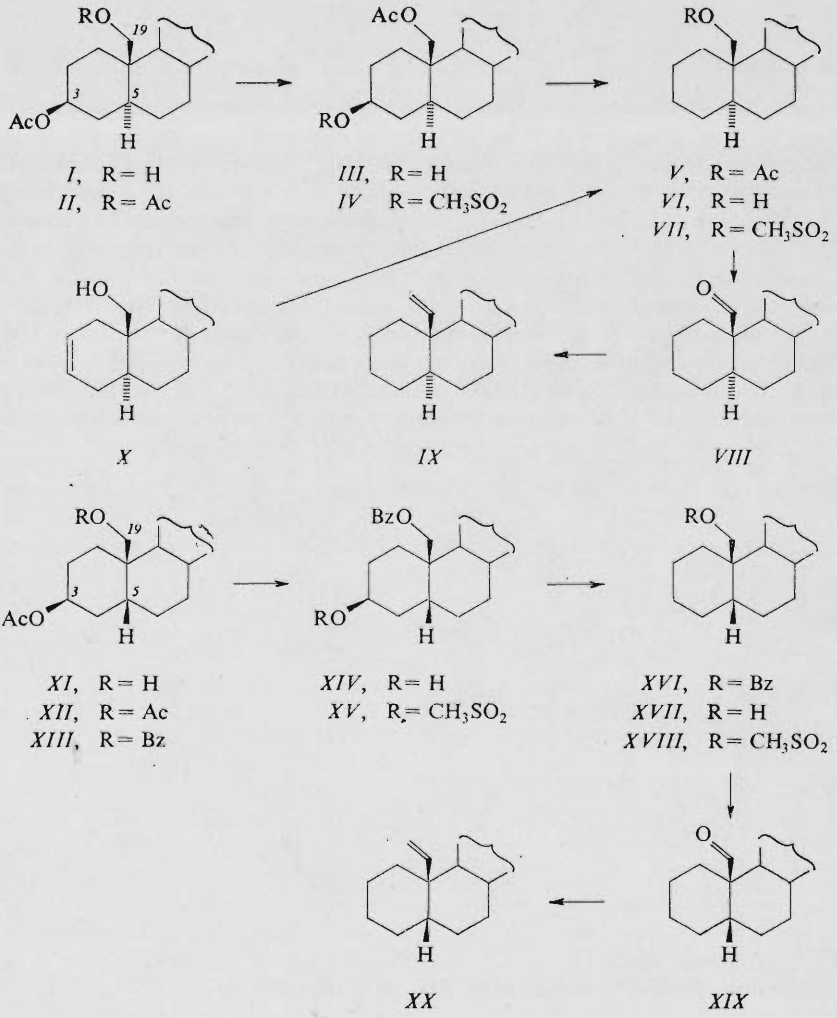
lowing manner (Fig. 1): whereas in the 5α-series the 3β-acetoxy group is equatorial and protrudes from the molecule, the approach of the reagent to the neopentyl 19-acetoxy group is strongly hindered by axial hydrogens at the positions 2β, 4β, 6β, 8β and 11β (Fig. 1). Consequently, the diacetate of the 5α-series (*II*) preferentially is hydrolysed at the position 3; when potassium hydrogen carbonate is used, not even a trace of the competition product with 19-hydroxyl is detected. On the other hand, the 3β-acetoxy group in the 5β-series is axial and, consequently, less reactive. At the same time, the change in annelation of the A/B rings makes the 19-acetoxy group more accessible since interactions with axial hydrogens at $C_{(2)}$ and $C_{(4)}$ are no longer present. In this case, therefore, the 19-acetoxyl becomes more reactive.



Since the planned synthesis required blocking of the 19-hydroxyl and selective removal of the substituent from the 3-position we prepared the acetoxy benzoate *XIII* from the monoacetate *XI*. In the diester *XIII* the acetoxy group can be hydrolysed in acid medium selectively with retention of the protecting group at $C_{(19)}$. This procedure yielded the 3β-hydroxy derivative *XIV* which was subjected to the same sequence of reactions as applied to the 5α-series: conversion to mesylate *XV* was followed by reduction with zinc and sodium iodide readily yielding the 3-deoxy derivative *XVI*. The protecting group at position 19 was removed by reduction with lithium aluminum hydride to give the alcohol *XVII* which was converted to the desired mesylate *XVIII*. The alcohol *XVII* was oxidized with Jones' reagent to yield the aldehyde *XIX* giving the desired 10β-vinyl derivative *XX* by Wittig reaction.

