SYNTHESIS OF 2-PROPYNYL ETHERS OF STEROID ALCOHOLS*

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2-Propynyl ethers, derived from steroid alcohols with hydroxyl in position 3β, 17 or 20, were prepared by reaction with propargyl bromide and sodium hydroxide under conditions of phase transfer catalysis. Other hydroxy groups in the steroid molecule were protected with the methoxymethyl or 2-tetrahydropyranyl group.

2-Propynyl ethers of steroids have been used[1] as precursors for the preparation of steroid carboranyl methyl ethers consisting in insertion of an acetylene unit into the decaborane(14) skeleton under formation of stable C-1 substituted 1,2-dicarba-*closo*--dodecaboranes(12). These carborane derivatives were tested for boron neutron capture therapy[2] of hormone-dependent tumours. This procedure has been described for the first time[1,3] for estrone 3-(2-propynyl) ether which can be easily prepared by reaction of sodium salt of estrone with propargyl bromide.

The aim of our recent work is the preparation of 2-propynyl ethers derived from variously substituted 3β-hydroxy- and 17β-hydroxyandrostane and 17β-hydroxyestrane derivatives (i.e. from alicyclic secondary alcohols). As shown by preliminary experiments with cholesterol (*I*), the above-mentioned method is not suitable for this type of hydroxy derivatives; the sodium salt of cholesterol (prepared in situ by treatment with sodium hydride) reacted with propargyl bromide in tetrahydrofuran to give the desired 2-propynyl ether *II* in a yield of only 11%. Therefore, we tried to perform the etherification under conditions of phase-transfer catalysis[4]. Although the preparation of 2-propynyl ethers of steroid alcohols under these conditions is already known[5,6], it was reported only for 16β-hydroxy derivatives without any experimental details. For this reason, we performed the reaction with cholesterol (*I*) in order to find optimum reaction conditions under which the formation of compound *II* is accompanied with as little of side-products as possible and which would allow

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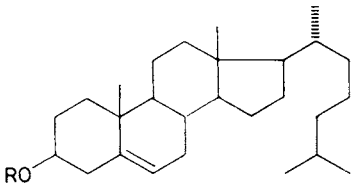
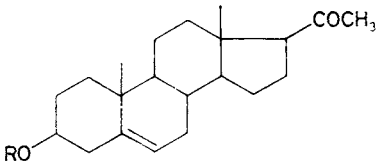
to recover (and re-use) the starting hydroxy derivative. The results are summarized in Table I.

Using benzene as organic phase, the highest yields were obtained with tetrabutylammonium hydrogen sulfate as well as Aliquat 336 (tricaprylmethylammonium chloride). Since steroid derivatives which contain additional oxygen substituents are less soluble in benzene than cholesterol, some catalysts were tested also in a benzene–acetonitrile (2 : 1) mixture as organic phase. In this case, tetrabutylammonium hydrogen sulfate gave the same yield as in benzene alone whereas the reaction catalyzed with Aliquat 336 led to a considerably lower yield. In the system chloroform (or dichloromethane)–19M aqueous sodium hydroxide the reaction afforded many side-products as evidenced by thin-layer chromatography (TLC).



I, R = H
II, R = $CH_2C{\equiv}CH$



III, R = H
IV, R = $CH_2C{\equiv}CH$

The structure of compound *II* follows from its IR spectrum which shows no hydroxyl band; the presence of the terminal triple bond is confirmed by a ≡C—H

TABLE I

Experimental conditions and yields of products in the preparation of 2-propynyl ether *II* (at room temperature)

Quaternary ammonium salt	Solvent	Yield *II*	Recovered *I*
$Bu_4N^+ HSO_4^-$	C_6H_6	32%	59%
$Bu_4N^+ HSO_4^-$	C_6H_6[a]	32%	55%
$Bu_4N^+ HSO_4^-$	C_6H_6–CH_3CN (2 : 1)	32%	59%
Aliquat 336	C_6H_6	30%	60%
Aliquat 336	C_6H_6–CH_3CN (2 : 1)	8%	85%
$Bu_4N^+ Br^-$	C_6H_6	19%	75%
$C_{16}H_{33}NMe_3^+ Br^-$	C_6H_6	14%	75%
$C_6H_5CH_2NMe_3^+ Cl^-$	C_6H_6	14%	73%

[a] Temperature + 50°C.

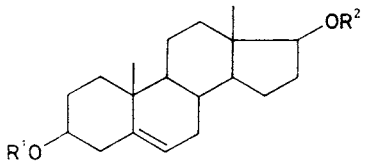
band at 3 310 cm^{-1} and a C≡C band at 2 120 cm^{-1}. The ^1H NMR spectrum exhibits characteristic C≡C—H signal as a triplet at 2·38 ppm (^4J = 2·4 Hz) and $CH_2'C{\equiv}C$ signal as a doublet at 4·18 ppm (^4J = 2·4 Hz). The multiplet at 3·33 ppm (W = 36 Hz) due to H-3 and the broad doublet at 5·34 ppm (J = 4·5 Hz) due to H-6 confirm that the compound *II* contains an unrearranged 5-cholestene skeleton with an ether substituent in position 3β. Structures of the further described steroid 2-propynyl ethers have been confirmed analogously.

Using the above-described procedure (tetrabutylammonium hydrogen sulfate, benzene–acetonitrile), we converted pregnenolone (*III*) into the 2-propynyl ether *IV*. Derivatives of 5-androstene-3β,17β-diol can afford two types of compounds: 3β-(2-propynyl) or 17β-(2-propynyl) ethers, depending on which of the hydroxyl groups in the starting diol is protected. As the starting compound for preparation of the first series we employed the derivative *VII* in which the 17β-hydroxyl was protected with the methoxymethyl (MOM) group. The preparation of *VII* started from monoacetate *V* which on reaction with chloromethyl methyl ether and N,N-diisopropylethylamine, followed by hydrolysis of the intermediate *VI*, was converted into compound *VII*. Compound *VII* was treated with propargyl bromide and the obtained 3β-(2-propynyl) ether *VIII* was deprotected to give 17β-hydroxy derivative *IX*. Oxidation of the compound *IX* with Jones reagent furnished ketone *XX* which was also prepared directly from hydroxy ketone *XIX* and propargyl bromide.

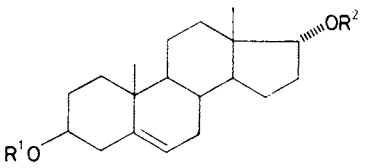
The second series of ethers was prepared starting from compounds *X* and *XII* in which the 3β-hydroxyl group was protected with the MOM or tetrahydropyranyl (THP) group. The synthesis of *X* has already been described[7], compound *XII*, with the THP protecting group in position 3β, was synthesized by a modification of its described[8] preparation from hydroxy ketone *XIX* whose reaction with dihydropyran and subsequent hydride reduction were carried out without isolation of the intermediate ketone with protected hydroxyl. On reaction with propargyl bromide, compounds *X* and *XII* were converted into the corresponding 2-propynyl ethers *XI* and *XIII*, respectively, which after deprotection in position 3 afforded 3-hydroxy derivative *XIV*. This was subjected to Oppenauer oxidation (1-methyl-4-piperidone and aluminium isopropoxide[9]) to afford unsaturated ketone *XXIII*; this ketone was also obtained by reaction of testosterone (*XXII*) with propargyl bromide.

