SYNTHESIS OF SOME 2,3- AND 5,6-UNSATURATED 19-HOMOSTEROIDS BEARING AN OXYGEN CONTAINING GROUP AT THE POSITION 19a*

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A synthesis of 5,6- and 2,3-unsaturated 19a-methoxy-19a-homocholestane derivatives *XVII* and *XXI* is reported. The key steps in the synthesis of the former compound is protecting the 3β-hydroxyl group and 5,6-double bond by conversion to a cyclosteroid (*IX* → *VI*), selective hydroboration of the protected steroid followed by methylation (*VI* → *X* → *XI*) and reductive removal of the 3β-substituent (*XVI* → *XVII*). The 2,3-unsaturated methyl ether *XXI* was obtained by elimination from the mesylate *XX* prepared from the 5,6-unsaturated derivative *XV* in three steps.

For the study of neighboring group participation in electrophilic additions[1-3] we needed 2,3- and 5,6-unsaturated 19a-homosteroids of the types *1* and *2* bearing an oxygen-containing groups (in particular a methoxyl) at position 19a. An obvious method for homologization in position 19 and introduction of an oxygen function into position 19a seemed to be the Wittig reaction of the corresponding aldehyde (3→4) followed by selective hydroboration of the 10β-vinyl group in the presence of a double in 5,6 or 2,3-position, respectively (Scheme 1). However, owing to strong hindrance[4], selective hydroboration of the 10β-vinyl in a diene of the type 4 cannot be carried out with, for instance, 9-borabicyclo[3,3,1]nonane. Attempt at hydroboration using a reagent of less steric requirement, as *e.g.* borane–tetrahydrofuran or borane–dimethyl sulfide complex, leads to a mixture of products (the endocyclic double bond most likely reacts preferentially as on treatment with electrophilic reagents[4]). When planning a synthesis of the compounds of the type 1 and 2 it was necessary to seek such starting compounds in which a hydroboration of the 10β-vinyl group could be accomplished in the presence of a protected or latent double bond located in the position 2,3 or 5,6. For synthesis of the 2,3-unsaturated derivative of the type *1*, it appeared possible to consider the mesylate of the type *5* as intermediate which could be obtained in several steps by hydrogenation of the precursor of the type *6*. Reductive removal of the 3β-substituent (*6*, R^2 = Ms) should lead to the second

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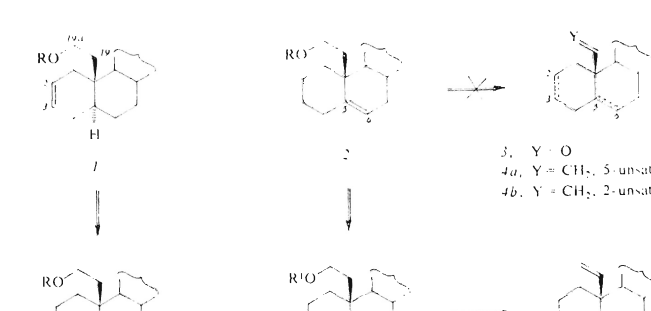
target compound of the type 2. These considerations of the synthesis of the target compounds (types *1* and *2*) lead to a conclusion that a pivot precursor must contain an oxygen substituent in 3β-position and a double bond in 5,6-position (compound of the type *6*.)

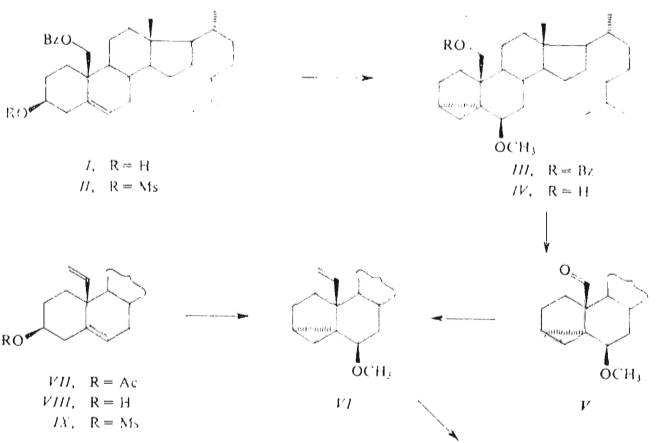


SCHEME 1

A possible synthon for this grouping, at the same time playing the role of a protecting group at the intended hydroboration of the 10β-vinyl, is 3α,5α-cyclo-6β-Y arrangement; such compounds are accessible by i-steroid rearrangement of a 5,6-unsaturated 3β-mesylate[5]. Thus, a compound of the type 7 (Y = OCH_3) would comprise both a latent 5,6-double bond and 3β-substituent. Its hydroboration and reversed i-steroid rearrangement should lead to an intermediate of the type *6*.

