PREPARATION OF SELECTIVELY PROTECTED DERIVATIVES OF 21-NOR-5-PREGNENE-3β,20-DIOL*

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The preparation of selectively protected derivatives of the title diol (*III*) is described. Derivatives with protected hydroxyl in position 3 (*IV*, *V* and *VI*) were obtained by *p*-toluenesulfonic acid-catalyzed reaction of etienic acid (*I*) with dihydropyran, ethyl vinyl ether and methyl vinyl ether, respectively, and subsequent hydride reduction. The protection of the free primary hydroxyl in these compounds and the subsequent removal of the acetal protecting group in position 3 represents a suitable approach to 20-protected derivatives. The relative rates of cleavage of the acetal protecting groups and reaction conditions are discussed.

In our preceding papers we have described the preparation of steroidal unsaturated esters[1-4], maleimides[5] and unsaturated lactones[6]. These syntheses started from derivatives of the diol *III* in which the 3β-hydroxyl was selectively protected as an acetate (compound *VII*), a methoxymethyl (MOM) ether (compound *VIII*), or as a monosuccinate unit[2].

The present communication concerns the preparation of further derivatives of diol *III*, selectively protected in position 3β with the tetrahydropyranyl (THP), 1-ethoxyethyl (EE) and 1-methoxyethyl (ME) groups (compounds *IV*–*VI*). We also prepared derivatives protected in position 20 with the MOM, 2-methoxyethoxymethyl (MEM), tert-butyldimethylsilyl (TBDMS), tert-butyldiphenylsilyl (TBDPS) and thexyldimethylsilyl (TXDMS) ether groups (compounds *XII*, *XVI*, *XX*, *XXIV*, and *XXVIII*).

The different reactivity of the primary and secondary hydroxyl group in the diol *III* can be utilized in its reaction with trityl chloride[2] or 4,4-dimethoxytrityl chloride[3]. Reaction with sterically less bulky reagents leads to mixtures of 3- and 20-protected derivatives: thus e.g. the diol *III* reacts with chloromethyl methyl ether and N,N-diisopropylethylamine to give a mixture containing, in addition to the unreacted diol *III* and the bis-MOM derivative, predominantly a 1 : 2·3 mixture (^{1}H NMR spectrum) of the mono-MOM derivatives *VIII* and *XII* which can be separated only with difficulty.

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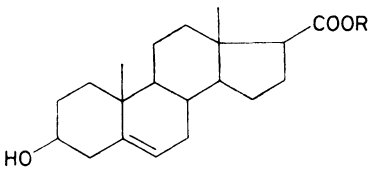
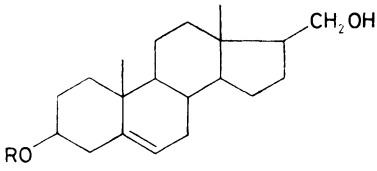
An alternative approach to 20-protected derivatives starts from the 3-protected derivatives and is based on the exchange of the protecting groups; this, however, requires their orthogonality. Very suitable in this respect is the 3-acetyl derivative *VII*



I, R = H
II, R = CH_3

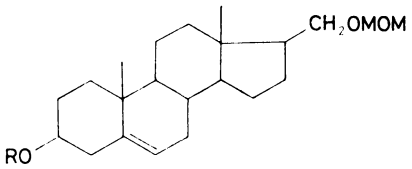


III, R = H
IV, R = THP
V, R = EE
VI, R = ME
VII, R = $COCH_3$
VIII, R = MOM

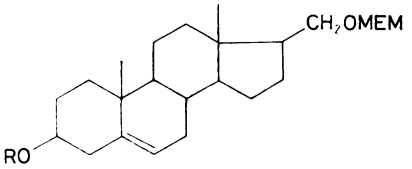
EE 1-ethoxyethyl ; ME 1-methoxyethyl ; MOM methoxymethyl
THP tetrahydro-2H-pyran-2-yl

because it enables a facile preparation of compounds having in position 20 an alkali-resistant protecting group, e.g. the TBDMS or the nitrate group[2]. Since, however, the 3-acetyl derivative *VII* is prepared from etienic acid (*I*) in a yield of only 70% (ref.[5]), we turned our attention to protecting groups of the acetal type. These groups are advantageous in that their rate of cleavage depends on the number of hydrogen atoms bonded to the acetal carbon atom.

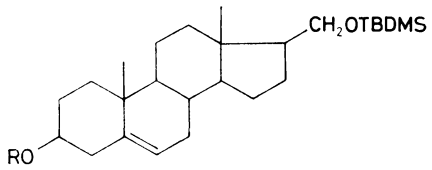
For the synthesis of the 3-THP derivative *IV* we used a modification of the known procedure[7] based on the reaction of etienic acid (*I*) with dihydropyran, catalyzed with *p*-toluenesulfonic acid monohydrate. Without isolation, the obtained 3-THP-ether-20-THP-ester was directly reduced with sodium bis(2-methoxyethoxy)-aluminium hydride to the 3-THP derivative *IV* in 95% yield. Analogously, the reaction of etienic acid (*I*) with ethyl vinyl ether or methyl vinyl ether afforded the respective 3-EE and 3-ME derivatives (*V* and *VI*). The 20-hydroxy derivatives *IV*–*VI* were treated with methoxymethyl chloride or 2-methoxyethoxymethyl chloride in dichloromethane in the presence of N,N-diisopropylethylamine. Reactions with tert-butyldimethylsilyl chloride, tert-butyldiphenylsilyl chloride and thexyldimethylsilyl chloride[8,9] were performed in dichloromethane in the presence of triethylamine and 4-dimethylaminopyridine[2]. The derivatives with different protecting groups in positions 3 and 20 were isolated in 77–95% yields. The acetal protecting group in position 3 can be selectively cleaved[10] with magnesium bromide in a benzene – ether mixture. Under these conditions the reagent removes selectively the THP, EE, and ME protecting groups in position 3 whereas the MEM, TBDMS, TBDPS, and TXDMS groups in position 20 are practically intact. However, this method fails for the MOM group[10] which is cleaved with magnesium bromide too.