In order to extend the series of 17-(2-propynyloxy) derivatives we also prepared compound *XVIII* with 17α-configuration, i.e. opposite to that in compound *XIV*. These derivatives were synthesized from the known[7] tosylate *XV* which on reaction with sodium nitrite in dimethyl sulfoxide[10] afforded the 17α-hydroxy derivative *XVI*. Its structure was confirmed by ^1H NMR spectrum: the H-17β signal appears as a broad doublet at 3·75 ppm (J = 5·5 Hz) which on transformation into the corresponding trichloroacetylcarbamate (prepared[11,12] in situ by reaction with trichloroacetyl isocyanate) was shifted downfield to 4·91 ppm. The structure of *XVI* was further confirmed by its oxidation with Jones reagent leading to the known[7]

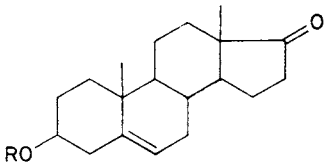
ketone *XXI*. The 2-propynyl ether *XVII* was prepared under the same conditions as the epimeric *XI*. Removal of the MOM protecting group in position 3 furnished the hydroxy derivative *XVIII*.



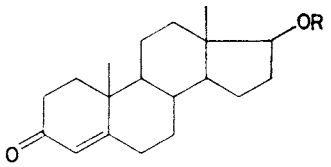
V, R^1 = Ac ; R^2 = H
VI, R^1 = Ac ; R^2 = MOM
VII, R^1 = H ; R^2 = MOM
VIII, R^1 = $CH_2C{\equiv}CH$; R^2 = MOM
IX, R^1 = $CH_2C{\equiv}CH$; R^2 = H
X, R^1 = MOM ; R^2 = H
XI, R^1 = MOM ; R^2 = $CH_2C{\equiv}CH$
XII, R^1 = THP ; R^2 = H
XIII, R^1 = THP ; R^2 = $CH_2C{\equiv}CH$
XIV, R^1 = H ; R^2 = $CH_2C{\equiv}CH$
XV, R^1 = MOM ; R^2 = Tos



XVI, R^1 = MOM ; R^2 = H
XVII, R^1 = MOM ; R^2 = $CH_2C{\equiv}CH$
XVIII, R^1 = H ; R^2 = $CH_2C{\equiv}CH$



XIX, R = H
XX, R = $CH_2C{\equiv}CH$
XXI, R = MOM

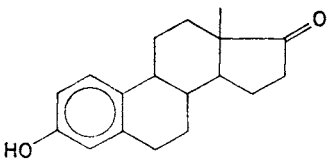


XXII, R = H
XXIII, R = $CH_2C{\equiv}CH$

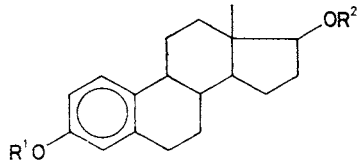
Ac = acetyl ; MOM = methoxymethyl ; Tos = *p*-toluenesulfonyl ; THP = tetrahydropyranyl

Another compound, used for the preparation of 2-propynyl ether, was estradiol. The properties of its known[1] 3-(2-propynyl) ether show that substitution in position 3 lowers markedly the estrogenic activity. For this reason we tried to prepare the isomeric 17-(2-propynyl) ether *XXVII*. As the starting compound we used 17β--hydroxy derivative *XXV*, protected in position 3 with the THP group, which was prepared from estrone (*XXIV*) analogously as the hydroxy derivative *XII* from the ketone *XIX*. The derivative *XXV* was treated with propargyl bromide and the ob-

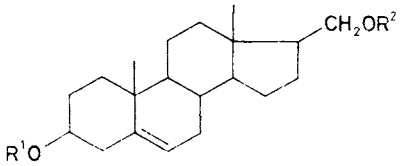
tained 2-propynyl ether *XXVI* was deprotected to give the desired derivative *XXVII*. Its structure was confirmed by analysis of the ^{1}H NMR spectrum; in addition to signals due to the 2-propynyloxy group (a doublet at 4·13 ppm (J = 2·4 Hz) and a triplet at 2·43 ppm (J = 2·4 Hz)), the spectrum contained signal of the 3-hydroxy group at 4·94 ppm.



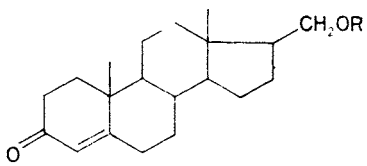
XXIV



XXV, R^1 = THP ; R^2 = H
XXVI, R^1 = THP ; R^2 = $CH_2C{\equiv}CH$
XXVII, R^1 = H ; R^2 = $CH_2C{\equiv}CH$



XXVIII, R^1 = MOM ; R^2 = H
XXIX, R^1 = MOM ; R^2 = $CH_2C{\equiv}CH$
XXX, R^1 = H ; R^2 = $CH_2C{\equiv}CH$
XXXI, R^1 = H ; R^2 = MOM



XXXII, R = MOM
XXXIII, R = H
XXXIV, R = $CH_2C{\equiv}CH$

The last series of 2-propynyl ethers, 21-norpregnan-20-ol derivatives *XXX* and *XXXIV*, was prepared with the aim to separate more the bulky carborane substituent from the 17β-position of the steroid skeleton: they thus represent homologues of compounds *XIV* and *XXIII* with methylene group inserted between C-17 and the oxygen atom of the 2-propynyloxy group. As the starting compound we chose the known[13] 20-hydroxy derivative *XXVIII* which on reaction with propargyl bromide gave 2-propynyl ether *XXIX* and further, after deprotection in position 3, the hydroxy compound *XXX*. Oppenauer oxidation (1-methyl-4-piperidone, aluminium isopropoxide[9]) converted *XXX* into the unsaturated ketone *XXXIV* which was also prepared by reaction of hydroxy derivative *XXXIII* with propargyl bromide. The seven-step synthesis of *XXXIII* from etienic acid (3β-hydroxy-21-nor-5-pregnen-20-oic acid) is described in ref.[14]. We started our synthesis from hydroxy derivative *XXXI*, available from etienic acid in three steps[15]. Oxidation[9] of *XXXI* afforded unsaturated ketone *XXXII* which on removal of the MOM protecting group gave the desired hydroxy derivative *XXXIII*, making thus its preparation one step shorter.

The above-mentioned method of preparing 2-propynyl ethers is the subject of several patent applications[16-18].

EXPERIMENTAL

Melting points were determined on a micro melting point apparatus Boetius (G.D.R.). Optical rotations were measured at 25°C on a Perkin–Elmer 141 MC polarimeter. Infrared spectra were recorded on a Perkin–Elmer 580 spectrometer (wavenumbers in cm^{-1}). ^1H NMR spectra were taken on a Tesla BS-476 instrument (CW mode, 60 MHz) or a Tesla BS-497 instrument (FT mode, 100 MHz) at 23°C in deuteriochloroform with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (J) and bandwidths (W) in Hz. All values were obtained by the first order analysis. Column chromatography was performed on silica gel (according to Pitra, 60–120 μm) or on neutral alumina (Reanal, activity II), thin-layer chromatography on silica gel G according to Stahl (Woelm). Prior to evaporation, solutions in organic solvents were dried over anhydrous sodium sulfate. Solvents were evaporated in vacuo (about 2 kPa). Analytical samples were dried over phosphorus pentoxide at 40°C/26 Pa for 12 h. Identity of samples prepared by different routes was checked by comparison of their IR and ^1H NMR spectra, thin-layer chromatography and mixture melting point determination. Propargyl bromide (Aldrich P5, 100–1) was used without further purification. 1-Methyl-4-piperidone (Koch-Light) was purified by distillation in vacuo, b.p. 59–61°C/1·87 kPa and was stored under argon.

