ON STEROIDS. CXXXIX.*

ADDITION OF HYPOBROMOUS ACID DERIVATIVES TO 5(6)-UNSATURATED B-NORSTEROIDS

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The addition of hypobromous acid, BrF, Br_2, $BrOCH_3$, and $BrOCOCH_3$ to Δ^5-B-norsteroids was investigated. Chemical correlation, CD, and PMR spectra show that the major product is in all instances a 6α-bromo derivative of 5β-series.

Hypobromous acid is added to olefins under formation of *trans*-bromohydrins while electronic, steric, and conformational[1] factors decide on the direction of the addition. Hasegawa and Sable[2] stressed the differences in the addition of hypobromous acid to cyclic olefins of various ring size and they show that with derivatives of cyclohexene the reaction is affected mainly by conformational factors, while with cyclopentene derivatives the product is determined mainly by electrostatic factors. This rule was also found fully valid in additions of hypobromous acid to Δ^5-steroids. In a series of normal steroids with a six-membered B-ring 5α-bromo-6β-hydroxy derivatives[3,4] are formed predominantly as products of *trans*-diaxial opening of the intermediary 5α,6α-epibromonium ion. In the series of B-norsteroids the main reaction product is 6α-bromo-5β-hydroxy derivative[5], *i.e.* a substance formed on opening of the corresponding 5α,6α-epibromonium ion[6] according to Markovnikov. In this paper we present experimental confirmation of the assumption that hypobromous acid derivatives, as for example bromine, bromine fluoride, methyl ester of hypobromous acid, and acetyl hypobromite, which with normal Δ^5-steroids lead to corresponding 5α-bromo compounds[7–10], afford with Δ^5-B-norsteroids corresponding 6α-bromo-B-norsteroids of the 5β-series. In view of the utilisability of single products we carried out single reactions with derivatives of B-norcholestene or 17β-hydroxy-17α-methyl-B-norandrostene, or in both series.

The addition of bromine was carried out in tetrachloromethane at $-10°C$ in order to suppress side-reactions[11]. B-Norcholesteryl acetate[12] (*I*) gives dibromide *II* in addition to 2 more polar components. In the PMR spectrum of substance *II* a signal occurs, due to one proton CHBr, at 4·98 p.p.m. which is split to a doublet[13]

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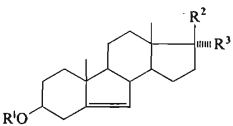
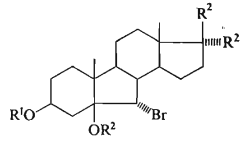
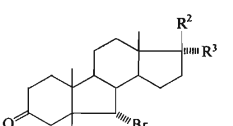
(J 5·2 Hz) by the proton at $C_{(8)}$. The addition of bromine to B-norcholesterol[12] (*III*) takes place in a similar manner, but the product *IV* is rather instable and liberates hydrogen bromide even at room temperature. The same is true of 3-keto derivative *V* obtained on oxidation of hydroxy derivative *IV* according to Jones[14]. The decomposition of bromo ketone *V* in boiling tetrachloromethane gives monobromo derivative the UV, IR, and PMR spectra of which agree with structure *VI*. The location of bromine on carbon $C_{(6)}$ is evident from the bathochromic shift of the $\pi \rightarrow \pi^*$ transition (+14 nm) in the UV spectrum of substance *VI* (254 nm), and from the signal of the proton bound with the bromine atom in the geminal position. Decoupling experiments show that the signal of this proton is split by a vicinal coupling with the proton at carbon atom $C_{(8)}$ as in the case of substance *II*, and also by the allylic coupling ($J_{4,6}$ 1·2 Hz) with the proton on the double bond. Substance *VI* is relatively stable; formation of a "different" bromo derivative could be observed only after one month standing at 0°C (using PMR spectroscopy). The fact that the isomer of substance *VI* may be distinguished in the PMR spectrum increases the probability of the correlation proofs presented later. The configuration of bromine was proved by the preparation of substance *VI* by another route where we started with substance *VII* in which the

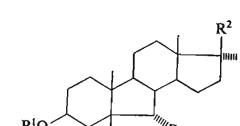




I, R^1 = Ac, R^2 = i-C_8H_{17}, R^3 = H
III, R^1 = H, R^2 = i-C_8H_{17}, R^3 = H
VIII, R^1 = Ac, R^2 = OH, R^3 = CH_3
XVII, R^1 = H, R^2 = OH, R^3 = CH_3

IX, R^1 = Ac, R^2 = H, R^3 = OH, R^4 = CH_3
XII, R^1 = R^2 = Ac, R^3 = i-C_8H_{17}, R^4 = H
XIII, R^1 = R^2 = H, R^3 = i-C_8H_{17}, R^4 = H
XVI, R^1 = Ac, R^2 = CH_3, R^3 = i-C_8H_{17}, R^4 = H
XVIII, R^1 = H, R^2 = CH_3, R^3 = OH, R^4 = CH_3