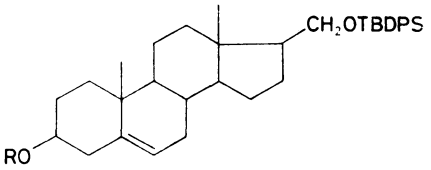
IX, R = THP *XI*, R = ME
X, R = EE *XII*, R = H



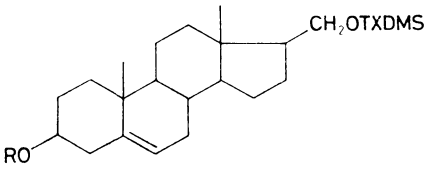
XIII, R = THP *XV*, R = ME
XIV, R = EE *XVI*, R = H



XVII, R = THP *XIX*, R = ME
XVIII, R = EE *XX*, R = H



XXI, R = THP *XXIII*, R = ME
XXII, R = EE *XXIV*, R = H

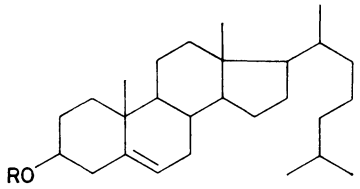


XXV, R = THP *XXVII*, R = ME
XXVI, R = EE *XXVIII*, R = H

EE 1-ethoxyethyl, ME 1-methoxyethyl, MEM 2-methoxyethoxymethyl,
MOM methoxymethyl, TBDMS tert-butyldimethylsilyl,
TBDPS tert-butyldiphenylsilyl, THP tetrahydro-2H-pyran-2-yl,
TXDMS thexyldimethylsilyl

Therefore, in the case of the MOM group we made use of an alternative method, consisting in selective cleavage of the THP, EE or ME group in position 3 with 2M-HCl in a benzene – methanol mixture. Under these conditions, the protecting group in position 3 (with an alkyl group on the acetal carbon atom) is cleaved substantially faster than the MOM protecting group in position 20. This procedure may also be used with derivatives containing a MEM group in position 20. In both cases the EE or ME groups in position 3 are cleaved faster than the THP group which leads to higher yields (increase at least 15%) of compounds *XII* and *XVI*. Using these procedures, we obtained 3-hydroxy derivatives containing the MOM

(compound *XII*), MEM (compound *XVI*), TBDMS (compound *XX*), TBDPS (compound *XXIV*) and TXDMS (compound *XXVIII*) groups in position 20.



XXIX, R = MOM *XXXII*, R = EE
XXX, R = MEM *XXXIII*, R = ME
XXXI, R = THP *XXXIV*, R = MIP

EE 1-ethoxyethyl ; ME 1-methoxyethyl ; MEM 2-methoxyethoxymethyl ; MIP 2-methoxyprop-2-yl ; MOM methoxymethyl ; THP tetrahydro-2H-pyran-2-yl

In order to prove the fact that the EE and ME ethers are cleaved faster than the corresponding THP ethers we compared the rates of acid cleavage of the corresponding protected cholesterol derivatives *XXIX*–*XXXIV*. Moreover, the results in Table I confirm the known fact that the cleavage rate of acetal derivatives increases

Table I
Time (s) required for removal of the protecting groups

Compound	Protecting group	Conditions *A*	Conditions *B*
XXIX[a]	MOM	[b]	$5{\cdot}8 \cdot 10^4$
XXX	MEM	[b]	$5{\cdot}8 \cdot 10^4$
XXXI[c]	THP	$1{\cdot}8 \cdot 10^3$	$1{\cdot}2 \cdot 10^2$
XXXXII[d]	EE	$2{\cdot}4 \cdot 10^2$	$1{\cdot}2 \cdot 10^2$
XXXIII	ME	$3{\cdot}0 \cdot 10^2$	$1{\cdot}2 \cdot 10^2$
XXXIV[d]	MIP	≈ 1	[e]
VIII[f]	MOM	[g]	$4{\cdot}7 \cdot 10^4$
IV	THP	$1{\cdot}1 \cdot 10^4$	$1{\cdot}2 \cdot 10^2$
V	EE	$3{\cdot}0 \cdot 10^3$	$1{\cdot}2 \cdot 10^2$
VI	ME	$3{\cdot}0 \cdot 10^3$	$1{\cdot}2 \cdot 10^2$

[a] The compound was prepared according to ref.[16]; [b] after 7 days (about $6 \cdot 10^5$ s) the reaction mixture contained the protected derivative and cholesterol in about 1 : 1 ratio (TLC); [c] prepared according to ref.[17]; [d] prepared according to ref.[18]; [e] the protecting group was cleaved in less than 1 s; [f] prepared according to ref.[6]; [g] after 7 days (about $6 \cdot 10^5$ s) the reaction mixture contained the protected derivative *VIII* and diol *III* in about 1 : 1 ratio (TLC).

in the order O—CH_2—O < O—CHR—O < O—CRR'—O. To make the study more complete, we also performed the cleavage of the available mono-protected derivatives of the 3,20-diol *III*. The results for this series of compounds (*IV*–*VI* and *VIII*) show again the same order of stability of the individual protecting groups as for the cholesterol derivatives.

As follows from the above-described experiments, the statement[10] about orthogonality of the THP protecting group and the silyl protecting groups (TBDMS and TBDPS) can be extended to the EE and ME acetal groups as well as to the recently described[8] TXDMS silyl group. We may further derive that the so far not common EE protecting group and the relatively rarely used ME group represent suitable alternatives to the generally used THP group in cases, where the cleavage requires a protic acid. On the contrary, when the cleavage is performed exclusively with protic acids, the MEM group appears to be less advantageous than the simplest acetal protecting group MOM; the MEM derivatives have more signals in the ^{1}H NMR spectrum and crystallize less readily; on the other hand, their stability is practically the same as that of the MOM derivatives.

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 Perkin–Elmer PE 580 spectrometer (wavenumbers in cm^{-1}). ^{1}H NMR spectra were taken on a Tesla BS-476 (CW mode, 60 MHz) and a Tesla BS-497 (FT mode, 100 MHz) instruments at 23°C in deuteriochloroform with tetramethylsilane as internal standard, unless stated otherwise. 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, unless stated otherwise. 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 ^{1}H NMR spectra, thin-layer chromatography and mixture melting point determination.