3β-(2-Propynyloxy)-5-cholestene (*II*)

Propargyl bromide (1·07 ml, 12 mmol), a quaternary ammonium salt (specified in Table I; 2 mmol) and 19M aqueous solution of sodium hydroxide (1 ml) were added to a solution of cholesterol (*I*; 1·56 g, 4 mmol) in the solvent specified in Table I. After stirring at room temperature for 10 h, the reaction mixture was diluted with ether (100 ml) and washed with water (100 ml). The aqueous phase was extracted with ether (3 × 50 ml), the combined organic phases were washed with water and filtered through a column of silica gel (20 g) layered with anhydrous sodium sulfate. The column was washed with ether and the solvents were evaporated in vacuo. The residue was chromatographed on a column of alumina (100 g). Benzene–ether (19 : 1) eluted the product *II*, further elution with benzene–ether (1 : 1) gave the unreacted cholesterol (*I*). The yields are given in Table I. An analytical sample of *II* was obtained by crystallization from hexane–ether; m.p. 111–113°C, $[\alpha]_D$ −47° (*c* 0·3, chloroform). IR spectrum (chloroform): 3 310, 2 120 (C≡C—H); 1 668 (C=C); 1 085 (C—O—C). ^1H NMR spectrum (60 MHz): 5·34 bd, 1 H (H-6, J = 4·5); 4·18 d, 2 H ($OCH_2C{\equiv}C$, J = 2·4); 3·33 m, 1 H (H-3, W = 36); 2·38 t, 1 H (C≡C—H, J = 2·4). For $C_{30}H_{48}O$ (424·7) calculated: 84·84% C, 11·39% H; found: 84·84% C, 11·56% H.

3β-(2-Propynyloxy)-5-pregnen-20-one (*IV*)

Propargyl bromide (0·3 ml, 3·4 mmol), tetrabutylammonium hydrogen sulfate (340 mg, 1 mmol) and 19M aqueous sodium hydroxide (0·5 ml) were added to a solution of pregnenolone (*III*; 633 mg, 2 mmol) in a mixture of benzene (10 ml) and acetonitrile (5 ml). After stirring at room temperature for 10 h, the mixture was diluted with ether (100 ml) and washed with water (100 ml). The aqueous phase was extracted with ether (3 × 50 ml), the combined organic phases were washed with water and filtered through a column of silica gel (10 g) layered with anhydrous sodium sulfate. The column was washed with ether and the solvents were evaporated in vacuo.

The residue was chromatographed on a column of silica gel (50 g) in benzene–ether (95 : 5), affording 141 mg (20%) of the product *IV*. Elution with benzene–ether (2 : 1) gave 378 mg (60%) of unreacted *III*. An analytical sample of *IV* was obtained by crystallization from hexane, m.p. 108–110°C, $[\alpha]_D$ +12° (*c* 0·3, chloroform). IR spectrum (chloroform): 3 315, 2 120 (C≡C—H); 1 699 (C=O); 1 085 (C—O). ^{1}H NMR spectrum (60 MHz): 5·36 bd, 1 H (H-6, J = 4·5); 4·18 d, 2 H ($OCH_2C{\equiv}C$, J = 2·4); 3·33 m, 1 H (H-3, W = 36); 2·37 t, 1 H (C≡C—H, J = 2·4); 2·10 s, 3 H (3 × H-21); 1·00 s, 3 H (3 × H-19); 0·62 s, 3 H (3 × H-18). For $C_{24}H_{34}O_2$ (354·5) calculated: 81·31% C, 9·67% H; found: 81·06% C, 9·93% H.

17β-Methoxymethoxy-5-androsten-3β-ol 3-Acetate (*VI*)

Chloromethyl methyl ether (8·8 ml, 116 mmol) was added dropwise at 0°C to a stirred and cooled solution of 5-androstene-3β,17β-diol 3-acetate (*V*; 20·0 g, 60 mmol) and N,N-diisopropylethylamine (30 ml, 172 mmol) in dichloromethane (250 ml). After stirring at room temperature for 17 h, the mixture was diluted with ether (500 ml), washed successively with saturated aqueous sodium chloride solution, dilute hydrochloric acid (1 : 4), water, saturated solution of potassium hydrogen carbonate, and water. Removal of the solvents in vacuo afforded 22·0 g (97%) of the product *VI* which was used in the next reaction step. An analytical sample was obtained by crystallization from acetone–water; m.p. 96–99°C, $[\alpha]_D$ −67° (*c* 0·3, chloroform). IR spectrum (tetrachloromethane): 3 030, 1 670 (C=C—H); 1 735, 1 244 (AcO); 1 150, 1 104, 1 049, 918 (OCH_2OCH_3). ^{1}H NMR spectrum (60 MHz): 5·37 bd, 1 H (H-6, J = 4·5); 4·63 s, 2 H (OCH_2O); 3·34 s, 3 H (OCH_3); 2·01 s, 3 H ($OOCCH_3$); 1·02 s, 3 H (3 × H-19); 0·78 s, 3 H (3 × H-18). For $C_{23}H_{36}O_4$ (376·5) calculated: 73·37% C, 9·64% H; found: 73·54% C, 9·49% H.

17β-Methoxymethoxy-5-androsten-3β-ol (*VII*)

A solution of potassium hydroxide (4·0 g, 71 mmol) in water (5 ml) and methanol (15 ml) was added to a solution of *VI* (21·5 g, 57 mmol) in dioxane (60 ml) and methanol (60 ml). After reflux for 15 min, the reaction mixture was diluted with a methanol–water mixture (1 : 2, 50 ml) and set aside in a refrigerator overnight. The separated material was collected, washed with methanol–water (1 : 2, 300 ml) and dried at +60°C, affording 18·0 g (94%) of *VII* which was used in the next reaction step. An analytical sample was obtained by crystallization from acetone–water; m.p. 124–125°C, $[\alpha]_D$ −69° (*c* 0·3, chloroform). IR spectrum (tetrachloromethane): 3 620, 3 350 (OH); 3 030, 1 680 (C=C—H); 1 150, 1 104, 1 048, 918 (OCH_2OCH_3). ^{1}H NMR spectrum (60 MHz): 5·33 bd, 1 H (H-6, J = 4·5); 4·61 s, 2 H (OCH_2O); 3·35 s, 3 H (OCH_3); 1·01 s, 3 H (3 × H-19); 0·79 s, 3 H (3 × H-18). For $C_{21}H_{34}O_3$ (334·5) calculated: 75·41% C, 10·25% H; found: 75·67% C, 10·30% H.

17β-Methoxymethoxy-3β-(2-propynyloxy)-5-androstene (*VIII*)

Propargyl bromide (1·7 ml, 12 mmol), tetrabutylammonium hydrogen sulfate (1·25 g, 3·7 mmol) and 19M aqueous sodium hydroxide (2 ml) were added to a solution of *VII* (2·27 g, 6·8 mmol) in a mixture of benzene (30 ml) and acetonitrile (15 ml). After stirring at room temperature for 10 h, the reaction mixture was diluted with ether (100 ml) and washed with water (100 ml). The aqueous phase was extracted with ether (3 × 50 ml), the combined organic phases were washed with water and filtered through a column of silica gel (20 g) layered with anhydrous sodium sulfate. The column was washed with ether and the solvents were evaporated in vacuo. The residue was chromatographed on a column of alumina (100 g) in light petroleum–benzene–ether (49 : 49 : 2), affording 818 mg (32%) of the product *VIII*. Light petroleum–benzene–ether (45 : 45 : 10) eluted

successively some impurities and then the unreacted hydroxy derivative *VII* (1·40 g, 62%). An analytical sample of *VIII* was obtained by crystallization from hexane–ether; m.p. 98–100°C, $[\alpha]_D$ −67° (*c* 0·2, chloroform). IR spectrum (tetrachloromethane): 3 315, 2 120 (C≡C—H); 1 669 (C=C); 1 150, 1 093, 1 050, 919 (OCH_2OCH_3). ^{1}H NMR spectrum (60 MHz): 5·35 bd, 1 H (H-6, *J* = 4·5); 4·63 s, 2 H (OCH_2O); 4·15 d, 2 H ($OCH_2C{\equiv}C$, *J* = 2·4); 3·33 s, 3 H (OCH_3); 2·37 t, 1 H (C≡C—H, *J* = 2·4); 1·00 s, 3 H (3 × H-19); 0·78 s, 3 H (3 × H-18). For $C_{24}H_{36}O_3$ (372·6) calculated: 77·38% C, 9·74% H; found: 77·56% C, 9·83% H.