We prepared the key compound, 3α,5α-cyclo-6β-methoxy-10β-vinyl derivative *VI*, by two routes (Scheme 2). In the first case, the known hydroxy benzoate[6] *I* was converted into the mesylate *II* which on heating in a methanolic solution buffered with sodium acetate yielded the 3,5-cyclo derivative *III* in a good yield. Removal of the benzoate group by the action of lithium aluminum hydride gave the alcohol *IV* which on buffered oxidation with pyridinium chlorochromate in dichloromethane smoothly yielded the aldehyde *V*. Reaction of this aldehyde with the ylide generated from triphenylmethylphosphonium iodide by 3 h treatment with sodium salt of dimethyl sulfoxide at 65°C gives rise to the 10β-vinyl derivative *VI*. In a different manner, we prepared this compound by rearrangement of the 3β-mesyloxy diene *IX* under conditions similar to those applied in the rearrangement of *II* to *III*. In this

case, the reaction time is longer and the yield of the product is lower than in the first case. This may be attributed to higher steric hindrance by the vinyl group in the mesylate *IX*. However, the second route appears to be more advantageous since the compound *VI* can be thus prepared from 5-cholestene-3β,19-diol 3-monoacetate in a five-step process whereas the first procedure is a seven-step synthesis[6,7].

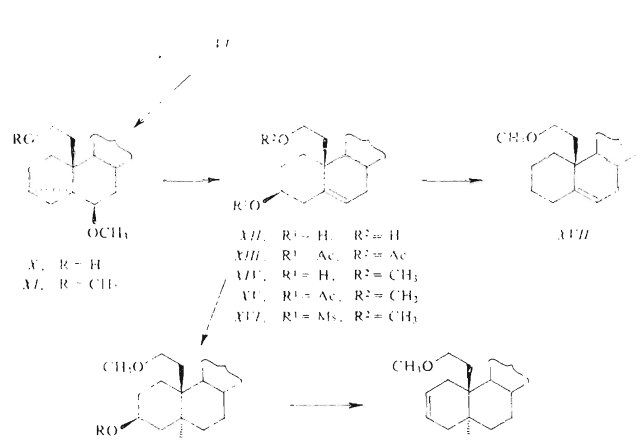


SCHEME 2

Hydroboration of the 10β-vinyl derivative *VI* gave a good yield of the alcohol *X* (Scheme 3) which on methylation with methyl iodide in the presence of sodium hydride in tetrahydrofuran yielded the methyl ether *XI*. The alcohol *X* was treated with aqueous perchloric acid to rearrange readily to 5,6-unsaturated diol *XII* characterized as the diacetate *XIII*. Similar treatment of the methyl ether *XI* led smoothly to the 5,6-unsaturated methoxy alcohol *XIV* characterized as the acetate *XV*. Conversion of *XIV* to the mesylate *XVI* followed by removal of the mesyloxy group by treatment with sodium iodide and zinc in moist 1,2-dimethoxyethane[8,9] yielded the target compound *XVII*.

Contrasting with the behavior of the homologs bearing an oxygenated substituent at $C_{(19)}$ (*cf.*[10]), hydrogenation of the 5,6-unsaturated 3β-acetoxy derivative *XV* on platinum in acetic acid shows considerable stereoselectivity. A single crystallization of the reaction product furnished practically pure derivative *XVIII* with *trans*

junction of the A and B rings. This compound (*via* the alcohol *XIX*) was converted into the mesylate *XX*. Treatment of the latter with boiling collidine gave a mixture of olefins which on chromatography yielded the 2,3-isomer *XXI* as the major product.