EXPERIMENTAL

Melting points were determined on a Kofler block. Analytical samples were dried at 50°C/26 Pa (0·2 Torr). Optical measurements were carried out in chloroform with an error of ±3°. The infrared spectra were recorded on a Zeiss UR 20 spectrometer in tetrachloromethane unless otherwise stated. The ^{1}H-NMR spectra were recorded on a Tesla BS 476 instrument (60 MHz) in deuteriochloroform at 30°C with tetramethylsilane as internal reference. Chemical shifts are given in ppm. Apparent coupling constants were obtained from the first order analysis. The mass spectra were recorded on a Jeol JMS D-100 spectrometer operating at 14—75 eV. The samples were introduced using a direct inlet at lowest temperature enabling evaporation. The elemental compositions of ions were determined by accurate mass measurements. The identity of the 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, water,

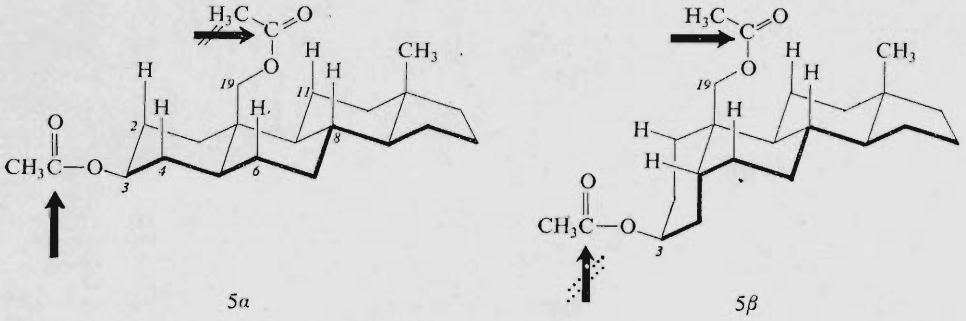


FIG. 1

Conformational effects in hydrolysis of the 5α- and 5β-diacetates *II* and *XII*

a 5% aqueous potassium hydrogen carbonate solution, water, drying with sodium sulfate and evaporation of the solvent *in vacuo*.

5α-Cholestane-3β,19-diol 3,19-Diacetate (*II*)

The alcohol[4] *I* (900 mg) in pyridine (8 ml) was treated with acetic anhydride (3 ml) at 100°C for 15 min. The mixture was decomposed with ice and water, product was taken up in ether and the ethereal layer was worked up as usual. The residue was dissolved in a mixture of light petroleum and benzene (90 : 10) and filtered through a column of aluminum oxide to yield the oily diacetate *II* (870 mg); $[\alpha]_D^{20}$ +9° (*c* 2·1). ^{1}H-NMR spectrum: 0·63 (3 H, s, 18-H), 2·00 (3 H, s, CH_3CO_2), 2·05 (3 H, s, CH_3CO_2), 4·30 (2 H, brd s, 19-H), 4·73 (1 H, m, $W = 30$ Hz, 3α-H). For $C_{31}H_{52}O_4$ (488·8) calculated: 76·18% C, 10·72% H; found: 76·07% C, 10·68% H.

5α-Cholestane-3β,19-diol 19-Monoacetate (*III*)

The diacetate *II* (840 mg) was dissolved in a mixture of benzene (30 ml) and methanol (50 ml) at 60°C and treated with a solution of potassium hydrogen carbonate (1 g) in a mixture of water (20 ml) and methanol (50 ml) at the same temperature for 48 h. The volume of the mixture was reduced to about 1/5 by evaporation *in vacuo* and the residue was distributed between ether and water. The organic phase was washed with water, dried and evaporated. The residue was crystallized from aqueous acetone to yield the monoester *III* (690 mg), m.p. 62—63°; $[\alpha]_D^{20}$ +12° (*c* 2·5). ^{1}H-NMR spectrum: 0·66 (3 H, s, 18-H), 2·05 (3 H, s, CH_3CO_2), 3·65 (1 H, m, $W = 30$ Hz, 3α-H), 4·13 (1 H, d, $J = 12$ Hz, 19-H), 4·38 (1 H, d, $J = 12$ Hz, 19-H). For $C_{29}H_{50}O_3$ (446·7) calculated: 77·97% C, 11·28% H; found: 77·74% C, 11·35% H.