3β-(2-Propynyloxy)-5-androsten-17β-ol (*IX*)

p-Toluenesulfonic acid monohydrate (810 mg, 4·3 mmol) was added to a solution of *VIII* (800 mg; 2·1 mmol) in a mixture of benzene (30 ml) and methanol (30 ml). After stirring at +45°C for 10 h, the solvents were evaporated in vacuo and the residue was partitioned between water and ether. The aqueous phase was extracted with ether (3×) and the combined organic phases were washed with saturated aqueous potassium hydrogen carbonate (2×) and water. The residue was chromatographed on a column of silica gel (60 g) in benzene–ether (9 : 1), affording 689 mg (98%) of the product *IX*, m.p. 135–137°C (hexane–ether), $[\alpha]_D$ −65° (*c* 0·2, chloroform). IR spectrum (chloroform): 3 615, 3 460 (OH); 3 310, 2 120 (C≡C—H); 1 669 (C=C); 1 083, 1 049 (C—O). ^{1}H NMR spectrum (60 MHz); 5·35 bd, 1 H (H-6, *J* = 4·5); 4·17 d, 2 H ($OCH_2C{\equiv}C$, *J* = 2·4); 2·37 t, 1 H (C≡C—H, *J* = 2·4); 1·00 s, 3 H (3 ≡ H-19); 0·75 s, 3 H (3 × H-18). ^{1}H NMR spectrum after addition of trichloroacetyl isocyanate (60 MHz): 8·34 bs, 1 H ($Cl_3CCONHCOO$); 5·34 bt, 1 H (H-6, *J* = 4·5); 4·71 bt, 1 H (H-17, *J* = 8·5); 4·17 d, 2 H ($OCH_2C{\equiv}C$, *J* = 2·5); 3·32 m, 1 H (H-3, *W* = 36); 2·39 t, 1 H (C≡C—H), *J* = 2·5); 1·02 s, 3 H (3 × H-19); 0·87 s, 3 H (3 × H-18). For $C_{22}H_{32}O_2$ (328·5) calculated: 80·44% C, 9·82% H; found: 80·65% C, 9·97% H.

3β-Methoxymethoxy-17β-(2-propynyloxy)-5-androstene (*XI*)

Propargyl bromide (0·3 ml, 3·4 mmol), tetrabutylammonium hydrogen sulfate (340 mg, 1 mmol) and 19M aqueous sodium hydroxide (0·5 ml) were added to a solution of *X* (ref.[7]; 669 mg, 2 mmol) in a mixture of benzene (10 ml) and acetonitrile (5 ml). After stirring at room temperature for 10 h, the reaction mixture was diluted with ether (100 ml) and washed with water (100 ml). The aqueous phase was extracted with ether (3 × 50 ml), the combined organic phases were washed with water and filtered through a column of silica gel (10 g) layered with anhydrous sodium sulfate. The column was washed with ether and the solvents were evaporated in vacuo. The residue was chromatographed on a column of silica gel (50 g). Elution with benzene–ether (95 : 5) gave 121 mg (16%) of the product *XI*, further elution with benzene–ether (2 : 1) furnished 408 mg (61%) of unreacted *X*. An analytical sample of *XI* was obtained by crystallization from hexane; m.p. 74–77°C, $[\alpha]_D$ −51° (*c* 0·3, chloroform). IR spectrum (chloroform): 3 315, 2 120 (C≡C—H); 1 668 (C=C); 1 146, 1 100, 1 040, 913 (OCH_2OCH_3); 1 087 (C—O). ^{1}H NMR spectrum (60 MHz): 5·34 bd, 1 H (H-6, *J* = 4·5); 4·67 s, 2 H (OCH_2O); 4·15 d, 2 H ($OCH_2C{\equiv}C$, *J* = 2·4); 3·33 s, 3 H (OCH_3); 2·37 t, 1 H (C≡C—H, *J* = 2·4); 1·01 s, 3 H (3 × H-19); 0·78 s, 3 H (3 × H-18). For $C_{24}H_{36}O_3$ (372·6) calculated: 77·38% C, 9·74% H; found: 77·52% C, 9·94% H.

3β-(2-Tetrahydropyranyloxy)-5-androsten-17β-ol (*XII*)

Dihydropyran (10 ml, 110 mmol) was added dropwise to a mixture of 3β-hydroxy-5-androsten-17-one (*XIX*; 9·15 g, 32 mmol), *p*-toluenesulfonic acid monohydrate (57 mg, 0·3 mmol) and benzene (200 ml). The mixture was stirred at room temperature for 3·5 h and 3·5M solution of bis(2-methoxyethoxy)aluminium hydride in benzene (20 ml) was added. After refluxing under

argon with stirring for 1 h, the mixture was cooled to room temperature and the excess hydride was decomposed with moist ether and then with water. After dilution with ether (300 ml), the organic phase was separated, washed with water and taken down. The residue was chromatographed on a column of alumina (500 g) in benzene–ether (9 : 1), affording 11·9 g (91%) of the product *XII* which was used directly in the next reaction step. An analytical sample was obtained by crystallization from ethanol; m.p. 161–162°C, $[\alpha]_D$ −45° (*c* 1·9, chloroform) (reported[8] m.p. 161–162°C).

17β-(2-Propynyloxy)-3β-(2-tetrahydropyranyloxy)-5-androstene (*XIII*)

Propargyl bromide (0·89 ml, 10 mmol), tetrabutylammonium hydrogen sulfate (0·97 g, 2·86 mmol) and 19M aqueous sodium hydroxide (2 ml) were added to a solution of *XII* (2·03 g, 5·4 mmol) in a mixture of benzene (25 ml) and acetonitrile (12·5 ml). After stirring at room temperature for 10 h, the reaction mixture was diluted with ether (200 ml) and washed with water (100 ml). The aqueous phase was extracted with ether (3 × 50 ml), the combined organic phases were washed with water and filtered through a column of silica gel (20 g) layered with anhydrous sodium sulfate. The column was washed with ether and the solvents were evaporated in vacuo. The residue was chromatographed on a column of silica gel (200 g; treated with ammonia vapours for 24 h) in light petroleum–benzene–ether (49 : 49 : 2) to give 488 mg (22%) of the product *XIII*. Further elution with light petroleum–benzene–ether (2 : 2 : 1) afforded 1·33 g (66%) of unreacted *XII*. An analytical sample of *XIII* was obtained by crystallization from hexane–ether; m.p. 114–116°C, $[\alpha]_D$ −59° (*c* 0·3, chloroform). IR spectrum (tetrachloromethane): 3 315, 2 120 (C≡C—H); 1 668 (C=C); 1 134, 1 094, 1 033 (C—O). ^{1}H NMR spectrum (60 MHz): 5·35 bd, 1 H (H-6, J = 4·5); 4·70 bs, 1 H (H-2′ of tetrahydropyranyloxy group); 4·02 d, 2 H ($OCH_2C{\equiv}C$, J = 2·4); 2·72 t, 1 H (C≡C—H, J = 2·4); 1·02 s, 3 H (3 × H-19); 0·79 s, 3 H (3 × H-18). For $C_{27}H_{40}O_3$ (412·6) calculated: 78·60% C, 9·77% H; found: 78·81% C, 9·85% H.