SCHEME 3

EXPERIMENTAL

Melting points were determined on a Kofler block. Analytical samples were dried at 50°C/26 Pa or at 20°C/26 Pa. Optical rotations were measured in chloroform with an error of ±3°. The infrared spectra were recorded on a Zeiss UR 20 or on a Perkin–Elmer 580 spectrometer in tetrachloromethane unless stated otherwise. The ^{1}H NMR spectra were recorded on a Tesla B 476 (60 MHz) instrument at 25°C in deuteriochloroform with tetramethylsilane as internal reference. Chemical shifts are given in δ (ppm) scale. All values were taken from the first order analysis. Mass spectra were recorded on a AEI MS 901 spectrometer. The identity of the samples prepared by different routes was checked by mixture melting point determination, thin-layer chromatography (TLC), infrared, ^{1}H NMR and mass spectra. Usual workup of an ethereal solution means washing the solution with 5% aqueous hydrochloric acid, water, a 5% aqueous potassium hydrogen carbonate solution, water, drying with sodium sulfate and evaporation of the solvent *in vacuo*. Neutral aluminum oxide (grade II) was used for filtrations.

6β-Methoxy-3α,5-cyclo-5α-cholestan-19-ol 19-Benzoate (*III*)

A mixture of the mesylate[6] *II* (12 g) and dry potassium acetate (9 g) in dioxane (60 ml) and methanol (150 ml) was refluxed for 2 h. The volume of the mixture was reduced to about 1/4 by evaporation *in vacuo*, the residue was diluted with ether and water, the ethereal layer was washed with water, 5% aqueous potassium hydrogen carbonate solution, water, dried and evaporated. The residue was chromatographed on a column of silica gel (350 g) with a mixture of light petroleum and benzene (70 : 30). Corresponding fraction was evaporated to yield the oily cyclosteroid *III* (6·9 g), $[\alpha]_D^{20} + 51°$ (*c* 2·1). ^{1}H NMR spectrum: 0·68 (3 H, s, 18-H), 2·77 (1 H, m, $W = 9$ Hz, 6α-H), 3·32 (3 H, s, CH_3O), 4·53 (2 H, s, 19-H). For $C_{35}H_{52}O_3$ (520·8) calculated: 80·72% C, 10·06% H; found: 80·49% C, 9·93% H.

6β-Methoxy-3α,5-cyclo-5α-cholestan-19-ol (*IV*)

The benzoate *III* (6 g) was dissolved in ether (100 ml) and treated with lithium aluminum hydride (600 mg) at room temperature for 4 h. The mixture was decomposed with saturated aqueous solution of sodium sulfate, the inorganic material was filtered off, the solution was washed with water, dried and evaporated. The residue was dissolved in light petroleum and the solution was filtered through a column of aluminum oxide. The filtrate was evaporated and the residue was crystallized from aqueous acetone to yield the alcohol *IV* (2·7 g), m.p. 85–86°C, $[\alpha]_D^{20} + 64°$ (*c* 1·9). For $C_{28}H_{48}O_2$ (416·7) caclulated: 80·71% C, 11·61% H; found: 80·59% C, 11·53% H.

6β-Methoxy-3α,5-cyclo-5α-cholestan-19-al (*V*)

Pyridinium chlorochromate (4 g) was added in ten portions into a stirred mixture of the alcohol *IV* (2·4 g), potassium acetate (1 g) and sodium sulfate (1 g) in dichloromethane (40 ml) at room temperature and the mixture was stirred overnight at room temperature. The mixture was filtered through a column of aluminum oxide and evaporated. The residue was chromatographed on a column of silica gel (60 g) impregnated with ammonia using a mixture of light petroleum and benzene (80 : 20) as eluent. The corresponding fraction was evaporated to yield the aldehyde *V* (2·1 g), $[\alpha]_D^{20} + 60°$ (*c* 1·9). For $C_{28}H_{46}O_2$ (414·7) calculated: 81·10% C, 11·18% H; found: 80·93% C, 11·14% H.

6β-Methoxy-3α,5-cyclo-19-homo-5α-cholest-19(19a)-ene (*VI*)

A) Triphenylmethyl phosphonium ioxide (5 g) was added at room temperature to s stirred solution prepared from sodium hydride (1·1 g) and dimethyl sulfoxide (10 ml). The mixture was stirred at room temperature for 30 min. Then a solution of the aldehyde *V* (5 g) in tetrahydrofuran (30 ml) was added at room temperature and the mixture was stirred at 65°C for 3 h. The mixture was diluted with ether and water, the organic layer was washed with water, a 5% aqueous potassium hydrogen carbonate solution, water, dried and evaporated. The residue was dissolved in a mixture of benzene and light petroleum (30 : 70) and the solution was filtered through a column of aluminum oxide. The filtrate was evaporated to yield the oily olefin *VI* (3·8 g), $[\alpha]_D^{20} + 67°$ (*c* 4·8). For $C_{29}H_{48}O$ (412·7) calculated: 84·40% C, 11·72% H; found: 84·25% C, 11·66% H.