3β-(2-Tetrahydropyranyloxy)-21-nor-5-pregnen-20-ol (*IV*)

Dihydropyran (5 ml, 55 mmol) and *p*-toluenesulfonic acid monohydrate (28 mg, 0·15 mmol) were added to a suspension of etienic acid (*I*; 5 g, 15·7 mmol) in benzene (100 ml). After stirring at room temperature for 5 h, the mixture was heated at reflux with 3·5M solution of sodium bis(2-methoxyethoxy)aluminium hydride in benzene (20 ml) for 5 h under argon. After cooling to room temperature, the excess hydride was decomposed with moist ether and water and the mixture was poured into a mixture of ethyl acetate (400 ml) and water (150 ml). The aqueous phase was extracted with ethyl acetate and the combined organic phases were washed with saturated aqueous solution of sodium chloride (3×). The solvent was evaporated and the residue was chromatographed on a column of alumina (500 g). Elution with light petroleum – benzene – – ether (45 : 45 : 10) removed the nonpolar impurities; the same solvents in the ratio 40 : 40 : 20

eluted the product *IV* (5·75 g, 91%), m.p. 154—157°C (acetone), $[\alpha]_D$ −53° (*c* 0·4, chloroform); reported m.p. 152—155·5°C, $[\alpha]_D$ −51·14° (ref.[11]) and m.p. 151—152°C, $[\alpha]_D$ −50·5° (ref.[12]). IR spectrum (chloroform): 3 620, 3 460 (OH); 1 668 (C=C). ^{1}H NMR spectrum (60 MHz): 5·37 bd, 1 H (H-6, J = 4·5); 4·74 bs, 1 H (H-2′ of tetrahydropyranyloxy group); 1·05 s, 3 H (3 × H-19); 0·68 s, 3 H (3 × H-18).

3β-(1-Ethoxyethoxy)-21-nor-5-pregnen-20-ol (*V*)

The title compound was prepared from etienic acid (*I*; 5 g, 15·7 mmol) and ethyl vinyl ether (5·26 ml, 55 mmol) analogously as described in the preceding preparation; yield 4·1 g (69%) of *V*, m.p. 99—102°C (light petroleum), $[\alpha]_D$ −34° (*c* 0·5, chloroform). IR spectrum (tetrachloromethane): 3 635, 3 490 (OH); 3 030, 1 668 (C=C—H); 1 131, 1 103, 1 058, 1 045 (C—O). ^{1}H NMR spectrum (60 MHz): 5·30 bd, 1 H (H-6, J = 4·5); 4·90 q, 1 H (O—CH—O, J = 5); 3·93—3·33 m, 5 H (H-3, 2 × H-20, $CH_3\mathbf{CH_2}O$); 1·30 d, 3 H (O—CH($\mathbf{CH_3}$)—O, J = 5); 1·21 t, 3 H ($\mathbf{CH_3}CH_2O$, J = 7); 1·00 s, 3 H (3 × H-19); 0·67 s, 3 H (3 × H-18). For $C_{24}H_{40}O_3$ (376·6) calculated: 76·55% C, 10·71% H; found: 76·88% C, 10·51% H.

3β-(1-Methoxyethoxy)-21-nor-5-pregnen-20-ol (*VI*)

p-Toluenesulfonic acid monohydrate (30 mg, 0·16 mmol) was added to a suspension of etienic acid (*I*; 5 g, 15·7 mmol) in a mixture of benzene (45 ml) and toluene (45 ml). Liquid methyl vinyl ether[13,14] (4·4 ml, 55 mmol) was added at 0°C and the mixture was stirred at 0°C for 10 min and at room temperature for 3 h. Analogous procedure as in the preceding experiment afforded 4·76 g (85%) of product *VI*, m.p. 141—144°C (benzene), $[\alpha]_D$ −55° (*c* 0·3, chloroform). IR spectrum (tetrachloromethane): 3 635, 3 435 (OH); 1 668 (C=C); 1 132, 1 100, 1 043 (C–O). ^{1}H NMR spectrum (100 MHz): 5·33 bd, 1 H (H-6, J = 4·5); 4·70 q, 1 H (O–CH–O, J = 5); 3·30 s, 3 H (CH_3O); 1·32 d, 3 H (O–CH($\mathbf{CH_3}$)–O, J = 5); 1·02 s, 3 H (3 × H-19); 0·66 s, 3 H (3 × H-18). For $C_{23}H_{38}O_3$ (362·6) calculated: 76·20% C, 10·56% H; found: 76·39% C, 10·60% H.

General Procedure for Preparation of Derivatives *IX*—*XI* and *XIII*—*XV*

Chloromethyl methyl ether (304 μl, 4 mmol) or 2-methoxyethoxymethyl chloride (457 μl, 4 mmol) was added to a solution of the hydroxy derivative (2 mmol) and N,N-diisopropylethylamine (1·05 ml, 6 mmol) in dichloromethane (15 ml). After stirring at room temperature for 12 h the reaction mixture was diluted with ether (150 ml) and washed successively with water, saturated aqueous solution of potassium hydrogen carbonate and water. After drying over anhydrous potassium carbonate and evaporation of the solvent, the residue was chromatographed on a column of silica gel (50 g, pretreated with ammonia vapours for 24 h) in benzene – light petroleum – ether (95 : 95 : 10).

20-Methoxymethoxy-3β-(2-tetrahydropyranyloxy)-21-nor-5-pregnene (*IX*)

Reaction of hydroxy derivative *IV* (777 mg, 2 mmol) with chloromethyl methyl ether (304 μl, 4 mmol) afforded 796 mg (92%) of derivative *IX*, m.p. 74—77°C (hexane), $[\alpha]_D$ −35° (*c* 0·3, chloroform). IR spectrum (tetrachloromethane): 1 668 (C=C); 1 195, 1 110, 1 055, 1 040, 1 030 (C–O). ^{1}H NMR spectrum (60 MHz): 5·30 bd, 1 H (H-6, J = 4·5); 4·67 bs, 1 H (H-2′ of tetrahydropyranyloxy group); 4·55 s, 2 H (OCH_2O); 3·32 s, 3 H (CH_3O); 0·98 s, 3 H (3 × H-19); 0·63 s, 3 H (3 × H-18). For $C_{27}H_{44}O_4$ (432·6) calculated: 74·96% C, 10·25% H; found: 75·11% C, 10·21% H.