17β-(2-Propynyloxy)-5-androsten-3β-ol (*XIV*)

A) *p*-Toluenesulfonic acid monohydrate (380 mg, 2 mmol) was added to a solution of *XIII* (380 mg, 0·92 mmol) in a mixture of benzene (10 ml) and methanol (10 ml). After stirring at +45°C for 10 h, the solvents were evaporated in vacuo and the residue was dissolved in water and ether. The aqueous phase was extracted with ether and the combined ethereal phases were washed with saturated aqueous potassium hydrogen carbonate solution and water. Chromatography of the residue on a column of silica gel (35 g) in benzene–ether (9 : 1) gave 293 mg (97%) of the product *XIV*; m.p. 132–134°C (hexane–ether), $[\alpha]_D$ −75°, (*c* 0·3, chloroform). IR spectrum (chloroform): 3 620, 3 440 (OH); 3 310, 2 115 (C≡C—H); 1 668 C=C); 1 086, 1 044 (C—O). ^{1}H NMR spectrum (60 MHz): 5·34 bd, 1 H (H-6, J = 4·5); 4·15 d, 2 H ($OCH_2C{\equiv}C$, J = 2·3); 3·53 m, 2 H (H-3 and H-17); 2·37 m, 1 H (C≡C—H); 1·00 s, 3 H (3 × H-19); 0·78 s; 3 H (3 × H-18). ^{1}H NMR spectrum after addition of trichloroacetyl isocyanate (60 MHz): 8·31 bs, 1 H ($Cl_3CCONHCOO$); 5·39 bd, 1 H (H-6, J = 4·5); 4·61 m, 1 H (H-3, W = 36); 4·12 d, 2 H ($OCH_2C{\equiv}C$, J = 2·4); 3·55 bt, 1 H (H-17, J = 8); 2·38 t, 1 H (C≡C—H, J = 2·4); 1·02 s, 3 H (3 × H-19); 0·78 s, 3 H (3 × H-18). For $C_{22}H_{32}O_2$ (328·5) calculated: 80·44% C, 9·82% H; found: 80·63% C, 9·99% H.

B) *p*-Toluenesulfonic acid monohydrate (72 mg, 0·38 mmol) was added to a solution of *XI* (70 mg, 0·19 mmol) in a mixture of benzene (4 ml) and methanol (4 ml). After stirring at +45°C for 10 h, the solvents were evaporated in vacuo and the residue was dissolved in ether (10 ml) and filtered through a column of alumina (5 g). The column was washed with ether and the

solvent was evaporated in vacuo. Crystallization from hexane–ether afforded 45 mg (73%) of the product, m.p. 131—133°C, identical with the compound prepared under *A*).

3β-Methoxymethoxy-5-androsten-17α-ol (*XVI*)

Sodium nitrite (7·5 g, 109 mmol) was added to a solution of *XV* (ref.[7]; 2·5 g, 5·1 mmol) in dimethyl sulfoxide (75 ml) and the mixture was stirred at 130°C for 26 h. After cooling, it was poured into ether (500 ml) and the organic phase was washed with saturated solution of ammonium sulfate (2×) and water (3×). The solvent was evaporated and the residue chromatographed on a column of silica gel (100 g). Elution with light petroleum–ether (9 : 1) removed non-polar side-products, elution with light petroleum–ether (8 : 2) afforded 725 mg (42%) of the product *XVI*, m.p. 114—116°C (hexane-ether), $[\alpha]_D$ −72° (*c* 0·3, chloroform). IR spectrum (chloroform): 3 615, 3 470 (OH); 1 680 (C=C); 1 148, 1 103, 1 043, 913 (OCH_2OCH_3). ^{1}H NMR spectrum (60 MHz): 5·38 bd, 1 H (H-6, J = 4·5); 4·67 s, 2 H (OCH_2O); 3·75 bd, 1 H (H-17, J = 5·5); 3·37 s, 3 H (OCH_3); 1·02 s, 3 H (3 × H-19); 0·68 s, 3 H (3 × H-18). ^{1}H NMR spectrum after addition of trichloroacetyl isocyanate (60 MHz): 8·36 bs, 1 H ($Cl_3CCONHCOO$); 5·35 m, 1 H (H-6); 4·91 bd, 1 H (H-17, J = 6); 4·67 s, 2 H (OCH_2O); 3·33 s, 3 H (OCH_3); 1·01 s, 3 H (3 × H-19); 0·79 s, 3 H (3 × H-18). For $C_{21}H_{34}O_3$ (334·5) calculated: 75·41% C, 10·25% H; found: 75·57% C, 10·42% H.

3β-Methoxymethoxy-17α-(2-propynyloxy)-5-androstene (*XVII*)

Propargyl bromide (0·66 ml, 7·4 mmol), tetrabutylammonium hydrogen sulfate (420 mg, 1·2 mmol) and 19M aqueous sodium hydroxide (1·5 ml) were added to a solution of *XVI* (836 mg, 2·5 mmol) in a mixture of benzene (15 ml) and acetonitrile (10 ml). After stirring at room temperature for 10 h, the mixture was diluted with ether (50 ml) and washed with water (50 ml). The aqueous phase was extracted with ether (3 × 50 ml), the combined organic phases were washed with water and filtered through a column of silica gel (10 g) layered with anhydrous sodium sulfate. The column was washed with ether and the solvents were evaporated in vacuo. The residue was chromatographed on a column of silica gel (100 g) and the product *XVII* (169 mg, 18%) was eluted with light petroleum–benzene–ether (49 : 49 : 2). Further elution with light petroleum–benzene–ether (4 : 4 : 2) afforded 650 mg (78%) of the unreacted *XVI*. An analytical sample of *XVII* was obtained by crystallization from hexane–ether; m.p. 101—104°C, $[\alpha]_D$ −72° (*c* 0·3, chloroform). IR spectrum (tetrachloromethane): 3 315, 2 115 (C≡C—H); 3 030 1 668 (C=C—H); 1 149, 1 106, 1 045, 918 (OCH_2OCH_3). ^{1}H NMR spectrum (100 MHz): 5·38 bd, 1 H (H-6, J = 4·5); 4·69 s, 2H (OCH_2O); 4·07 d, 2 H ($OCH_2C{\equiv}C$, J = 2·4); 3·50 bd, 1 H (H-17, J = 6); 3·37 s, 3 H (OCH_3); 2·35 t, 1 H (C≡C—H, J = 2·4); 1·00 s, 3 H (3 × H-19); 0·70 s, 3 H (3 × H-18). For $C_{24}H_{36}O_3$ (372·6) calculated: 77·38% C, 9·74% H; found: 77·51% C, 9·87% H.