5α-Cholestane-3β,19-diol 3-Methanesulfonate 19-Acetate (*IV*)

The alcohol *III* (800 mg) in pyridine (10 ml) was treated with methanesulfonyl chloride (2 ml) at 0°C for 1 h. The mixture was decomposed with ice and water, the product was extracted with ether and the ethereal layer was worked up as usual to yield the oily mesylate *IV* (790 mg); $[\alpha]_D^{20}$ +8° (2·1). ^{1}H-NMR spectrum: 0·64 (3 H, s, 18-H), 2·05 (3 H, s, CH_3CO_2), 2·98 (3 H, s, CH_3SO_3), 4·28 (2 H, d, $J = 2$ Hz, 19-H), 4·70 (1 H, m, $W = 30$ Hz, 3α-H). For $C_{30}H_{52}O_5S$ (524·8) calculated: 68·66% C, 9·99% H, 6·11% S; found: 68·45% C, 10·12% H, 6·03% S.

5α-Cholestan-19-ol 19-Acetate (*V*)

The mesylate *IV* (400 mg) was dissolved in a mixture of 1,2-dimethoxyethane (5 ml) and dioxane (10 ml) and stirred at 80°C with zinc (1 g) and sodium iodide (1 g) for 8 h. The inorganic material was filtered off, the filtrate was concentrated *in vacuo*, then distributed between ether and water and the organic layer was washed with water, 5% aqueous hydrochloric acid, water, a 5% aqueous potassium hydrogen carbonate solution, a 5% aqueous sodium thiosulfate solution, water, dried and evaporated. The residue was dissolved in acetic acid (15 ml) and hydrogenated over platinum oxide (100 mg) to reduce the olefinic by-products. The mixture was filtered, the filtrate was concentrated *in vacuo*, treated with ether and water, the ethereal layer was washed with water, a 5% aqueous potassium hydrogen carbonate solution, water, dried and evaporated to afford the oily product *V* (310 mg), $[\alpha]_D^{20}$ +17° (*c* 2·7). ^{1}H-NMR spectrum: 0·63 (3 H, s, 18-H), 2·02 (3 H, s, CH_3CO_2), 4·30 (2 H, s, 19-H). For $C_{29}H_{50}O_2$ (430·7) calculated: 80·87% C, 11·70% H; found; 80·77% C, 11·74% H.

5α-Cholestan-19-ol (*VI*)

a) *From 5α-cholestan-19-ol 19-acetate* (V): The acetate *V* (400 mg) in ether (20 ml) was reduced with lithium aluminum hydride (100 mg) at room temperature overnight. The mixture was decomposed with water, then treated with ether and 5% aqueous hydrochloric acid and the ethereal layer was worked up as usual. The residue was crystallized from a mixture of acetone, methanol and water to yield the alcohol *VI* (260 mg), m.p. 87—88°C; $[\alpha]_D^{20}$ +31° (*c* 2·5). ^{1}H-NMR spectrum: 0·67 (3 H, s, 18-H), 3·82 (2 H, brd s, 19-H). For $C_{27}H_{48}O$ (388·7) calculated: 83·44% C, 12·45% H; found: 83·15% C, 12·41% H.

b) *From 5α-cholest-2-en-19-ol* (X): The olefin[7] *X* (500 mg) was dissolved in acetic acid (30 ml), platinum oxide (100 mg) was added and the mixture was hydrogenated under the atmospheric pressure. The mixture was then filtered, the filtrate was concentrated *in vacuo*, the residue was treated with ether and water, the ethereal phase was washed with water, a 5% aqueous potassium hydrogen carbonate solution, water, dried and evaporated. The residue was crystallized from acetone, methanol and water to yield the product, m.p. 87—88°C, identical with the compound described under *a*).