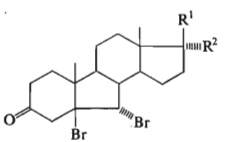


VII, R^1 = H, R^2 = i-C_8H_{17}, R^3 = H
X, R^1 = H, R^2 = OH, R^3 = CH_3
XV, R^1 = Ac, R^2 = i-C_8H_{17}, R^3 = H
XIX, R^1 = R^3 = CH_3, R^2 = OH

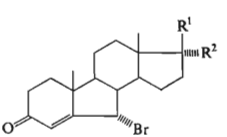
II, R^1 = Ac, R^2 = i-C_8H_{17}, R^3 = H
IV, R^1 = H, R^2 = i-C_8H_{17}, R^3 = H

6α-configuration of bromine was proved earlier[5]: dehydration of hydroxy ketone *VII* was carried out at room temperature with thionyl chloride in ether. The product was found to be identical with substance *VI* on the basis of its IR and PMR spectra. In an analogous manner we also prepared the corresponding unsaturated ketone *XI* for correlation purposes from the acetate of B-normethylandrost-5-ene-3β,17β-diol[15] (*VIII*).

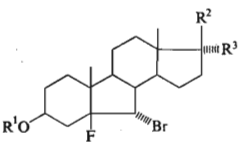
The addition of acetyl hypobromite[10] to B-norcholesteryl acetate (*I*) gives 3β,5β-diacetoxy-6α-bromo-B-nor-5β-cholestane (*XII*) as the only product. Its PMR spectrum is in full agreement with the proposed structure: two singlets of $COC\underline{H}_3$ (1·96 and 1·98 p.p.m.) and only one one-proton multiplet at 5·18 p.p.m., which confirm that one of the two acetoxyl substituents is on a tertiary carbon. The doublet of the Br—C—H signal at 4·74 p.p.m. has a coupling constants close to the above given values ($J_{6,8}$ 6·0 Hz). The double shielding by two acetoxy groups shifts the protons on $C_{(4)}$ from the methylene envelope; decoupling experiments show that the β-proton appears as a quartet ($J_{3\alpha,4\beta}$ 6·0 Hz, $J_{4\alpha,4\beta}$ 15·9 Hz) at 2·26 p.p.m. and the α-proton as a quartet at 2·72 p.p.m. ($J_{3\alpha,4\alpha}$ 3·5 Hz). Acid hydrolysis of substance *XII* gives the diol *XIII* identical with the authentic 3β,5-dihydroxy-6α-bromo-B-nor-5β-cholestane[5]. Attempts at partial hydrolysis of diacetate *XII* were unsuccessful even in weakly alkaline medium where 5β,6β-epoxy-B-nor-5β-cholestan-3β-ol[6,10] (*XIV*) is formed. An attempt to prepare 5β-acetoxy derivative *XV* by acetylation of bromohydrin *VII* was similarly unsuccessful. In all instances only dehydration to unsaturated bromo ketone *VI* takes place.



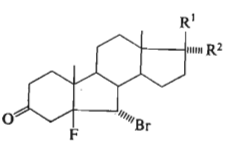
V, $R^1 = i\text{-}C_8H_{17}$, $R^2 = H$



VI, $R^1 = i\text{-}C_8H_{17}$, $R^2 = H$
XI, $R^1 = OH$, $R^2 = CH_3$

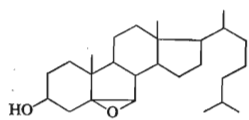


XX, $R^1 = Ac$, $R^2 = i\text{-}C_8H_{17}$, $R^3 = H$
XXI, $R^1 = H$, $R^2 = i\text{-}C_8H_{17}$, $R^3 = H$
XXIII, $R^1 = Ac$, $R^2 = OH$, $R^3 = CH_3$
XXIV, $R^1 = H$, $R^2 = OH$, $R^3 = CH_3$



XXII, $R^1 = i\text{-}C_8H_{17}$, $R^2 = H$
XXV, $R^1 = OH$, $R^2 = CH_3$

The addition of methyl ester of hypobromous acid[9] was carried out with N-bromoacetamide in methanol. Under these conditions B-norcholesteryl acetate changes to methoxy derivative *XVI*. The signal of the proton in geminal position to bromine atom appears in the PMR spectrum similarly as in other 6α-bromines of this series (4·47 p.p.m., $J_{6,8}$ 6·0 Hz); the three-proton singlet at 3·19 p.p.m. is indicative of the attachment of the methoxy group to a tertiary carbon atom. On reaction with dihydroxy derivative *XVII* a partial oxidation of the primary product takes place and therefore we oxidised the reaction mixture to ketone *XIX*. 5β-Fusion of the A/B rings is corroborated by the CD curve which is close to other 6α-bromo ketones described in this paper (Table I).