B) A mixture of the mesylate *IX* (4 g) and dry potassium acetate (3 g) in dioxane (20 ml) and methanol (50 ml) was refluxed for 20 h. The volume of the mixture was reduced to about 1/4 by evaporation *in vacuo*, the residue 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 chromatographed on a column of silica gel (100 g) impregnated with ammonia using a mixture of light petroleum and benzene (70 : 30) as eluent. The corresponding

fraction was evaporated to yield the oily *VI* (1·1 g), $[\alpha]_D^{20}$ +69° (*c* 2·0) identical with the compound prepared under *A*.

19-Homocholesta-5,19-dien-3β-ol (*VIII*)

A solution of the acetate[7] *VII* (2·5 g) and potassium hydroxide (2 g) in acetone (50 ml) and methanol (150 ml) was refluxed for 5 min. The volume of the solution was reduced to about 1/5 by evaporation *in vacuo*, the residue was diluted with ether and water and the ethereal layer was worked up as usual. The residue was crystallized from aqueous acetone to yield the alcohol *VIII* (2·3 g), m.p. 109–110°C, $[\alpha]_D^{20}$ −82° (*c* 2·7). For $C_{28}H_{46}O$ (398·7) calculated: 84·36% C, 11·63% H; found: 84·22% C, 11·61% H.

19-Homocholesta-5,19-dien-3β-ol 3-Methanesulfonate (*IX*)

The alcohol *VIII* (2 g) was dissolved in pyridine (20 ml) and treated with methanesulfonyl chloride (2 ml) at 0°C for 30 min. The mixture was decomposed with ice and water, the product was taken up in ether and the ethereal phase was worked up as usual to yield the crude mesylate *IX* (1·95 g), m.p. 104–107°C (dec.), which was directly used for preparation of *VI*.

6β-Methoxy-3α,5-cyclo-19-homo-5α-cholestan-19a-ol (*X*)

Boron trifluoride etherate (0·5 ml) in tetrahydrofuran (10 ml) was added dropwise to a solution of sodium borohydride (250 mg) in tetrahydrofuran (20 ml) at 0°C and the mixture was stirred at 0°C for 30 min. To this mixture a solution of the olefin *VI* (1 g) in tetrahydrofuran (20 ml) was added at 0°C and the mixture was stirred for 6 h at the same temperature. The excess of reagents was decomposed with water, and the mixture was then stirred with a solution of potassium hydroxide (500 mg) in water (5 ml) and 30% hydrogen peroxide (3 ml) at 0°C for 1 h and then refluxed for 2 h while stirring. The mixture was diluted with ether and water, the ethereal layer was washed with water, dried and evaporated. The residue was chromatographed on a column of silica gel (60 g) impregnated with ammonia using a mixture of light petroleum, ether and acetone (88 : 10 : 2). The corresponding fraction was evaporated to yield the oily alcohol *X* (720 mg), $[\alpha]_D^{20}$ +26° (*c* 1·4). ^{1}H NMR spectrum: 0·65 (3 H, s, 18-H), 3·22 (3 H, s, CH_3O), 3·65 (3 H, m, W = 25 Hz, 6α-H and 19a-H). For $C_{29}H_{50}O_2$ (430·7) calculated: 80·87% C, 11·70% H; found: 80·94% C, 11·49% H.

6β,19-Dimethoxy-3α,5-cyclo-19-homo-5α-cholestane (*XI*)

The alcohol *X* (600 mg) was dissolved in tetrahydrofuran (20 ml) and stirred with sodium hydride (200 mg) and methyl iodide (2 ml) at 60°C for 2 h. The excess of reagent was decomposed with water, the mixture was diluted with ether and water and the organic phase 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 afford the oily *XI* (530 mg), $[\alpha]_D^{20}$ +23° (*c* 2·0). For $C_{30}H_{52}O_2$ (444·7) calculated: 81·02% C, 11·79% H; found: 80·94% C, 11·84% H.

19-Homo-5-cholestene-3β,19a-diol (*XII*)

The cyclosteroid *X* (400 mg) in acetone (15 ml) was refluxed with a solution of 72% perchloric acid (1 ml) in water (2 ml) for 1 h. 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 crystallized from a mixture of acetone and n-heptane to yield the diol *XII* (280 mg), m.p. 196–198°C, $[\alpha]_D^{20}$ −37° (*c* 1·6). ^{1}H NMR spectrum: 0·70

(3 H, s, 18-H), 3·65 (3 H, m, $W = 50$ Hz, 3α-H and 19a-H), 5·47 (1 H, m, $W = 17$ Hz, 6-H). For $C_{28}H_{48}O_2$ (416·7) calculated: 80·71% C, 11·61% H; found: 80·58% C, 11·50% H.