3β-(1-Ethoxyethoxy)-20-methoxymethoxy-21-nor-5-pregnene (*X*)

Hydroxy derivative *V* (753 mg, 2 mmol) was treated with chloromethyl methyl ether (304 μl, 4 mmol) to give 673 mg (80%) of derivative *X*, m.p. 48—49°C (ether), $[\alpha]_D$ −35° (*c* 0·2, chloroform). IR spectrum (tetrachloromethane): 3 030, 1 668 (C=C—H); 1 146, 1 109, 1 044, 929 (OCH_2OCH_3); 1 050, 1029 (C–O). ^{1}H NMR spectrum (100 MHz): 5·31 bd,1 H (H-6, *J* = 4·5); 4·80 q, 1 H (O–CH–O, *J* = 6); 4·60 s, 2 H (OCH_2O); 3·78—3·30 m, 5 H (H-3,2 × H-20, CH_3CH_2O); 3·36 s, 3 H (CH_3O); 1·32 d, 3 H (O–CH(CH_3)–O, *J* = 6); 1·20 t, 3 H (CH_3CH_2O, *J* = 7); 1·01 s, 3 H (3 × H-19); 0·65 s, 3 H (3 × H-18). For $C_{26}H_{44}O_4$ (420·6) calculated: 74·24% C, 10·54% H; found: 74·12% C, 10·45% H.

3β-(1-Methoxyethoxy)-20-methoxymethoxy-21-nor-5-pregnene (*XI*)

Reaction of hydroxy derivative *VI* (725 mg, 2 mmol) with chloromethyl methyl ether (304 μl, 4 mmol) afforded 691 mg (85%) of the title compound *XI*, m.p. 56—59°C (ethanol), $[\alpha]_D$ −37° (*c* 0·2, chloroform). IR spectrum (tetrachloromethane): 1 668 (C=C); 1 144, 1 130, 1 109, 1 043 (C–O). ^{1}H NMR spectrum (100 MHz): 5·34 bd, 1 H (H-6, *J* = 4·5); 4·70 q, 1 H (O–CH–O, *J* = 6); 4·60 s, 2 H (OCH_2O); 3·73—3·15 m, 3 H (H-3, 2 × H-20); 3·37 s, 3 H (CH_3OCH_2); 3·31 s, 3 H (CH_3O); 1·31 d, 3 H (O–CH(CH_3)–O, *J* = 6); 1·00 s, 3 H (3 × H-19); 0·62 s, 3 H (3 × H-18). For $C_{25}H_{42}O_4$ (406·6) calculated: 73·85% C, 10·41% H; found: 73·70% C, 10·39% H.

20-(2-Methoxyethoxymethoxy)-3β-(2-tetrahydropyranyloxy)-21-nor-5-pregnene (*XIII*)

Hydroxy derivative *IV* (777 mg, 2 mmol) and 2-methoxyethoxymethyl chloride (457 μl, 4 mmol) reacted to give 734 mg (77%) of oily derivative *XIII*, $[\alpha]_D$ −32° (*c* 2·0, chloroform). IR spectrum (tetrachloromethane): 3 035, 1 668 (C=C—H); 1 136, 1 115, 1 058, 1 032 (C–O). ^{1}H NMR spectrum (60 MHz): 5·35 bd, 1 H (H-6, *J* = 4·5); 4·68 bs, 3 H (H-2′ of tetrahydropyranyloxy group and OCH_2O); 3·38 s, 3 H (CH_3O); 1·00 s, 3 H (3 × H-19); 0·63 s, 3 H (3 × H-18). For $C_{29}H_{48}O_5$ (476·7) calculated: 73·07% C, 10·15% H; found: 73·08% C, 10·19% H.

3β-(1-Ethoxyethoxy)-20-(2-methoxyethoxymethoxy)-21-nor-5-pregnene (*XIV*)

Rection of hydroxy derivative *V* (753 mg, 2 mmol) and 2-methoxyethoxymethyl chloride (457 μl, 4 mmol) furnished 744 mg (80%) of the oily product *XIV*, $[\alpha]_D$ −37° (*c* 1·6, chloroform). IR spectrum (tetrachloromethane): 3 030, 1 668 (C=C—H); 1 130, 1 117, 1 100, 1 059, 1 046 (C–O). ^{1}H NMR spectrum (100 MHz): 5·36 bd, 1 H (H-6, *J* = 4·5); 4·77 q, 1 H (O–CH–O, *J* = 6); 4·70 s, 2 H (OCH_2O); 3·40 s, 3 H (CH_3O); 1·33 d, 3 H (O–CH(CH_3)–O, *J* = 6); 1·20 t, 3 H (CH_3CH_2O, *J* = 7); 1·01 s, 3 H (3× H-19); 0·63 s, 3 H (3 × H-18). For $C_{28}H_{48}O_5$ (464·7) calculated: 72·37% C, 10·41% H; found: 72·04% C, 10·41% H.

3β-(1-Methoxyethoxy)-20-(2-methoxyethoxymethoxy)-21-nor-5-pregnene (*XV*)

Reaction of hydroxy derivative *VI* (725 mg, 2 mmol) with 2-methoxyethoxymethyl chloride (457 μl, 4 mmol) gave 694 mg (77%) of derivative *XV*, m.p. 33—38°C, $[\alpha]_D$ −34° (*c* 0·2, chloroform). IR spectrum (tetrachloromethane): 1 668 (C=C); 1 131, 1 115, 1 099, 1 043 (C–O). ^{1}H NMR spectrum (100 MHz): 5·36 bd, 1 H (H-6, *J* = 4·5); 4·74 q, 1 H (O–CH–O, *J* = 6); 4·70 s, 2 H (OCH_2O); 3·40 s, 3 H ($CH_3OCH_2CH_2O$); 3·30 s, 3 H (CH_3O); 1·33 d, 3 H (O–CH(CH_3)–O, *J* = 6); 1·01 s, 3 H (3 × H-19); 0·65 s, 3 H (3 × H-18). For $C_{27}H_{46}O_5$ (450·7) calculated: 71·96% C, 10·29% H; found: 72·55% C, 10·43% H.

General Procedure for Preparation of Silyl Derivatives *XVII*—*XIX*, *XXI*—*XXIII* and *XXV*—*XXVII*

The corresponding chlorosilane (2·2 mmol) was added to a mixture of the hydroxy derivative (2 mmol), triethylamine (335 μl, 2·4 mmol), 4-dimethylaminopyridine (10 mg, 82 μmol) and dichloromethane (7 ml). After stirring at room temperature for 12 h, the reaction mixture was diluted with ether (150 ml), washed successively with water, saturated aqueous solution of potassium hydrogen carbonate, water, and dried over anhydrous potassium carbonate. The solvent was evaporated and the residue chromatographed on a column of alumina (50 g) in benzene – light petroleum – ether (99 : 99 : 2).