5α-Cholestan-19-ol 19-Methanesulfonate (*VII*)

The alcohol *VI* (180 mg) was disolved in pyridine (3 ml) and treated with methanesulfonyl chloride (0·2 ml) at 0°C for 30 min. The mixture was decomposed with ice and water, the product was taken up into ether and the ethereal layer was worked up as usual. The residue was crystallized from aqueous acetone to yield the mesylate *VII* (120 mg), m.p. 76—79°C, $[\alpha]_D^{20}$ +17° (*c* 1·8). ^{1}H-NMR spectrum: 0·67 (3 H, s, 18-H), 2·98 (3 H, s, CH_3SO_3), 4·28 (1 H, d, J = 10 Hz, 19-H), 4·50 (1 H, d, J = 10 Hz, 19-H). For $C_{28}H_{50}O_3S$ (466·8) calculated: 72·05% C, 10·80% H, 6·87% S; found: 71·94% C, 10·86% H, 6·99% S.

5α-Cholestan-19-al (*VIII*)

The alcohol *VI* (700 mg) was dissolved in acetone (20 ml) and treated with Jones' reagent at 0°C for 5 min. The excess of the reagent was decomposed with methanol, the mixture was diluted with ether and water, the ethereal phase was washed with water, a 5% aqueous potassium hydrogen carbonate solution, water, dried and evaporated. The residue was crystallized from aqueous acetone to afford the aldehyde *VIII* (535 mg), m.p. 90—93°C (dec.), $[\alpha]_D^{20}$ +47° (*c* 2·1). IR spectrum: 1 715, 1 721, 2 819 cm^{-1}. For $C_{27}H_{46}O$ (386·7) calculated: 83·87% C, 11·99% H; found: 83·65% C, 12·04% H.

19-Nor-10β-vinyl-5α-cholestane (*IX*)

Triphenylmethylphosphonium iodide (1·5 g) was added at room temperature to a stirred solution prepared from sodium hydride (300 mg) and dimethyl sulfoxide (12 ml). The mixture was stirred at room temperature for 30 min. Then a solution of the aldehyde *VIII* (400 mg) in tetrahydrofurane (8 ml) was added at room temperature and the mixture was stirred at 65°C for 2 h. The mixture was cooled, diluted with ether and water and the ethereal layer was worked up as usual. The residue was dissolved in a mixture of light petroleum and benzene (90 : 10) and the solution was filtered through a column of aluminum oxide. The filtrate was evaporated and the residue was crystallized from a mixture of ether and acetone to yield the olefin *IX* (260 mg), m.p. 57—59°C, $[\alpha]_D^{20}$ +60° (*c* 2·7). IR spectrum: 917, 1 004, 1 412, 1 632, 3 080 cm^{-1}. For $C_{28}H_{48}$ (384·7) calculated: 87·42% C, 12·58% H; found: 87·23% C, 12·69% H.

5β-Cholestane-3β,19-diol 3,19-Diacetate (*XII*)

The alcohol[4] *XI* (250 mg) was dissolved in pyridine (3 ml) and treated with acetic anhydride (1 ml) at 100°C for 15 min. The mixture was decomposed with ice and water, the product extracted with ether and the etheral layer was worked up as usual. The residue was crystallized from a mixture of acetone, methanol and water, to afford the diacetate *XII* (140 mg), m.p. 92 to 93°C, $[\alpha]_D^{20}$ +26° (*c* 2·1). ^{1}H-NMR spectrum: 0·63 (3 H, s, 18-H), 2·03 (3 H, s, CH_3CO_2), 2·07 (3 H, s, CH_3CO_2), 4·07 (1 H, d, J = 12 Hz, 19-H), 4·38 (1 H, d, J = 12 Hz, 19-H), 5·07 (1 H, m, W = 12 Hz, 3α-H). For $C_{31}H_{52}O_4$ (488·8) calculated: 76·18% C, 10·72% H; found: 76·09% C, 10·80% H.