19-Homo-5-cholesten-3β,19a-diol 3,19-Diacetate (*XIII*)

The diol *XII* (900 mg) was dissolved in pyridine (7 ml) and treated with acetic anhydride (3 ml) at room temperature overnight. The mixture was worked up as usual. The residue was crystallized from a mixture of acetone, methanol and water to yield the diacetate *XIII* (620 mg), m.p. 101–103°C, $[\alpha]_D^{20}$ −42° (*c* 2·0). ^{1}H NMR spectrum: 0·73 (3 H, s, 18-H), 2·00 (6 H, s, 2 × CH_3CO_2), 4·00 (2 H, m, $W = 45$ Hz, 19a-H), 4·65 (1 H, m, $W = 30$ Hz, 3α-H), 5·58 (1 H, m, $W = 14$ Hz, 6-H). For $C_{32}H_{52}O_2$ (500·8) calculated: 76·75% C, 10·47% H; found: 76·62% C, 10·55% H.

19a-Methoxy-19-homo-5-cholesten-3β-ol (*XIV*)

The cyclosteroid *XI* (250 mg) was dissolved in acetone (10 ml) and refluxed with a solution of 72% aqueous perchloric acid (1 ml) in water (1 ml) for 30 min. The mixture was diluted with ether and water and worked up as in the previous experiment (*XII*). The residue was crystallized from aqueous acetone to afford the alcohol *XIV* (140 mg), m.p. 109–111°C, $[\alpha]_D^{20}$ −45° (*c* 1·7). ^{1}H NMR spectrum: 0·70 (3 H, s, 18-H), 3·28 (3 H, s, CH_3O), 3·95 (3 H, m, $W = 40$ Hz, 3α-H and 19a-H), 5·50 (1 H, m, $W = 13$ Hz, 6-H). For $C_{29}H_{50}O_2$ (430·7) calculated: 80·87% C, 11·70% H; found: 80·69% C, 11·73% H.

19a-Methoxy-19-homo-5-cholesten-3β-ol 3-Acetate (*XV*)

The alcohol *XIV* (800 mg) was dissolved in pyridine (5 ml) and treated with acetic anhydride (2 ml) at room temperature overnight. The mixture was decomposed with ice and water, the product was extracted with ether and the ethereal solution was worked up as usual .The residue was crystallized from a mixture of acetone, methanol and water to yield the acetate *XV* (540 mg), m.p. 106–108°C, $[\alpha]_D^{20}$ −49° (*c* 2·0). ^{1}H NMR spectrum: 0·72 (3 H, s, 18-H), 2·01 (3 H, s, CH_3CO_2), 3·33 (3 H, s, CH_3O), 4·60 (1 H, m, $W = 30$ Hz, 3α-H). For $C_{31}H_{52}O_3$ (472·8) calculated: 78·76% C, 11·09% H; found: 78·62% C, 11·18% H.

19a-Methoxy-19-homo-5-cholestene (*XVII*)

The alcohol *XIV* (400 mg) was dissolved in pyridine (5 ml) and treated with methanesulfonyl chloride (0·5 ml) at 0°C for 30 min. 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 crude mesylate *XVI* (*c*. 420 mg). The mesylate *XVI* (350 mg) was dissolved in a mixture of 1,2-dimethoxyethane (10 ml) and water (1 ml) and stirred at 80°C with sodium iodide (500 mg) and zinc (500 mg) for 2 h. The inorganic material was filtered off, the solution was concentrated by evaporation *in vacuo*, the residue treated with ether and 5% aqueous hydrochloric acid and the ethereal phase was worked up as usual. The residue was crystallized from aqueous acetone to afford *XVII* (180 mg), m.p. 81–82°C, $[\alpha]_D^{20}$ −66° (*c* 2·1). For $C_{29}H_{50}O$ (414·7) calculated: 83·99% C, 12·15% H; found: 83·71% C, 12·34% H.