17α-(2-Propynyloxy)-5-androsten-3β-ol (*XVIII*)

p-Toluenesulfonic acid monohydrate (300 mg, 1·58 mmol) was added to a solution of *XVII* (285 mg, 0·76 mmol) in a mixture of benzene (8 ml) and methanol (8 ml). After stirring at +45°C for 10 h, the solvents were evaporated in vacuo and the residue was partitioned between water and ether. The aqueous phase was extracted with ether and the combined ethereal phases were washed with saturated aqueous solution of potassium hydrogen carbonate and water. After removal of the solvent, the residue was chromatographed on a column of silica gel (30 g) in benzene–ether (9 : 1) to give 240 mg (96%) of the product *XVIII*, m.p. 126—128°C (hexane–ether), $[\alpha]_D$ −86° (*c* 0·3, chloroform). IR spectrum (chloroform): 3 625 (OH); 3 315, 2 115 (C≡C—H); 3 030, 1 668 (C=C—H); 1 083, 1 050 (C—O). ^{1}H NMR spectrum (100 MHz): 5·35 bd, 1 H

(H-6, $J = 4{\cdot}5$); 4·07 d, 2 H ($OCH_2C{\equiv}C$, $J = 2{\cdot}5$); 3·48 m, 2 H (H-3 and H-17); 2·37 t, 1 H (C≡C—H, $J = 2{\cdot}5$); 1·01 s, 3 H (3 × H-19); 0·70 s, 3 H (3 × H-18). ^{1}H NMR spectrum after addition of trichloroacetyl isocyanate (100 MHz): 8·33 bs, 1 H ($CH_3CCONHCOO$); 5·41 bd, 1 H (H-6, $J = 4{\cdot}5$); 4·68 m, 1 H (H-3, $W = 36$); 4·09 d, 2 H ($OCH_2C{\equiv}C$, $J = 2{\cdot}5$); 3·51 bd, 1 H (H-17, $J = 6$); 2·37 t, 1 H (C≡C—H, $J = 2{\cdot}5$); 1·03 s, 3 H (3 × H-19); 0·71 s, 3 H (3 × H-18). For $C_{22}H_{32}O_2$ (328·5) calculated: 80·44% C, 9·82% H; found: 80·64% C, 9·87% H.

3β-(2-Propynyloxy)-5-androsten-17-one (*XX*)

A) Propargyl bromide (5·4 ml, 60 mmol), tetrabutylammonium hydrogen sulfate (3·54 g, 10·4 mmol) and 19M aqueous solution of sodium hydroxide (5 ml) were added to a solution of 3β-hydroxy-5-androsten-17-one (*XIX*; 5·92 g, 20·5 mmol) in a mixture of benzene (100 ml) and acetonitrile (50 ml). After stirring at room temperature for 10 h, the mixture was diluted with ether (500 ml) and washed with water. The aqueous phase was extracted with ether, the combined organic phases were washed with water and filtered through a column of silica gel (50 g) layered with anhydrous sodium sulfate. The column was washed with ether and the solvents were evaporated in vacuo. The residue was chromatographed on a column of alumina (350 g) in benzene–ether (19 : 1) to give 1·56 g (23%) of the product *XX*. Elution with benzene–ether (9 : 1) afforded 4·2 g (71%) of unreacted *XIX*. An analytical sample of *XX* was obtained by crystallization from hexane–ether; m.p. 143—145°C, $[\alpha]_D$ −9° (*c* 0·3, chloroform). IR spectrum (chloroform): 3 310, 2 120 (C≡C—H); 1 734 (C=O); 1 668 (C=C); 1 085 (C—O). ^{1}H NMR spectrum (60 MHz): 5·37 bd, 1 H (H-6, $J = 4{\cdot}5$); 4·18 d, 2 H ($OCH_2C{\equiv}C$, $J = 2{\cdot}4$); 3·32 m, 1 H (H-3, $W = 36$); 2·35 t, 1 H (C≡C—H, $J = 2{\cdot}4$); 1·02 s, 3 H (3 × H-19); 0·88 s, 3 H (3 × H-18). For $C_{22}H_{30}O_2$ (326·5) calculated: 80·94% C, 9·26% H; found: 80·84% C, 9·59% H.

B) Jones reagent was added dropwise in excess to a stirred solution of *IX* (150 mg, 0·46 mmol) in acetone (10 ml). After stirring at room temperature for 5 min, the excess reagent was destroyed with sodium sulfite, the reaction mixture was partitioned between ether and water and the aqueous phase was extracted with ether. The combined organic phases were washed successively with saturated aqueous solution of potassium hydrogen carbonate, saturated aqueous ammonium sulfate and water. Preparative TLC on silica gel (200 × 200 × 0·7 mm plate) in benzene–ether (19 : 1) afforded 115 mg (77%) of the product *XX*, m.p. 145—147°C (hexane–ether), identical with the compound prepared under *A*).

3β-Methoxymethoxy-5-androsten-17-one (*XXI*)

Jones reagent was added dropwise in an excess to a stirred solution of *XVI* (50 mg, 0·15 mmol) in acetone (3·5 ml). After stirring at room temperature for 5 min, the excess reagent was destroyed with sodium sulfite, the reaction mixture was diluted with ether (50 ml), washed with saturated aqueous solution of potassium hydrogen carbonate and saturated aqueous solution of ammonium sulfate and taken down. Crystallization from hexane–ether afforded 35 mg (70%) of the product *XXI*, m.p. 123—125°C, identical with an authentic sample[7].

17β-(2-Propynyloxy)-4-androsten-3-one (*XXIII*)

A) 1-Methyl-4-piperidone (1·5 ml, 12·2 mmol) was added under argon to a solution of *XIV* (609 mg, 1·85 mmol) in toluene (50 ml). A part (3 ml) of the toluene was distilled off and 1M aluminium isopropoxide in toluene (2·5 ml) was added. After refluxing under argon for 9 h, the mixture was cooled, diluted with ether (200 ml) and successively washed with dilute hydrochloric acid (1 : 4), water, saturated aqueous solution of potassium hydrogen carbonate and with water.

After evaporation of the solvent, the residue was chromatographed on a column of silica gel (50 g) in light petroleum–benzene–ether (20 : 20 : 1) to afford 354 mg (58%) of the product *XXIII*, m.p. 97–98°C (hexane–ether), $[\alpha]_D$ +60° (*c* 0·1, chloroform). IR spectrum (tetrachloromethane): 3 315, 2 120 (C≡C—H); 1 677, 1 620 (C=C—C=O). ^{1}H NMR spectrum (60 MHz): 5·72 bs, 1 H (H-4); 4·15 d, 2 H ($OCH_2C{\equiv}C$, *J* = 2·4); 3·53 bt, 1 H (H-17, *J* = 8); 1·17 s, 3 H (3 × H-19); 0·80 s, 3 H (3 × H-18). For $C_{22}H_{30}O_2$ (326·5) calculated: 80·94% C, 9·26% H; found: 81·03% C, 9·41% H.

B) Propargyl bromide (0·27 ml, 3 mmol), tetrabutylammonium hydrogen sulfate (170 mg, 0·5 mmol) and 19M aqueous sodium hydroxide solution (0·5 ml) were added to a solution of testosterone (*XXII*; 288 mg, 1 mmol) in a mixture of benzene (5 ml) and acetonitrile (3 ml). After stirring at room temperature for 10 h, the reaction mixture was diluted with ether (50 ml) and washed with water (50 ml). The aqueous phase was extracted with ether (3 × 20 ml), the combined organic phases were washed with water and filtered through a column of silica gel (5 g) layered with anhydrous sodium sulfate. The column was washed with ether and the solvents were evaporated in vacuo. The residue was chromatographed on a column of silica gel (30 g) in light petroleum–benzene–ether (10 : 20 : 1) to give 65 mg of the crude product *XXIII*. Further elution with light petroleum–benzene–ether (10 : 20 : 3) afforded 195 mg (68%) of unreacted testosterone (*XXII*). The product *XXIII* was further purified by preparative TLC (200 × 200 × 0·7 mm plate) in benzene–ether (9 : 1); yield 53 mg (16%) of pure *XXIII*, m.p. 95–97°C, identical with the compound prepared under *A*).