20-Tert-butyldimethylsilyloxy-3β-(2-tetrahydropyranyloxy)-21-nor-5-pregnene (*XVII*)

Hydroxy derivative *IV* (777 mg, 2 mmol) was reacted with tert-butyldimethylsilyl chloride (332 mg, 2·2 mmol) to give 845 mg (84%) of silyl derivative *XVII*, m.p. 98—101°C (hexane), $[\alpha]_D$ −40° (*c* 0·3, chloroform). IR spectrum (tetrachloromethane): 1 668 (C=C); 1 030 (C–O); 1 256, 848, 838 (Si–C). ^{1}H NMR spectrum (60 MHz, external lock): 5·30 bd, 1 H (H-6, J = 4·5); 4·66 bs, 1 H (H-2′ of tetrahydropyranyloxy group); 1·02 s, 3 H (3 × H-19); 0·90 s, 9 H ($SiC(CH_3)_3$); 0·65 s, 3 H (3 × H-18); 0·06 s, 6 H ($Si(CH_3)_2$). For $C_{31}H_{54}O_3Si$ (502·9) calculated: 74·05% C, 10·82% H; found: 73·30% C, 10·53% H.

20-Tert-butyldimethylsilyloxy-3β-(1-ethoxyethoxy)-21-nor-5-pregnene (*XVIII*)

Hydroxy derivative *V* (753 mg, 2 mmol) and tert-butyldimethylsilyl chloride (332 mg, 2·2 mmol) afforded 785 mg (80%) of silyl derivative *XVIII*, m.p. 71—75°C (methanol), $[\alpha]_D$ −48° (*c* 0·2, chloroform). IR spectrum (tetrachloromethane): 3 030, 1 668 (C=C—H); 1 247, 850, 840 (Si–C); 1 130, 1 102, 1 087, 1 048 (C–O). ^{1}H NMR spectrum (100 MHz): 5·32 bd, 1 H (H-6, J = 4·5); 4·78 q, 1 H (O–CH–O, J = 5); 1·30 d, 3 H (O–CH(CH_3)–O, J = 5); 1·21 t, 3 H (CH_3CH_2O; J = 7); 1·00 s, 3 H (3 × H-19); 0·88 s, 9 H ($SiC(CH_3)_3$); 0·62 s, 3 H (3 × H-18); 0·01 s, 6 H ($Si(CH_3)_2$). For $C_{30}H_{54}O_3Si$ (490·8) calculated: 73·41% C, 11·09% H; found: 72·95% C, 11·39% H.

20-Tert-butyldimethylsilyloxy-3β-(1-methoxyethoxy)-21-nor-5-pregnene (*XIX*)

Reaction of hydroxy derivative *VI* (725 mg, 2 mmol) with tert-butyldimethylsilyl chloride (332 mg, 2·2 mmol) afforded 830 mg (87%) of silyl derivative *XIX*, m.p. 94—97°C (methanol – – acetone), $[\alpha]_D$ −42° (*c* 0·2, chloroform). IR spectrum (tetrachloromethane): 1 668 (C=C); 1 256, 848, 838 (Si–C); 1 128, 1 100, 1 046 (C–O). ^{1}H NMR spectrum (100 MHz): 5·35 bd, 1 H (H-6, J = 4·5); 4·73 q, 1 H (O–CH–O, J = 5); 3·30 s, 3 H (CH_3O); 1·30 d, 3 H (O–CH(CH_3)–O, J = 5); 1·01 s, 3 H (3 × H-19); 0·88 s, 9 H ($SiC(CH_3)_3$); 0·65 s, 3 H (3 × × H-18); 0·04 s, 6 H ($Si(CH_3)_2$). For $C_{29}H_{52}O_3Si$ (476·8) calculated: 73·05% C, 10·99% H; found: 73·17% C, 11·24% H.

20-Tert-butyldiphenylsilyloxy-3β-(2-tetrahydropyranyloxy)-21-nor-5-pregnene (*XXI*)

Reaction of hydroxy derivative *IV* (777 mg, 2 mmol) with tert-butylchlorodiphenylsilane (572 μl, 2·2 mmol) gave 1·17 g (93%) of amorphous silyl derivative *XXI*, $[\alpha]_D$ −21° (*c* 0·3, chloroform). IR spectrum (tetrachloromethane): 1 668 (C=C); 1 591 (arom. system); 1 114, 1 032 (C–O); 825 (Si–C). ^{1}H NMR spectrum (60 MHz): 7·75—7·23 m, 10 H (arom. H); 5·33 bd, 1 H (H-6, J = 4·5); 4·68 bs, 1 H (H-2′ of tetrahydropyranyloxy group); 1·00 s, 12 H (3 × H-19 and $SiC(CH_3)_3$; 0·60 s, 3 H (3 × H-18). For $C_{41}H_{58}O_3Si$ (627·0) calculated: 78·54% C, 9·32% H; found: 79·08% C, 9·02% H.

20-Tert-butyldiphenylsilyloxy-3β-(1-ethoxyethoxy)-21-nor-5-pregnene (*XXII*)

Reaction of hydroxy derivative *V* (753 mg, 2 mmol) with tert-butylchlorodiphenylsilane (572 μl, 2·2 mmol) afforded 1·14 g (93%) of amorphous silyl derivative *XXII*, $[\alpha]_D$ −32° (*c* 0·2, chloroform). IR spectrum (tetrachloromethane): 3 075, 3 050, 1 590 (arom. system); 1 668 (C=C); 1 128, 1 114, 1 085, 1 047 (C–O). ^{1}H NMR spectrum (100 MHz): 7·75—7·25 m, 10 H (arom. H); 5·32 bd, 1 H (H-6, *J* = 4·5); 4·77 q, 1 H (O–CH–O, *J* = 5); 3·85—3·25 m, 5 H (H-3, 2 × H-20 $CH_3\mathbf{CH_2}O$); 1·31 d, 3 H (O–CH($\mathbf{CH_3}$)–O, *J* = 5); 1·21 t, 3 H ($\mathbf{CH_3}CH_2O$, *J* = 7); 1·03 s, 9 H ($SiC(CH_3)_3$); 1·00 s, 3 H (3 × H-19); 0·62 s, 3 H (3 × H-18). For $C_{40}H_{58}O_3Si$ (615·0) calculated: 78·12% C, 9·51% H; found: 77·89% C, 9·64% H.