XIV

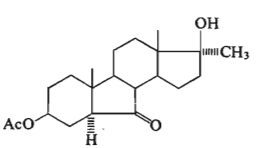
For the addition of bromine fluoride to B-norcholesteryl acetate we used a method employing N-bromoacetamide in liquid hydrogen fluoride[8]. From the reaction mixture we isolated by thin-layer chromatography substance *XX* the polarity of which is equal to that of the starting material. This substance when hydrolysed gives hydroxy derivative *XXI* and on oxidation fluoro derivative *XXII*. The 5β-configuration or fluorine in this compound follows from vicinal and long-range interactions[16] of fluorine with protons on carbon atoms 4, 6 and 19: the protons on $C_{(4)}$ appear as two quartets at 2·66 p.p.m. (4β-H) and 3·30 p.p.m. (4α-H) with a geminal coupling constant $J_{4\alpha,4\beta}$ 15·7 Hz and vicinal constants $J_{4\beta,F}$ 18·4 Hz and $J_{4\alpha,F}$ 26·5 Hz. Protons on carbon $C_{(19)}$ appear as a doublet with a coupling constant of 3 Hz. The signal Br—C—H appears as a quartet ($J_{6,8}$ 4·0, $J_{6,F}$ 16·5 Hz).

TABLE I

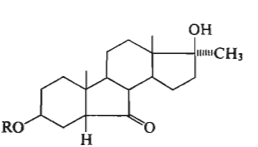
Molecular Ellipticity of Some 3-Oxo-B-norsteroids in Chloroform

Compound	λ, nm	[Θ]	Compound	λ, nm	[Θ]
B-Nor-5α-cholestan-3-one[23]	296	+7 100	*X*	292	−5 600
B-Nor-5β-cholestan-3-one[23,24]	294	−5 300	*XIX*	291	−9 600
5-Hydroxy-B-nor-5β-cholestan-3-one[25]	292	−6 600	*XXV*	294	−2 000
VII[26]	292	−6 300			

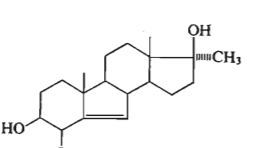
The above method of the addition of bromine fluoride was not suitable for very weakly soluble substances as for example androstane derivative *VIII*; for this case we made use of an alternative method[17] in which monobromo fluoride is generated from anhydrous silver fluoride and bromine. By chromatography of the product on silica gel we isolated 3 substances. Beilstein's test demonstrated the presence of halogen only in the component which was closest to the starting material by its polarity. The elemental analysis of this substance agrees with the supposed structure *XXIII*; 5β-configuration of fluorine again follows from the long-range coupling of fluorine with protons on $C_{(19)}$ ($J_{19,F}$ 6·0 Hz), *trans*-fusion of bromine with respect to fluorine in compound *XXIII* follows from the vicinal coupling of the $C_{(6\beta)}$-proton with fluorine ($J_{6,F}$ 14·0). The hydrolysis of acetate *XXII* in acid medium gives rise to hydroxy derivative *XXIV* which on oxidation gives keto derivative *XXV*. The character of single couplings in the PMR spectrum is approximately identical to the case of cholestane derivative *XXII*. We carried out chemical correlation of *XXV* by conversion to unsaturated bromo ketone *XI* identical with the substance prepared



XXVI



XXVII, R = H
XXVIII, R = Ac



XXIX

above. On comparison of bromo ketone *V* and fluoro ketone *XXV* the greater thermal stability of fluoro ketone[7,18] becomes evident: under the conditions sufficient for the transformation of bromo ketone to unsaturated ketone *VI*, fluoro ketone *XXV* remains unchanged. Reaction of bromine fluoride with B-norsteroids under the given conditions leads to maximum 30% yields. From the reaction mixture we isolated another two substances; to the less polar one we assigned the structure of 6-oxo-17α-methyl-B-nor-5α-androstane-3β,17β-diol 3β-monoacetate (*XXVI*) on the follow-

ing evidence: elemental analysis and the mass spectrum agree with the composition $C_{21}H_{32}O_4$, the IR spectrum confirms that a keto group on a five-membered ring is added to the molecule (1730 cm^{-1}). Alkaline hydrolysis of the acetoxy group is accompanied by a negative shift of molecular rotation, which is a phenomenon known to occur during the isomerisation of the less thermodynamically stable 5α-B-norcholestan-6-one to its 5β-isomer. The reacetylation of hydroxy derivative *XXVII* does not give rise to the original acetate *XXVI*, but to the more levorotatory isomer of *XXVIII*. A more polar component of the reaction mixture after the preparation of fluoro derivative *XXIII* is the acetate of 17α-methyl-B-norandroste-5-ene-3β, 4β,17β-triol (*XXIX*), as follows from the following data: elemental analysis shows that a single oxygen atom was introduced into the molecule. In the PMR spectrum there is a signal of a proton on a trisubstituted double bond. The multiplet of the 3α-proton is shifted upfield in comparison with the starting substance, similarly as in the case of the hydrolysis of the acetoxy group. The signal of $\underline{C}HOCOCH_3$ appears as a doublet (J 3·5 Hz) at a much lower field than would correspond to a substitution in the position 3. Strongly negative molecular rotation (M_D −698°) is in accordance[19] with the proposed structure.