5β-Cholestane-3β,19-diol 3-Acetate 19-Benzoate (*XIII*)

The alcohol *XI* (1·5 g) was dissolved in pyridine (15 ml) and treated with benzoyl chloride (2·5 ml) at 40°C for 30 min. The mixture was then decomposed with ice and water, the product extracted with ether and the ethereal layer was worked up as usual. The residue was dissolved in light petroleum and filtered through a column of aluminum oxide. The filtrate was evaporated to yield the oily diester *XIII* (1·4 g), $[\alpha]_D^{20}$ +21° (*c* 2·6). ^{1}H-NMR spectrum: 0·67 (3 H, s, 18-H), 2·03 (3 H, s, CH_3CO_2), 4·23 (1 H, d, J = 11 Hz, 19-H), 4·70 (1 H, d, J = 11 Hz, 19-H), 5·12 (1 H, W = 12 Hz, 3α-H). For $C_{36}H_{54}O_4$ (550·8) calculated: 78·50% C, 9·88% H; found: 70·32% C, 9·91% H.

5β-Cholestane-3β,19-diol 19-Monobenzoate (*XIV*)

The diester *XIII* (1·5 g) was dissolved in a mixture of chloroform (10 ml) and methanol (50 ml) and treated with concentrated hydrochloric acid at 40°C for 20 h. The mixture was concentrated *in vacuo*, the residue was treated with ether and water, the organic phase was washed with water, a 5% aqueous potassium hydrogen carbonate solution, water, dried and evaporated. The residue was dissolved in light petroleum and filtered through a column of aluminum oxide. The impurities were eluted by a mixture of light petroleum and benzene (90 : 20) and the product by a mixture of the same solvents in a 1 : 1 ratio. The filtrate was evaporated and the residue crystallized from aqueous acetone to yield the alcohol *XIV* (0·9 g), m.p. 123—124°C, $[\alpha]_D^{20}$ +24° (*c* 2·3). ^{1}H-NMR spectrum: 0·65 (3 H, s, 18-H), 4·25 (1 H, d, J = 11 Hz, 19-H), 4·13 (1 H, m, W = 10 Hz, 3α-H), 4·67 (1 H, d, J = 11 Hz, 19-H). For $C_{34}H_{52}O_3$ (508·8) calculated: 80·26% C, 10·30% H; found: 80·13% C, 10·54% H.

5β-Cholestane-3β,19-diol 3-Methanesulfonate 19-Benzoate (*XV*)

The alcohol *XIV* (500 mg) was dissolved in pyridine (7 ml) and treated with methanesulfonyl chloride (0·5 ml) at 0°C for 1 h. The mixture was then decomposed with ice and water, the product extracted with ether and the ethereal phase was worked up as usual to yield the foam of the mesylate *XV* (510 mg), $[\alpha]_D^{20}$ +20° (*c* 2·1). ^{1}H-NMR spectrum: 0·67 (3 H, s, 18-H), 2·97 (3 H, s, CH_3SO_3), 4·23 (1 H, d, J = 11 Hz, 19-H), 4·67 (1 H, d, J = 11 Hz, 19-H), 5·10 (1 H, m, W = = 14 Hz, 3α-H). For $C_{35}H_{54}O_5S$ (586·9) calculated: 71·63% C, 9·27% H, 5·46% S; found: 71·49% C, 9·36% H, 5·29% S.

5β-Cholestan-19-ol 19-Benzoate (*XVI*)

The mesylate *XV* (400 mg) was dissolved in a mixture of 1,2-dimethoxyethane (5 ml) and dioxane (5 ml) and stirred with sodium iodide (1 g) and zinc (1 g) at 80°C for 6 h. The inorganic material

was then filtered off, the filtrate concentrated *in vacuo*, the residue was treated with ether and water, and the organic phase was worked up as usual. The residue was dissolved in chloroform (10 ml) and treated with *m*-chloroperoxybenzoic acid (100 mg) at room temperature for 2 h to remove the olefinic by-products. The solution was diluted with ether and water and the organic layer was washed with water, a 5% aqueous potassium hydrogen carbonate solution, a 5% aqueous sodium thiosulfate solution, water, dried and evaporated. The residue was dissolved in light petroleum and filtered through a column of aluminum oxide. The filtrate was evaporated to furnish the oily benzoate *XVI* (330 mg), $[\alpha]_D^{20}$ +22° (*c* 2·2). ^{1}H-NMR spectrum: 0·66 (3H, s, 18-H), 4·22 (1 H, d, J = 11 Hz, 19-H), 4·65 (1 H, d, J = 11 Hz, 19-H). For $C_{34}H_{52}O_2$ (492·8) calculated: 82·87% C, 10·64% H; found: 82·80% C, 10·69% H.