20-Tert-butyldiphenylsilyloxy-3β-(1-methoxyethoxy)-21-nor-5-pregnene (*XXIII*)

Reaction of hydroxy derivative *VI* (725 mg, 2 mmol) with tert-butylchlorodiphenylsilane (572 μl, 2·2 mmol) afforded 1·05 g (87%) of oily silyl derivative *XXIII*, $[\alpha]_D$ −25° (*c* 0·9, chloroform). IR spectrum (tetrachloromethane): 1 668 (C=C); 1 590 (arom. system); 1 113, 1 065, 1,047 (C–O); 825 (Si–C). ^{1}H NMR spectrum (100 MHz): 7·84—7·24 m, 10 H (arom. H); 5·36 bd, 1 H (H-6, *J* = 4·5); 4·73 q, 1 H (O–CH–O, *J* = 5); 3·91—3·20 m, 3 H (H-3 and 2 × H-20); 3·30 s, 3 H (CH_3O); 1·30 d, 3 H (O–CH($\mathbf{CH_3}$)–O, *J* = 5); 1·03 s, 9 H ($SiC(CH_3)_3$); 1·01 s, 3 H (3 × H-19); 0·63 s, 3 H (3 × H-18). For $C_{39}H_{56}O_3Si$ (601·0) calculated: 77·95% C, 9·39% H; found: 77·65% C, 9·54% H.

3β-(2-Tetrahydropyranyloxy)-20-thexyldimethylsilyloxy-21-nor-5-pregnene (*XXV*)

Reaction of hydroxy derivative *IV* (777 mg, 2 mmol) with dimethylthexylsilyl chloride[9] (433 μl, 2·2 mmol) afforded 1·01 g (95%) of silyl derivative *XXV*, m.p. 70—72°C (methanol), $[\alpha]_D$ −37° (*c* 0·3, chloroform). IR spectrum (tetrachloromethane): 1 668 (C=C); 1 250, 845, 830 (Si–C); 1 134, 1 112, 1 077, 1 031 (C–O). ^{1}H NMR spectrum (100 MHz): 5·32 bd, 1 H (H-6, *J* = 4·5); 4·70 bs, 1 H (H-2′ of tetrahydropyranyloxy group); 1·01 s, 3 H (3 × H-19); 0·87 d, 6 H ($CH(\mathbf{CH_3})_2$, *J* = 7·8); 0·83 s, 6 H ($C(CH_3)_2$); 0·62 s, 3 H (3 × H-18); 0·06 s, 6 H ($Si(CH_3)_2$). For $C_{33}H_{58}O_3Si$ (530·9) calculated: 74·66% C, 11·01% H; found: 74·41% C, 11·28% H.

3β-(1-Ethoxyethoxy)-20-thexyldimethylsilyloxy-21-nor-5-pregnene (*XXVI*)

Reaction of hydroxy derivative *V* (753 mg, 2 mmol) with dimethylthexylsilyl chloride[9] (433 μl, 2·2 mmol) afforded 851 mg (82%) of oily silyl derivative *XXVI*, $[\alpha]_D$ −31° (*c* 0·8, chloroform). IR spectrum (tetrachloromethane): 1 668 (C=C); 1 251, 845, 830 (Si–C); 1 129, 1 100, 1 075, 1 046 (C–O). ^{1}H NMR spectrum (100 MHz): 5·34 bd, 1 H (H-6, *J* = 4·5); 4·77 q, 1 H (O–CH–O, *J* = 5); 1·30 d, 3 H (O–CH($\mathbf{CH_3}$)–O, *J* = 5); 1·18 t, 3 H ($\mathbf{CH_3}CH_2O$, *J* = 7·7); 1·00 s, 3 H (3 × H-19); 0·87 d, 6 H ($CH(\mathbf{CH_3})_2$, *J* = 7·7); 0·83 s, 6 H ($C(CH_3)_2$); 0·63 s, 3 H (3 × H-18); 0·06 s, 6 H ($Si(CH_3)_2$). For $C_{32}H_{58}O_3Si$ (518·9) calculated: 74·07% C, 11·27% H; found: 74·25% C, 11·05% H.

3β-(1-Methoxyethoxy)-20-thexyldimethylsilyloxy-21-nor-5-pregnene (*XXVII*)

Reaction of hydroxy derivative *VI* (725 mg, 2 mmol) with dimethylthexylsilyl chloride[9] (433 μl, 2·2 mmol) gave 868 mg (86%) of silyl derivative *XXVII*, m.p. 70—72°C (methanol), $[\alpha]_D$ −37° (*c* 0·3, chloroform). IR spectrum (tetrachloromethane): 1 668 (C=C); 1 250, 845, 830 (Si–C); 1 134, 1 112, 1 077, 1 031 (C–O). ^{1}H NMR spectrum (100 MHz): 5·33 bd, 1 H (H-6, *J* = 4·5); 4·73 q, 1 H (O–CH–O, *J* = 5); 3·30 s, 3 H (OCH_3); 1·29 d, 3 H (O–CH($\mathbf{CH_3}$)–O, *J* = 5); 1·00 s,

6 H (3 × H-19); 0·88 d, 6 H ($CH(CH_3)_2$, J = 7·8); 0·83 s, 6 H ($C(CH_3)_2$); 0·63 s, 3 H (3 × H-18); 0·06 s, 6 H ($Si(CH_3)_2$). For $C_{31}H_{56}O_3Si$ (504·9) calculated: 73·75% C, 11·18% H; found: 73·21% C, 11·01% H.

General Procedure for Preparation of Hydroxy Derivatives *XVI*, *XX*, *XXIV* and *XXVIII* by Cleavage of Acetal Protecting Groups with Magnesium Bromide.

To a solution of the protected derivative (1 mmol) in a mixture of benzene (5 ml) and ether (5 ml) was added 1·2M solution of magnesium bromide in benzene – ether (1 : 1, 2·5 ml). The reaction course was followed by TLC in benzene – ether (1 : 1); the time required for complete removal of the protecting group was 4–6 h. The reaction mixture was diluted with ether (200 ml), washed with saturated aqueous solution of ammonium chloride and with water, dried and the solvent was evaporated. The residue was subjected to chromatography on a column of silica gel (30 g) in light petroleum – benzene – ether (50 : 49 : 1), unless stated otherwise.