19a-Methoxy-19-homo-5α-cholestan-3β-ol 3-Acetate (*XVIII*)

The olefin *XV* (1·5 g) was dissolved in acetic acid (100 ml), platinum dioxide (200 mg) was added and the mixture was shaken in hydrogen atmosphere for 1 h. The catalyst was filtered off, the volume of the filtrate was reduced to *ca* one quarter by evaporation *in vacuo*, the residue diluted

with ether and water, the ethereal phase was washed with water, a 5% aqueous potassium hydrogen carbonate solution, water, dried with sodium sulfate and the solvent was evaporated to yield the crude product *XVIII* (1·45 g). A sample was crystallized from a mixture of acetone, methanol and water to furnish the pure *XVIII*, m.p. 99–100°C, $[\alpha]_D^{20}$ +16° (*c* 2·5). ^{1}H NMR spectrum: 0·67 (3 H, s, 18-H), 2·00 (3 H, s, CH_3CO_2), 3·33 (3 H, s, CH_3O), 3·50 (2 H, m, W = 25 Hz, 19a-H), 3·67 (1 H, m, W = 30 Hz, 3α-H). For $C_{31}H_{54}O_3$ (474·8) calculated: 78·43% C, 11·46% H; found: 78·29% C, 11·51% H.

19a-Methoxy-19-homo-5α-cholestan-3β-ol (*XIX*)

The acetate *XVIII* (1·3 g) was dissolved in a mixture of acetone (50 ml) and methanol (200 ml) and refluxed with a solution of potassium hydroxide (2·5 g) in water (10 ml) for 10 min. The mixture was concentrated by evaporation *in vacuo*, the residue diluted with ether and water and the ethereal layer was worked up as usual. The residue was crystallized from aqueous acetone to yield the alcohol *XIX* (960 mg), m.p. 152–153°C, $[\alpha]_D^{20}$ +23° (*c* 1·7). For $C_{29}H_{52}O_2$ (432·7) calculated: 80·49% C, 12·11% H; found: 80·36% C, 12·25% H.

19a-Methoxy-19-homo-5α-cholest-2-ene (*XXI*)

The alcohol *XIX* (1·2 g) was dissolved in pyridine (50 ml) and treated with methanesulfonyl chloride (1 ml) at 0°C for 1 h. The mixture was decomposed with ice and water, the product taken up into ether and the ethereal layer was worked up as usual to yield the crude mesylate *XX* (1·2 g), m.p. 90–93°C. This mesylate (1·1 g) was refluxed in *syn*-collidine (15 ml) for 1 h, collidine was distilled off *in vacuo*, the residue was treated with ether and water and the ethereal phase worked up as usual. The residue was dissolved in a mixture of light petroleum and benzene (9 : 1) and filtered through a column of aluminum oxide. The filtrate was evaporated and the residue was chromatographed on a column of silica gel (60 g) using a mixture of light petroleum and benzene (95 : 5). The corresponding fraction was evaporated to yield the oily olefin *XXI* (730 mg). $[\alpha]_D^{20}$ +56° (*c* 2·2). ^{1}H NMR spectrum: 0·67 (3 H, s, 18-H), 3·28 (3 H, s, CH_3O), 3·38 (2 H, m, W = = 25 Hz, 19a-H), 5·58 (2 H, m, W = 9 Hz, 2-H and 3 H). For $C_{29}H_{50}O$ (414·7) calculated: 83·99% C, 12·15% H; found: 83·72% C, 12·38% 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.* ^{1}H NMR *spectra were recorded by Mrs J. Jelinková and M. Snopková.*

REFERENCES

1. Kočovský P., Černý V., Synáčková M.: This Journal *44*, 1483 (1979).
2. Kočovský P., Kohout L., Černý V.: This Journal *45*, 1496 (1979).
3. Kočovský P., Černý V.: This Journal *45*, 3030 (1980).
4. Kočovský P., Tureček F.: This Journal *46*, 2877 (1981).
5. Kirk D. N., Hartshorn M. P.: *Steroid Reaction Mechanism*. Elsevier, Amsterdam 1968.
6. Kočovský P.: This Journal *45*, 3008 (1980).
7. Cubberley B. W., Guest I. G., Ll. Jones J. G., Marples B. A.: J. Chem. Soc. Perkin Trans. 1. *1977*, 1916.
8. Fujimoto Y., Tatsuno T.: Tetrahedron Lett. *1976*, 3325.
9. Kočovský P., Černý V.: This Journal *44*, 246 (1979).
10. Watanabe Y., Mizuhara Y., Shiota M.: J. Org. Chem. *31*, 3785 (1966).

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