3-(2-Tetrahydropyranyloxy)-1,3,5(10)estratrien-17β-ol (*XXV*)

Dihydropyran (1·3 ml, 14·3 mmol) was added dropwise to a mixture of estrone (*XXIV*; 1·10 g, 4·1 mmol), *p*-toluenesulfonic acid monohydrate (8 mg, 0·04 mmol) and benzene (25 ml). After stirring at room temperature for 3 h, 3·5M solution of bis(2-methoxyethoxy)aluminium hydride in benzene (2·5 ml) was added and the stirred mixture was refluxed under argon for 2 h. After cooling to room temperature, the excess hydride was destroyed with moist ether and water, the mixture was diluted with ether (250 ml) and the organic phase was separated and washed with water. The solvent was evaporated and the residue was chromatographed on a column of alumina (100 g) in light petroleum–benzene–ether (10 : 10 : 1) to give 1·08 g (74%) of the product *XXV*, m.p. 134–144°C (reported[19] m.p. 142–148°C). IR spectrum (chloroform): 3 615, 3 460 (OH); 1 606, 1 575, 1 497 (aromatic system). ^{1}H NMR spectrum (100 MHz): 7·26 m and 6·82 m, 3 H (H-1, H-2 and H-4); 5·38 bs, 1 H (H-2′, tetrahydropyranyl group); 0·77 s, 3 H (3 × H-18). ^{1}H NMR spectrum after addition of trichloroacetyl isocyanate (100 MHz): 8·39 bs, 1 H ($Cl_3CCONHCOO$); 7·24 m and 6·82 m, 3 H (H-1, H-2 and H-4); 5·38 bs, 1 H (H-2′,tetrahydropyranyl group): 4·79 bt, 1 H (H-17, *J* = 8); 0·98 s, 3 H (3 × H-18).

17β-(2-Propynyloxy)-3-(2-tetrahydropyranyloxy)-1,3,5(10)estratriene (*XXVI*)

Propargyl bromide (0·75 ml, 8·4 mmol), tetrabutylammonium hydrogen sulfate (490 mg, 1·4 mmol) and 19M aqueous sodium hydroxide solution (2·5 ml) were added to a solution of *XXV* (980 mg, 2·8 mmol) in a mixture of benzene (15 ml) and acetonitrile (10 ml). After stirring at room temperature for 12 h, the reaction mixture was diluted with ether (100 ml) and washed with water (100 ml). The aqueous phase was extracted with ether (3 × 50 ml), the combined organic phases were washed with water and filtered through a column of silica gel (20 g) layered with anhydrous sodium sulfate. The column was washed with ether and the solvents were evaporated in vacuo. The residue was chromatographed on a column of alumina (110 g). Light petroleum–benzene–ether (49 : 49 : 2) eluted 345 mg (32%) of the product *XXVI*. Further elution with

light petroleum–benzene–ether (1 : 1 : 1) afforded 627 mg (64%) of unreacted *XXV*. The oily product *XXVI* was used without further purification in the next reaction step. IR spectrum (tetrachloromethane): 3 315, 2 115 (C≡C—H); 1 608, 1 575, 1 499 (aromatic system). ^{1}H NMR spectrum (60 MHz): 7·23 m and 6·85 m, 3 H (H-1, H-2 and H-4); 5·38 bs, 1 H (H-2′, tetrahydropyranyl group); 4·17 d, 2 H ($OCH_2C\equiv C$, J = 2·2); 2·40 t, 1 H (C≡C—H, J = 2·2); 0·79 s, 3 H (3 × H-18).

17β-(2-Propynyloxy)-1,3,5(10)estratrien-3-ol (*XXVII*)

p-Toluenesulfonic acid monohydrate (192 mg, 1 mmol) was added to a solution of crude *XXVI* (310 mg, 0·88 mmol) in a mixture of benzene (10 ml) and methanol (10 ml). After stirring at +45°C for 10 h, the solvents were evaporated in vacuo and the residue was partitioned between water and ether. The aqueous phase was extracted with ether and the combined ethereal phases were washed with saturated aqueous solution of potassium hydrogen carbonate and water. Chromatography on a column of alumina (40 g) in light petroleum–benzene–ether (7 : 7 : 6) afforded 157 mg (63%) of the product *XXVII*, m.p. 132—133°C (hexane–ether), $[\alpha]_D$ +44° (*c* 1·0, chloroform). IR spectrum (chloroform): 3 595, 3 370 (OH); 3 310, 2 115 (C≡C—H); 1 610, 1 585, 1 500 (aromatic system); 1 088 (C—O). ^{1}H NMR spectrum (60 MHz): 7·11 m) and 6·59 m, 3 H (H-1, H-2 and H-4); 4·94 s, 1 H (O—H); 4·13 d, 2 H ($OCH_2C\equiv C$, J = 2·2 d; 2·43 t, 1 H (C≡C—H, J = 2·2); 0·82 s, 3 H (3 × H-18). For $C_{21}H_{26}O_2$ (310·4) calculated: 81·25% C, 8·44% H; found: 81·35% C, 8·74% H.

3β-Methoxymethoxy-20-(2-propynyloxy)-21-nor-5-pregnene (*XXIX*)

Propargyl bromide (4·6 ml, 52 mmol), tetrabutylammonium hydrogen sulfate (3·25 g, 9·6 mmol) and 19M aqueous sodium hydroxide solution (8 ml) were added to a solution of *XXVIII* (ref.[13]; 6·20 g, 17·8 mmol) in a mixture of benzene (60 ml) and acetonitrile (40 ml). After stirring at room temperature for 10 h, the reaction mixture was diluted with ether (500 ml) and washed with water (300 ml). The aqueous phase was extracted with ether (3 × 200 ml) and the combined organic phases were washed with water and filtered through a column of silica gel (50 g) layered with anhydrous sodium sulfate. The column was washed with ether and the solvents were evaporated in vacuo. Chromatography on a column of alumina (200 g) in light petroleum–benzene–ether (9 : 9 : 1) afforded 2·2 g (32%) of the product *XXIX*. Further elution with light petroleum–benzene–ether (1 : 1 : 1) gave 3·79 g (61%) of unreacted *XXVIII*. An analytical sample of *XXIX* was obtained by crystallization from hexane–ether; m.p. 68—69°C, $[\alpha]_D$ −41° (*c* 0·3, chloroform). IR spectrum (tetrachloromethane): 3 315, 2 120 (C≡C—H); 1 669 (C=C); 1 150, 1 106, 1 042, 917 (OCH_2OCH_3). ^{1}H NMR spectrum (60 MHz): 5·34 bd, 1 H (H-6, J = 4·5); 4·67 s, 2 H (OCH_2O); 4·11 d, 2 H ($OCH_2C\equiv C$, J = 2·5); 3·36 s, 3 H (OCH_3); 2·37 t, 1 H (C≡C—H, J = 2·5); 1·01 s, 3 H (3 × H-19); 0·65 s, 3 H (3 × H-18). For $C_{25}H_{38}O_3$ (386·6) calculated: 77·68% C, 9·11% H; found: 77·79% C, 9·28% H.