20-(2-Methoxyethoxymethoxy)-21-nor-5-pregnen-3β-ol (*XVI*)

A) Derivative *XIII* (477 mg, 1 mmol) was reacted as described in the general procedure. Chromatography in light petroleum – benzene – ether (45 : 45 : 10) and further in light petroleum – benzene – ether (45 : 40 : 15) gave 302 mg (77%) of hydroxy derivative *XVI*, m.p. 118–120°C (ether), $[\alpha]_D$ −43° (*c* 0·2, chloroform). IR spectrum (chloroform): 3 610, 3 455 (OH); 1 668 (C=C); 1 116, 1 094, 1 044 (C–O). ^{1}H NMR spectrum (60 MHz): 5·35 bd, 1 H (H-6, J = 4·5); 4·70 s, 2 H (OCH_2O); 3·38 s, 3 H (CH_3O); 1·00 s, 3 H (3 × H-19); 0·63 s, 3 H (3 × H-18). For $C_{24}H_{40}O_4$ (392·6) calculated: 73·43% C, 10·27% H; found: 73·78% C, 10·03% H.

B) Reaction of derivative *XIV* (465 mg, 1 mmol), followed by chromatography in light petroleum – benezene – ether (45 : 40 : 15), afforded 274 mg (63%) of hydroxy derivative *XVI*, identical with the product obtained by procedure *A*.

C) Reaction of derivative *XV* (451 mg, 1 mmol), followed by chromatography in light petroleum – bezene – ether (45 : 40 : 15), gave 314 mg (80%) of hydroxy derivative *XVI*, identical with the product obtained by procedure *A*.

20-Tert-butyldimethylsilyloxy-21-nor-5-pregnen-3β-ol (*XX*)

A) Derivative *XVII* (503 mg, 1 mmol) afforded 360 mg (86%) of hydroxy derivative *XX*, identical with an authentic sample[2].

B) Derivative *XVIII* (491 mg, 1 mmol) was converted into hydroxy derivative *XX* (272 mg, 65%), identical with the product prepared by procedure *A*.

C) Derivative *XIX* (477 mg, 1 mmol) was converted into hydroxy derivative *XX* (245 mg, 68%), identical with the product prepared by procedure *A*.

20-Tert-butyldiphenylsilyloxy-21-nor-5-pregnen-3β-ol (*XXIV*)

A) Derivative *XXI* (627 mg, 1 mmol) was converted into 402 mg (74%) of the title compound *XXIV*, m.p. 57–60°C, $[\alpha]_D$ −35° (*c* 0·2, chloroform). IR spectrum (tetrachloromethane): 3 623, 3 340 (OH); 1 668 (C=C); 1 591 (arom. system); 1 114, 826 (C–Si). ^{1}H NMR spectrum (60 MHz): 7·85–7·22 m, 10 H (arom. H); 5·36 bd, 1 H (H-6, J = 4·5); 1·03 s, 12 H (3 × H-19 and $SiC(CH_3)_3$); 0·63 s, 3 H (3 × H-18). ^{1}H NMR spectrum after addition of TAI (60 MHz): 8·30 bs, 1 H ($Cl_3CCONHCOO$); 7·72–7·23 m, 10 H (arom. H); 5·41 bd, 1 H (H-6, J = 4·5);

4·70 m, 1 H (H-3, $W = 36$); 3·60 m, 2 H (2 × H-20); 1·03 s, 12 H (3 × H-19 and $SiC(CH_3)_3$) 0·63 s, 3 H (3 × H-18). For $C_{36}H_{50}O_2Si$ (542·9) calculated: 79·65% C, 9·28% H; found: 79·86% C 9·01% H.

B) Derivative *XXII* (615 mg, 1 mmol) was converted into 331 mg (61%) of the title compound *XXIV*, identical with the product prepared by procedure *A*.

C) Derivative *XXIII* (601 mg, 1 mmol) was converted into 461 mg (85%) of the title compound *XXIV*, identical with the product prepared by procedure *A*.

20-Thexyldimethylsilyloxy-21-nor-5-pregnen-3β-ol (*XXVIII*)

A) Reaction of derivative *XXV* (531 mg, 1 mmol) afforded the title hydroxy derivative *XXVIII* (331 mg, 74%), m.p. 83–84°C (methanol), $[\alpha]_D$ −37° (*c* 0·2, chloroform). IR spectrum (tetrachloromethane): 3 610, 3 340 (OH); 1 668 (C=C); 1 251, 844, 830 (C–Si); 1 046 (C–O). ^{1}H NMR spectrum (100 MHz): 5·31 bd, 1 H (H-6, $J = 4·5$); 3·75–3·32 m, 3 H (H-3 and 2 × H-20); 1·01 s, 3 H (3 × H-19); 0·87 d, 6 H ($CH(CH_3)_2$, $J = 7·7$); 0·83 s, 6 H ($C(CH_3)_2$); 0·63 s, 3 H (3 × H-18); 0·06 s, 6 H ($Si(CH_3)_2$. For $C_{28}H_{50}O_2Si$ (446·8) calculated: 75·27% C, 11·28% H; found: 75·12% C, 11·06% H.

B) Reaction of derivative *XXVI* (519 mg, 1 mmol) afforded the title compound *XXVIII* (286 mg, 64%) which was identical with the product obtained by procedure *A*.

C) Reaction of derivative *XXVII* (505 mg, 1 mmol) afforded the title compound *XXVIII* (277 mg, 62%), which was identical with the product prepared by procedure *A*.

General Procedure for Preparation of Hydroxy Derivatives *XII* and *XVI* by Cleavage of Acetal Protecting Groups with Hydrochloric Acid

A solution of the protected derivative (1 mmol) in a mixture of benzene (5 ml) and methanol (12 ml) was mixed with 2M-HCl (1·6 ml). The reaction mixture was stirred at ambient temperature and the reaction course was followed by TLC in benzene – ether (4 : 1). After dilution with ether (200 ml) the mixture was washed with saturated aqueous solution of potassium hydrogen carbonate and then with water, dried over anhydrous potassium carbonate and the solvents were evaporated. The residue was chromatographed on a column of silica gel (30 g) in benzene – ether (95 : 5).