5β-Cholestan-19-ol (*XVII*)

The benzoate *XVI* (380 mg) was dissolved in ether (10 ml) and treated with lithium aluminum hydride (100 mg) at room temperature overnight. The mixture was decomposed with water, diluted with ether and 5% hydrochloric acid and the ethereal phase was worked up as usual. The residue was crystallized from aqueous acetone to afford the alcohol *XVII* (160 mg), m.p. 139 to 140°C, $[\alpha]_D^{20}$ +36° (*c* 1·9). ^{1}H-NMR spectrum: 0·62 (3 H, s, 18-H), 3·45 (1 H, d, J = 11 Hz, 19-H), 3·92 (1 H, d, J = 11 Hz, 19-H). IR spectrum: 3 420, 3·642 cm^{-1}. For $C_{27}H_{48}O$ (388·7) calculated: 83·44% C, 12·45% H; found: 83·32% C, 12·49% H.

5β-Cholestan-19-ol 19-Methanesulfonate (*XVIII*)

The alcohol *XVII* (110 mg) was dissolved in pyridine (4 ml) and trated with methanesulfonyl chloride (0·2 ml) at 0·C for 2 h. The mixture was decomposed with ice and water, the product extracted with ether and the ethereal layer was worked up as usual to yield the oily mesylate *XVIII* (95 mg), $[\alpha]_D^{20}$ +40° (*c* 2·0). For $C_{28}H_{50}O_3S$ (466·8) calculated: 72·05% C, 10·80% H, 6·87% S; found: 71·94% C, 10·85% H, 6·61% S.

5β-Cholestan-19-al (*XIX*)

The alcohol *XVII* (250 mg) was dissolved in a mixture of acetone (20 ml) and benzene (10 ml) and treated with Jones' reagent at 0°C for 5 min. The mixture was diluted with ether and water, the ethereal layer was washed with water, a 5% aqueous potassium hydrogen carbonate solution, water, dried and evaporated. The residue was dissolved in light petroleum and filtered through a column of aluminum oxide. The filtrate was evaporated to give the oily aldehyde *XIX* (110 mg), $[\alpha]_D^{20}$ +5° (*c* 2·6). ^{1}H-NMR spectrum: 0·70 (3 H, s, 18-H), 9·68 (1 H, s, 19-H). IR spectrum: 1 716, 2 820 cm^{-1}. For $C_{27}H_{46}O$ (386·7) calculated: 83·87% C, 11·99% H; found: 83·52% C, 12·16% H.

19-Nor-10β-vinyl-5β-cholestane (*XX*)

Triphenylmethylphosphonium iodide (1 g) was added at room temperature to a stirred solution prepared from sodium hydride (150 mg) and dimethyl sulfoxide (6 ml). The mixture was stirred at room temperature for 30 min. Then a solution of the aldehyde *XIX* (190 mg) in tetrahydrofurane (5 ml) was added at room temperature and the mixture was stirred at 70°C for 2 h. The mixture was cooled, diluted with ether and water and the ethereal layer was worked up as usual. The residue was dissolved in a mixture of light petroleum and benzene (90 : 10) and the solution was filtered through a column of aluminum oxide. The filtrate was evaporated to yield the oily olefin *XX* (53 mg), $[\alpha]_D^{20}$ +20° (*c* 5·0). IR spectrum: 913, 992, 1 416, 1 630, 3 080 cm^{-1}. For $C_{28}H_{48}$ (384·7) calculated: 87·42% C, 12·58% H; found: 87·29% C, 12·65% H.

The analyses were carried out in the Analytical Laboratory of this Institute (head Dr J. Horáček). The IR *spectra were recorded by Mrs K. Matoušková and interpreted by Dr S. Vašíčková. The* ^{1}H-NMR *spectra were recorded by Mrs J. Jelínková and Mrs M. Snopková.*

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