CD curves of some substances described above were also measured, *i.e.* of *VII*, *X*, *XIX*, and *XXV* (Table I). The fact that the introduction of bromine in position 6α of 5-hydroxy-B-nor-5β-cholestan-3-one (*XXX*) has only a negligible effect on the direction and the value of molecular ellipticity (substances *XXX* and *VII* in Table I) deserves attention. This fact is surprising from the point of view of earlier knowledge[20] on the flexibility of 3-oxo-B-nor-5β-steroids in which 6α-substitution was accompanied by a marked effect on amplitude, but on the other hand this fact agrees with the idea of a normal chair conformation of the A-ring in B-norsteroids[21]. In the case of the chair conformation of the ring A the 6α-substituent comes into the nodal plane of the octant projection, while the 5β-substituent is located in the negative octant. The fact that the fluoro derivative *XXV* shows a negative Cotton effect weaker than in other substances of this series agrees well with the anomalous behaviour of fluorine in optical measurements[22].

EXPERIMENTAL

Melting points were determined on a Kofler block and they are not corrected. Optical rotations and IR spectra were measured in chloroform, PMR spectra in deuteriochloroform on a Varian 100 apparatus.

3β-Acetoxy-5,6α-dibromo-B-nor-5β-cholestane (*II*)

B-Norcholesteryl acetate[12] (*I*, 400 mg) was dried by distillation with benzene. The material was dissolved in tetrachloromethane (5 ml) and mixed at −10°C with a 10% solution of bromine in tetrachloromethane (2 ml). After five minutes standing the reaction mixture was washed with aqueous sodium thiosulfate and water, and dried over sodium sulfate. After evaporation of the solvent *in vacuo* the dry residue was chromatographed on a thin layer of silica gel with benzene. The oily product (360 mg) (*II*) was dried for analysis and then used immediately for the further

reaction step. PMR-spectrum: 0·72 (s, 3 protons), 1·26 (s, 3 protons), 0·86 (d, *J* 6 Hz, 6 protons), 0·92 (d, *J* 6 Hz, 3 protons), 2·04 (s, 3 protons), 4·98 (d, *J* 5·2 Hz, 1 proton), and 5·25 (mt, 1 proton) p.p.m. $[\alpha]_D^{20}$ −46° (*c* 0·8). For $C_{28}H_{46}Br_2O_2$ (574·5) calculated: 58·54% C, 8·07% H, and 27·82% Br; found: 58·33% C, 7·87% H, 28·11% Br.

5,6α-Dibromo-B-nor-5β-cholestan-3β-ol (*IV*)

B-Norcholesterol[12] (*III*, 150 mg) was treated with bromine in tetrachloromethane as in the preceding experiment. Chromatography of the product on a thin layer of silica gel (10% of ether in benzene, R_F 0·35) gave 88 mg of dibromide *IV*, m.p. 138—141°C (ether), $[\alpha]_D^{20}$ −39° (*c* 2.1). For $C_{26}H_{44}Br_2O$ (532·5) calculated: 58·64% C, 8·33% H, 30·02% Br; found: 58·40% C, 8·28% H, 30·29% Br.

6α-Bromo-B-nor-4-cholesten-3-one (*VI*)

a) *From 5,6α-dibromo-*B-*nor-5β-cholestan-*3β-ol (IV): Dibromo derivative *IV* (160 mg) was oxidised with Jones reagent in acetone at 0°C, the reaction mixture was poured into a solution of potassium hydrogen carbonate, and the product was extracted with light petroleum and the extract dried and evaporated *in vacuo* to dryness. The residue was boiled in 5 ml tetrachloromethane for 1 hour and the product was chromatographed on a thin layer of silica gel in light petroleum–ether mixture (9 : 1). The product (108 mg) which would not crystallise was dried for analysis at room temperature at 0·2 Torr. IR spectrum: 1 663 cm^{-1}. UV spectrum: 254 nm (log ε 3·96). $[\alpha]_D^{20}$ +47° (*c* 0·8). PMR spectrum: 0·73 (*c*, 3 protons), 1·018 (s, 3 protons), 0·87 (d, *J* 6·2 Hz, 6 protons), 0·94 (d, *J* 6·0 Hz, 3 protons), 5·09 (dd, *J* 5·8 Hz and 1·5 Hz, 1 proton), and 6·10 (d, *J* 1·5 Hz, 1 proton) p.p.m. For $C_{26}H_{41}BrO$ (449·5) calculated: 69·47% C, 9·91% H, 17·78% Br; found: 69·80% C, 10·12% H, 17·54% Br.