20-Methoxymethoxy-21-nor-5-pregnen-3β-ol (*XII*)

A) Reaction of compound *IX* (433 mg, 1 mmol) for 2 h afforded 261 mg (75%) of hydroxy derivative *XII*, m.p. 96–98°C (ether), $[\alpha]_D$ −54° (*c* 0·1, chloroform). IR spectrum (tetrachloromethane): 3 610, 3 400 (OH); 1 668 (C=C); 1 140, 1 105, 1 040, 920 (C–O). ^{1}H NMR spectrum (60 MHz): 5·33 bd, 1 H (H-6, $J = 4·5$); 4·56 s, 2 H (OCH_2O); 3·35 s, 3 H (CH_3O); 1·00 s, 3 H (3 × H-19); 0·65 s, 3 H (3 × H-18). For $C_{22}H_{36}O_3$ (348·5) calculated: 75·82% C, 10·41% H; found: 75·85% C, 10·11% H.

B) Reaction of compound *X* (421 mg, 1 mmol) for 10 min furnished 317 mg (91%) of the title compound *XII*, identical with the sample prepared by procedure *A*.

C) Reaction of compound *XI* (407 mg, 1 mmol) for 10 min afforded 314 mg (90%) of the hydroxy derivative *XII*, identical with a sample prepared by procedure *A*.

20-(2-Methoxyethoxymethoxy)-21-nor-5-pregnen-3β-ol (*XVI*)

A) Reaction of derivative *XIII* (477 mg, 1 mmol) for 2 h afforded 287 mg (73%) of the title hydroxy derivative *XVI*, identical with a sample prepared by cleavage of the protecting group with magnesium bromide.

B) Reaction of derivative *XIV* (465 mg, 1 mmol) for 10 min afforded 365 mg (93%) of the hydroxy derivative *XVI*, identical with a sample prepared by procedure *A*.

C) Reaction of derivative *XV* (451 mg, 1 mmol) for 10 min afforded 373 mg (95%) of the hydroxy derivative *XVI*, identical with a sample prepared by procedure *A*.

Reaction of Diol *III* with Tert-butylchlorodiphenylsilane

Triethylamine (335 μl, 2·4 mmol), 4-dimethylaminopyridine (10 mg, 82 μmol) and tert-butylchlorodiphenylsilane (572 μl, 2·2 mmol) were added to a suspension of diol *III* (ref.[15]; 609 mg, 2 mmol) in dichloromethane (7 ml). After stirring at room temperature for 5 h, the reaction mixture was diluted with ether (150 ml), washed successively with water, saturated aqueous solution of potassium hydrogen carbonate and again with water. The residue was chromatographed on a column of silica gel (60 g) in benzene – light petroleum – ether (4 : 4 : 2) to give 651 mg (60%) of product *XXIV*, identical with products prepared by cleavage of the acetal protecting groups.

3β-(2-Methoxyethoxymethoxy)-5-cholestene (*XXX*)

2-Methoxyethoxymethyl chloride (457 μl, 4 mmol) was added to a solution of cholesterol (773 mg, 2 mmol) and N,N-diisopropylethylamine (1·05 ml, 6 mmol) in dichloromethane (10 ml). After stirring at room temperature for 12 h, the reaction mixture was diluted with ether (150 ml), washed successively with 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 (70 g) in light petroleum – benzene (1 : 1). Yield 807 mg (85%) of derivative *XXX*, m.p. 34–37°C, $[\alpha]_D$ −29° (*c* 2·0, chloroform). IR spectrum (tetrachloromethane): 1 668 (C=C); 1 113, 1 051 (C–O). ^{1}H NMR spectrum (100 MHz): 5·34 bd, 1 H (H-6, J = 4·5); 4·77 s, 2 H (OCH_2O); 3·63 m, 4 H (OCH_2CH_2O); 3·38 s, 3 H (CH_3O); 1·00 s, 3 H (3 × H-19); 0·86 d, 6 H (3 × H-26 and 3 × H-27, J = 6·3); 0·68 s, 3 H (3 × H-18). For $C_{31}H_{54}O_3$ (474·8) calculated: 78·43% C, 11·46% H; found: 78·67% C, 11·67% H.

3β-(1-Methoxyethoxy)-5-cholestene (*XXXIII*)

Pyridinium *p*-toluenesulfonate (150 mg, 0·6 mmol) was added to a solution of cholesterol (773 mg, 2 mmol) in dichloromethane (10 ml). After cooling to 0°C, liquid methyl vinyl ether[13,14] (0·6 ml, 6 mmol) was added and the reaction mixture was stirred at 0°C for 1 h and at room temperature for 1 h. Ether (200 ml) was added and the solution was washed with water and dried over anhydrous potassium carbonate. The solvent was evaporated and the residue was chromatographed on a column of alumina in light petroleum – benzene (1 : 1). After removal of nonpolar impurities by elution with light petroleum – benzene (1 : 1), the product *XXXIII* (640 mg, 72%) was eluted with light petroleum – benzene – ether (50 : 49 : 1); m.p. 93–95°C (acetone), $[\alpha]_D$ −12° (*c* 0·6, chloroform). IR spectrum (tetrachloromethane): 1 668 (C=C); 1 134, 1 102, 1 048 (C–O). ^{1}H NMR spectrum (100 MHz): 5·34 bd, 1 H (H-6, J = 4·5); 4·70 q, 1 H (O–CH–O, J = 5); 3·30 s, 3 H (CH_3O); 1·31 d, 3 H (O–CH(CH_3)–O, J = 5); 1·01 s, 3 H (3 × H-19); 0·68 s, 3 H (3 × H-18). For $C_{20}H_{52}O_2$ (444·7) calculated: 81·02% C, 11·79% H; found: 80·98% C, 11·67% H.

Comparison of Rates of Acid Cleavage of Acetal Protecting Groups in 3β-Position

A) A solution of concentrated hydrochloric acid (13 μl, 3 equivalents) in methanol (1·5 ml) was added to a solution of the protected derivative (0·05 mmol) in benzene (1·5 ml).

B) A solution of concentrated hydrochloric acid (127 μl, 30 equivalents) in methanol (1·5 ml) was added to a solution of the protected derivative (0·05 mmol) in benzene (1·5 ml).

The reaction was followed by TLC in benzene – ether (9 : 1) on silica gel plates (35 × 75 mm), preequilibrated in the atmosphere of concentrated aqueous ammonia for 1 h. The time, given in Table I, denotes the interval during which the concentration of the starting compound in the stirred mixture (at 22°C) dropped below the threshold of detection performed by spraying with concentrated sulfuric acid and subsequent heating to 150—200°C.

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