20-(2-Propynyloxy)-21-nor-5-pregnen-3β-ol (*XXX*)

p-Toluenesulfonic acid monohydrate (3·41 g, 18 mmol) was added to a solution of *XXIX* (3·52 g, 9·1 mmol) in a mixture of benzene (85 ml) and methanol (85 ml). After stirring at +45°C for 10 h, the solvents were evaporated in vacuo and the residue was partitioned between water and ether. The aqueous phase was extracted with ether and the combined ethereal phases were washed with saturated aqueous solution of potassium hydrogen carbonate and water. Removal of the solvents in vacuo afforded 3·0 g (97%) of the product *XXX*, m.p. 137—139°C (hexane–ether), $[\alpha]_D$ −48° (*c* 0·2, chloroform). IR spectrum (tetrachloromethane): 3 615, 3 440 (OH);

3 315, 2 115 (C≡C—H); 1 668 (C=C); 1 086, 1 047 (C—O). ^{1}H NMR spectrum (100 MHz): 5·38 bd, 1 H (H-6, J = 4·5); 4·11 d, 2 H ($OCH_2C{\equiv}C$, J = 2·5); 3·48 m, 3 H (H-3 and 2 × H-20); 2·39 t, 1 H (C≡C—H, J = 2·5); 1·01 s, 3 H (3 × H-19); 0·65 s, 3 H (3 × H-18). ^{1}H NMR spectrum after addition of trichloroacetyl isocyanate (100 MHz): 8·34 bs, 1 H ($Cl_3COONHCOO$); 5·42 bd, 1 H (H-6, J = 4·5); 4·69 m, 1 H (H-3, W = 36); 4·11 d, 2 H ($OCH_2C{\equiv}C$, J = 2·5); 3·51 m, 2 H (2 × H-20); 2·41 t, 1 H (C≡C—H, J = 2·5); 1·04 s, 3 H (3 × H-19); 0·67 s, 3 H (3 × H-18). For $C_{23}H_{34}O_2$ (342·5) calculated: 80·65% C, 10·01% H; found: 80·78% C, 10·11% H.

20-Methoxymethoxy-21-nor-4-pregnen-3-one (*XXXII*)

1-Methyl-4-piperidone (4 ml, 32·5 mmol) was added under argon to a solution of *XXXI* (ref.[15]; 2·0 g, 5·7 mmol) in toluene (80 ml). A part (10 ml) of the toluene was distilled off and 1M aluminium isopropoxide in toluene (5 ml) was added. After refluxing under argon for 6 h, the reaction mixture was cooled, diluted with ether (400 ml) and washed successively with dilute hydrochloric acid (1 : 4), water, saturated aqueous potassium hydrogen carbonate solution, and water. The solvents were evaporated and the residue was chromatographed on a silica gel column (150 g) in light petroleum–benzene–ether (45 : 45 : 10) to give 1·48 g (74%) of *XXXII*, m.p. 106—109°C (hexane–ether), $[\alpha]_D$ +99° (*c* 0·3, chloroform). IR spectrum (tetrachloromethane): 1 677, 1 619 (C=C—C=O); 1 147, 1 110, 1 046, 929 (OCH_2OCH_3). ^{1}H NMR spectrum (100 MHz): 5·72 bs, 1 H (H-4); 4·60 s, 2 H (OCH_2O); 3·50 m, 2 H (2 × H-20); 3·36 s, 3 H (OCH_3); 1·19 s, 3 H (3 × H-19); 0·69 s, 3 H (3 × H-18). For $C_{22}H_{34}O_4$ (346·5) calculated: 76·26% C, 9·89% H; found: 76·58% C, 9·96% H.

20-Hydroxy-21-nor-4-pregnen-3-one (*XXXIII*)

p-Toluenesulfonic acid monohydrate (1·35 g, 7·1 mmol) was added to a solution of *XXXII* (1·39 g, 4 mmol) in a mixture of benzene (30 ml) and methanol (30 ml). After stirring at +45°C for 6 h, the solvents were evaporated in vacuo and the residue was partitioned between water and ether. The aqueous phase was extracted with ether (2×), the combined ethereal phases were washed with saturated aqueous solution of potassium hydrogen carbonate (2×) and water. The residue was chromatographed on a column of silica gel (100 g) in benzene–ether (8 : 2) affording 920 mg (76%) of the product *XXXIII*, m.p. 154—156°C (acetone), $[\alpha]_D$ +96° (*c* 1·3, chloroform) (reported[14] m.p. 156—157·5°C, $[\alpha]_D$ +101°). IR spectrum (chloroform): 3 625, 3 450 (OH); 1 663, 1 625 (C=C—C=O). ^{1}H NMR spectrum (100 MHz): 5·72 bs, 1 H (H-4); 3·65 m, 2 H (2 × H-20); 1·19 s, 3 H (3 × H-19); 0·69 s, 3 H (3 × H-18).

20-(2-Propynyloxy)-21-nor-4-pregnen-3-one (*XXXIV*)

A) 1-Methyl-4-piperidone (4 ml, 32·5 mmol) was added under argon to a solution of *XXX* (1·42 g, 4·15 mmol) in toluene (70 ml). A part (10 ml) of the toluene was distilled off and 1M aluminium isopropoxide in toluene (5 ml) was added. After refluxing under argon for 9 h, the mixture was cooled, diluted with ether (400 ml) and washed successively with dilute hydrochloric acid (1 : 4), water, saturated aqueous solution of potassium hydrogen carbonate and water. The solvents were evaporated and the residue was chromatographed on a column of silica gel (150 g) in light petroleum–benzene–ether (45 : 45 : 10) to give 589 mg (41%) of the product *XXXIV*. Further elution with light petroleum–benzene–ether (40 : 40 : 10) afforded 687 mg (48%) of unreacted *XXX*. The product *XXXIV* had m.p. 106—109°C (hexane–ether), $[\alpha]_D$ +108° (*c* 0·2, chloroform). IR spectrum (tetrachloromethane): 3 315, 2 115 (C≡C—H); 1 677, 1 619 (C=C—C=O); 1 102 (C—O). ^{1}H NMR spectrum (100 MHz): 5·71 bs, 1 H (H-4); 4·10 d, 2 H ($OCH_2C{\equiv}C$, J = 2·5); 3·48 m, 2 H (2 × H-20); 2·42 t, 1 H (C≡C—H, J = 2·5); 1·19 s, 3 H

(3 × H-19); 0·70 s, 3 H (3 × H-18). For $C_{23}H_{32}O_2$ (340·5) calculated: 81·13% C, 9·47% H; found: 80·93% C, 9·24% H.

B) Propargyl bromide (0·53 ml, 6 mmol), tetrabutylammonium hydrogen sulfate (0·34 g, 1 mmol) and 19M aqueous sodium hydroxide (1 ml) were added to a solution of *XXXIII* (606 mg, 2 mmol) in a mixture of benzene (10 ml) and acetonitrile (6 ml). After stirring at room temperature for 10 h, the reaction mixture was diluted with ether (50 ml) and washed with water (50 ml). The aqueous phase was extracted with ether (3 × 50 ml), the combined organic phases were washed with water (3 × 150 ml) and filtered through a column of silica gel (10 g) layered with anhydrous sodium sulfate. The column was washed with ether and the solvents were evaporated in vacuo. The residue was chromatographed on a column of silica gel (60 g) in light petroleum–benzene–ether (46 : 46 : 8), affording 160 mg (23%) of the product *XXXIV*; further elution with light petroleum–benzene–ether (6 : 6 : 5) gave 376 mg (62%) of unreacted *XXXIII*. Compound *XXXIV* had m.p. 104—106°C (hexane–ether) and was identical with the product prepared under *A*).

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