b) *From 5-hydroxy-6α-bromo-*B-*nor-5β-cholestan-3-one* (VII) *and thionyl chloride*: 200 mg of hydroxy derivative *VII* were mixed with 4 ml of ether and 20 drops of thionyl chloride. After 2 hours standing the starting material passed into solution and a control chromatogram showed that a complete dehydration of substance *VII* to 6α-bromo-B-nor-4-cholesten-3-one took place. The solution was additioned with 3 ml of tetrachloromethane and the mixture was evaporated to dryness under reduced pressure. If larger batches were worked up, the evaporation with tetrachloromethane had to be repeated. The product (190 mg) shows IR and PMR spectra identical with those of a substance prepared as under *a*).

c) *From 5-fluoro-6α-bromo-*B-*nor-5β-cholestan-3-one* (XXII): A solution of fluoro ketone *XXII* (35 mg) in 5 ml of acetone was refluxed for 2 hours. It was then evaporated to dryness and chromatographed on a thin layer of silica gel as under *a*). According to its polarity and IR spectrum the product (22 mg) was identical with substance *VI*.

d) *From 5β-hydroxy-6α-bromo-*B-*nor-5β-cholestan-3-one with acetic anhydride*: Bromohydrin *VII* (16 mg) was added to 3 ml of an acetylation mixture[27] prepared from 10 ml of acetic acid and 3 ml of acetic anhydride and 0·1 ml of anhydrous perchloric acid 50%. After 15 minutes all the starting material passed into solution, after an additional 20 minutes the mixture was decomposed by pouring it into water. The product was extracted with light petroleum and the extract was washed with water, dried over sodium sulfate and evaporated to dryness. The product (9 mg), after purification by thin-layer chromatography on silica gel, had an IR spectrum identical with that of substance *VI*.

6α-Bromo-17-methyl-B-nor-5β-androstane-3β,5,17β-triol (*IX*)

To a solution of 17-methyl-B-nor-5-androstene-3β,17β-diol[15] (*XVII*, 100 mg) in tetrahydrofuran (3 ml) 0·6 ml of water and 0·3 ml of 8% perchloric acid in water were added, followed by 50 mg of N-bromoacetamide. After 90 minutes standing the mixture was poured into an aqueous sodium hydrogen sulfite solution and the product was extracted with chloroform, washed with water, and the extract was dried over sodium sulfate and evaporated to dryness under reduced pressure. The residue was crystallised from ether, m.p. 143–145°C (decomp.), yield 47 mg; IR spectrum: 3600 cm^{-1}; $[\alpha]_D^{20}$ −38° (*c* 0·8). For $C_{19}H_{31}BrO_3$ (387·4) calculated: 58·91% C, 8·07% H, 20·63% Br; found: 58·65% C, 8·19% H.

5,17β-Dihydroxy-6α-bromo-17-methyl-B-nor-5β-androstan-3-one (*X*)

Bromo derivative *IX* (700 mg) was oxidised according to Jones at 0°C, the product was extracted with dichloromethane crystallised from a mixture of dichloromethane and heptane; m.p. 176–178°C (decomp.); $[\alpha]_D^{20}$ −69° (*c* 1·1); IR spectrum: 1714, 3400, and 3600 cm^{-1}; PMR spectrum: 0·91 (s, 3 protons), 0·96 (s, 3 protons), 1·24 (s, 3 protons), 2·49 (d, J_{gem} 16 Hz, 1 proton), 3·27 (d, J_{gem} 16 Hz, 1 proton), 4·34 (d, *J* 4·5 Hz, 1 proton), and 4·56 (br. s, 1 proton) p.p.m. For $C_{19}H_{29}BrO_3$ (385·3) calculated: 59·22% C, 7·59% H, 20·74% Br; found: 58·99% C, 7·70% H, 20·55% Br.

6α-Bromo-17β-hydroxy-17-methyl-B-nor-4-androsten-3-one (*XI*)

a) *Dehydration of* XI: 30 mg of substance *XI* were suspended in 10 ml of ether and 10 drops of thionyl chloride were added to the mixture. After 2 hours standing the starting material dissolved completely and a control thin-layer chromatogram showed that the conversion is complete. Benzene (approx. 5 ml) was added to the mixture and the volatile components were evaporated to dryness *in vacuo*. Crystallisation of the product from a mixture of methylene chloride and heptane gave 21 mg of a substance, m.p. 166–168°C; $[\alpha]_D^{20}$ +73° (*c* 0·7); IR spectrum: 3605, 1665 cm^{-1}; UV spectrum: 252 nm (log ε 3·97); PMR spectrum: 0·92 (s, 3 protons), 1·09 (s, 3 protons), 1·27 (s, 3 protons), 2·4–2·7 (mt, 2 protons), 5·10 (dd, $J_{6,8}$ 6·1 Hz, $J_{6,4}$ 1·4 Hz, 1 proton), 6·11 (d, *J* 1·4 Hz, 1 proton) p.p.m.

b) *Dehydrohalogenation of* XXV: Substance *XXV* (30 mg) in acetone (5 ml) was refluxed for two hours and then evaporated to dryness. The residue was chromatographed on a thin layer of silica gel. The non-polar component (7 mg) had R_F value identical with the starting *XXV*; their IR spectra also coincided. The polar component (18 mg) had R_F value corresponding to that of the required substance *XI*; its m.p. after crystallisation from methylene chloride and heptane was undepressed when the substance prepared under *a* was admixed; the IR spectra of both substances were also identical.

3β,5-Diacetoxy-6α-bromo-B-nor-5β-cholestane (*XII*)

To a solution of substance *I* (300 mg) in 2 ml of tetrachloromethane a fresh solution of acetylhypobromite (approx. 400 mg in 3 ml of tetrachloromethane) was added and the mixture was allowed to stand at 0°C for 10 minutes. It was then poured into a solution of sodium hydrogen sulfite in water and the mixture was extracted with chloroform, washed with water, dried over sodium sulfate, and evaporated to dryness in a vacuum; m.p. 133–135°C (methanol; yield 190 mg); $[\alpha]_D^{20}$ −4° (*c* 1·7); IR spectrum: 1727, 1260, 1041, 1022 cm^{-1}; PMR spectrum: 0·69 (s, 3 protons), 1·03 (s, 3 protons), 0·87 (d, *J* 6·2 Hz, 6 protons), 0·93 (d, *J* 6·0 Hz, 3 protons),

1·96 (s, 3 protons), 1·98 (s, 3 protons), 2·72 (dd, J 3·5 and 15·8 Hz, 1 proton), 2·26 (dd, J 6·0 and 15·8 Hz, 1 proton), 4·74 (d, $J \neq 6{\cdot}0$ Hz, 1 proton), 5·18 (mt, 1 proton), p.p.m.. For $C_{30}H_{49}BrO_4$ (553·6) calculated: 65·08% C, 8·92% H; found: 64·96% C, 9·10% H.

6α-Bromo-B-nor-5β-cholestane-3β,5-diol (*XIII*)

To a solution of diacetate *XII* (95 mg) in 1 ml of chloroform (1 ml) a solution of conc. hydrochloric acid (0·1 ml) in methanol (10 ml) was added and then allowed to stand at 20°C for 26 hours. The reaction mixture was diluted with chloroform and washed with water, then dried over sodium sulfate, filtered, and evaporated to dryness at a bath temperature not exceeding 25°C. According to thin-layer chromatography on silica gel (in 20% ether in benzene) the mixture contained approximately 30% of the starting compound and also the main product the R_F value of which was identical with that of authentic 6α-bromo-B-nor-5β-cholestane-3β,5-diol[5]. Crystallisation from light petroleum gave a product (65 mg), m.p. 112—119°C. Further crystallisation from methylene chloride and heptane increased the melting point up to 132—140°C (42 mg) and eventually 142—144°C (30 mg). Chromatographic control shows that the main product of the reaction mixture does not change on crystallisation; $[\alpha]_D^{20}$ —18° (*c* 1·1); IR spectrum: 3505 cm^{-1}, identical with that of an authentic sample of *XIII*.

5,6β-Oxido-B-nor-5β-cholestan-3β-ol (*XIV*)

To a solution of 95 mg of diacetoxy derivative *XII* in tetrahydrofuran (1·5 ml) and methanol (2 ml) a solution of potassium carbonate (40 mg) in 1 ml of water was added and the mixture was shaken. After 24 hours a thin-layer chromatogram shows that the majority of the substance is unchanged. Only a small amount of a reaction product was visible, having the R_F value as oxide *XIV*. Preparative thin-layer chromatography gave 6 mg of this component and IR spectroscopy demonstrated that it is identical with an authentic sample[6] of *XIV*.

3β-Acetoxy-5-methoxy-6α-bromo-B-nor-5β-cholestane (*XVI*)

To a solution of 300 mg of N-bromoacetamide in 5 ml of methanol a solution of 240 mg of B-norcholesteryl acetate (*I*) in 4 ml of tetrahydrofuran was added dropwise under stirring and at room temperature. After 20 hours the reaction mixture was poured into an aqueous solution of potassium hydrogen carbonate and the separated product was extracted with light petroleum and chromatographed on 10 g of silica gel. Elution with a 30% solution of benzene in light petroleum gave 35 mg of the starting compound and 175 mg of substance *XVI* which would not crystallise. IR spectrum: 1721, 1255, 1028, 1084 and 1090 cm^{-1}; $[\alpha]_D^{20}$ —18° (*c* 0·7); PMR spectrum: 0·68 (s, 3 protons), 0·90 (s, 3 protons), 0·85 (d, J 6·5 Hz, 6 protons), 0·91 (d, J 6·0 Hz, 3 protons), 2·02 (s, 3 protons), 2·105 (d, J 5 Hz, 1 proton), 3·19 (s, 3 protons), 4·47 (d, J 6 Hz, 1 proton), 5·18 (br. mt., 1 proton) p.p.m. For $C_{29}H_{49}BrO_3$ (525·6) calculated: 66·26% C, 9·40% H, 15·21% Br; found: 65·97% C, 9·16% H, 15·50% Br.

5-Methoxy-6α-bromo-17β-hydroxy-17-methyl-B-nor-5β-androstan-3-one (*XIX*)

A solution of 17-methyl-B-nor-5-androstene-3β,17-diol (*XVII*) (350 mg) in 5 ml tetrahydrofuran was added under stirring to a solution of N-bromoacetamide (350 mg) in 5 ml of methanol and after 24 hours the reaction mixture was poured into an aqueous solution of sodium hydrogen sulfite. The separated product was extracted with methylene chloride, the extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo* to dryness. The IR spectrum of the crude product contains absorption maxima at 3600, 3500, 1660, and 1710 cm^{-1}. Hence,

substance *XVIII* is partly oxidised to keto derivative *XIX*. Therefore the product was submitted to oxidation in acetone (6 ml) with Jones reagent[14] at 0°C without further purification. The reaction mixture was decomposed by pouring it into a solution of potassium hydrogen carbonate and the product was extracted with ether and crystallised from a mixture of chloroform and heptane; yield 185 mg, m.p. 142—144°C (decomp.): $[\alpha]_D^{20}$ −86° (*c* 0·70); IR spectrum: 3600, 2830, 1717, 1092, and 1062 cm^{-1}; PMR spectrum: 0·89 (s, 3 protons), 0·93 (s, 3 protons), 1·23 (s, 3 protons), 2·81 (d, J_{gem} 16 Hz, 1 proton), 3·01 (d, J_{gem} 16 Hz, 1 proton), 3·15 (s, 3 protons), 4·48 (d, *J* 5·4 Hz, 1 proton) p.p.m. For $C_{20}H_{31}BrO_3$ (399·4) calculated: 60·14% C, 7·83% H, 20·01% Br; found: 60·08% C, 7·80% H, 20·23% Br.

5-Fluoro-6α-bromo-B-nor-5β-cholestan-3-one (*XXII*)

B-norcholesteryl acetate *I* (1·6 g) in a polyethylene vessel was mixed with 16 ml of acetic acid, 6 ml of tetrahydrofuran, and 6 ml of anhydrous hydrogen fluoride, and N-bromoacetamide (0·8 g) was added to the mixture under stirring. After one minute stirring an orange solution was obtained which was allowed to stand at room temperature for 20 hours. The reaction mixture was poured into water, the product was extracted with light petroleum, and the extract washed neutral with potassium hydrogen carbonate. Chromatography of the product on 50 g of silicagel (0·5% acetone in light petroleum) gave substance *XX* (550 mg, 16·89% Br, 3·87% F) in the form of an oil. A part of this product (500 mg) was dissolved in a mixture of chloroform (0·5 ml), methanol (5 ml), and hydrochloric acid (0·1 ml), and the solution was allowed to stand at 37°C for 18 hours. Concentration of the reaction mixture *in vacuo* and drying it in a chloroform solution over sodium sulfate and evaporation gave 420 mg of an oily product (*XXI*) which was oxidised directly in acetone with Jones reagent[14]. The reaction mixture was poured into a solution of potassium hydrogen carbonate and the product was extracted with light petroleum. The extract was evaporated and crystallised from acetone. Yield, 387 mg; m.p. 155—157°C $[\alpha]_D^{20}$ −3° (*c* 1·0); IR spectrum: 1720 cm^{-1}; PMR spectrum: 0·73 (s, 3 protons), 0·975 (d, *J* 6·8 Hz, 3 protons), 0·93 (d, *J* 6·4 Hz, 3 protons), 0·87 (d, *J* 6·5 Hz, 6 protons), 2·38 (sextet, 1 proton), 2·66 (dd, J_{gem} 15·7 Hz, $J_{4\beta,F}$ 18·4 Hz, 1 proton), 3·305 (dd, J_{gem} 15·7 Hz, $J_{4\alpha,F}$ 26·5 Hz, 1 proton), 4·39 (dd, $J_{6,8}$ 4·0 Hz, $J_{6,F}$ 16·6 Hz, 1 proton) p.p.m. For $C_{26}H_{42}BrFO$ (469·6) calculated: 66·50% C, 9·02% H, 17·02% Br, 4·05% F; found: 66·43% C, 9·16% H, 17·03% Br, 3·94% F.

3β-Acetoxy-5-fluoro-6α-bromo-17-methyl-B-nor-5β-androstan-17β-ol (*XXIII*)

To a solution of 3-acetate *VIII* (100 mg) in 4 ml of tetrahydrofuran 300 mg of dry silver fluoride was added. Then 66 mg of bromine were added dropwise to it under stirring at room temperature. The addition lasted 15 minutes and the stirring was continued for another 15 minutes. Inorganic material was then filtered off, washed with acetone, and the combined filtrates were evaporated to dryness. Preparative thin-layer chromatography on silice gel (in 10% acetone in light petroleum, double development) gave 49 mg of an oil the polarity of which was similar to that of the starting material (*VIII*). Repeated chromatography of this product on a silica gel thin layer (20% ether in benzene) afforded 29 mg of substance *XXIII*, m.p. 126—127°C (acetone–heptane), $[\alpha]_D^{20}$ −45° (*c* 1·2). For $C_{21}H_{32}BrFO_3$ (431·4) calculated: 58·46% C, 7·48% H, 18·53% Br, 4·40% F; found: 58·51% C, 7·74% H, 18·54% Br, 4·19% F.

5-Fluoro-6α-bromo-17-methyl-B-nor-5β-androstane-3β, 17β-diol (*XXIV*)

To a solution of acetate *XXIII* (300 mg) in chloroform (1·5 ml) and methanol (15 ml) hydrochloric acid (0·3 ml) was added and the mixture was allowed to stand at 37°C for 20 hours. The

reaction mixture was diluted with chloroform, concentrated *in vacuo* to a small volume (approx. 3 ml), additioned with chloroform, washed with potassium hydrogen carbonate and water, dried over sodium sulfate, filtered, and evaporated to dryness under reduced pressure. After crystallisation from ether the obtained substance *XXIV* melted at 156–157°C (decom.). Yield, 160 mg, $[\alpha]_D^{20}$ −40° (*c* 1·54); PMR spectrum: 0·91 (s, 3 protons), 0·98 (d, *J* 6·0 Hz, 3 protons), 1·25 (s, 3 protons), 4·15 (br. mt, 1 proton), 4·37 (dd, $J_{6,F}$ 15·5 Hz, $J_{6,8}$ 4·0 Hz, 1 proton) p.p.m. For $C_{19}H_{30}BrFO_2$ (389·4) calculated: 58·61% C, 7·77% H, 20·53% Br, 4·88% F; found: 58·46% C, 7·90% H, 20·72% Br, 4·64% F.

5-Fluoro-6α-bromo-17β-hydroxy-17-methyl-B-nor-5β-androstan-3-one (*XXV*)

A solution of dihydroxy derivative *XXIV* (85 mg) in 3 ml of acetone was cooled and oxidised with Jones reagent[14] at 0°C. After 2 minutes reaction the mixture was diluted with benzene, washed with an aqueous potassium hydrogen carbonate solution and water, and then filtered through a small column of sodium sulfate and silica gel. Substance *XXV* was crystallised from acetone and heptane. Yield, 63 mg, m.p. 149–151°C; $[\alpha]_D^{20}$ −40° (*c* 1·1)-IR spectrum: 3610 and 1722 cm^{-1}; PMR spectrum: 0·94 (s, 3 protons), 1·00 (d, *J* 6·8 Hz, 3 protons), 1·26 (s, 3 protons), 2·415 (sextet, 1 proton), 2·70 (dd, J_{gem} 16 Hz, J_{vic} 19 Hz, 1 proton), 3·32 (dd, J_{gem} 16 Hz, J_{vic} 27·0 Hz, 1 proton), 4·44 (d,, $J_{6,8}$ 5·0 Hz, $J_{6,F}$ 18 Hz, 1 proton) p.p.m. For $C_{19}H_{28}BrFO_2$ (387·3) calculated: 58·91% C, 7·29% H, 20·63% Br, 4·91% F; found: 58·88% C, 7·31% H, 20·79% Br, 4·66% F.

3β-Acetoxy-17β-hydroxy-17-methyl-B-nor-5α-androstan-6-one (*XXVI*)

In a preparation of fluoro derivative *XXIII* from 20 g of substance *VIII* we also isolated from the reaction mixture the more polar keto drivative *XXVI* (2·35 g), m.p. 169–170°C (acetone), $[\alpha]_D^{20}$ +50° (*c* 2·1); IR spectrum: 3610, 1730, 1255, 1114 cm^{-1}; Mass spectrum: M = 348; PMR spectrum: 0·87 (s, 3 protons), 0·91 (s, 3 protons), 1·38 (s, 3 protons), 2·07 (s, 3 protons), and 4·72 (br. mt, 1 proton) p.p.m. For $C_{21}H_{32}O_4$ (348·5) calculated: 72·38% C, 9·26% H; found: 72·06% C, 9·53% H. A further fraction gave 3.4 g of acetate *XXIX*, m.p. 190–191°C $[\alpha]_D^{20}$ −180° (*c* 2·0); IR spectrum: 3600, 1730, 1635, 1605, 1245 cm^{-1}. PMR spectrum: 0·87 (s, 3 protons), 0·98 (s, 3 protons), 1·21 (s, 3 protons), 2·05 (s, 3 protons), 2·43 (mt, 1 proton), 3·67 (mt, 1 proton), 5·535 (d, *J* 3·5 Hz, 1 proton), 5·90 (br. s, 1 proton) p.p.m. For $C_{21}H_{32}O_4$ (348·5) calculated: 72·38% C, 9·26% H; found: 72·36% C, 9·30% H.

3β,17β-Dihydroxy-17-methyl-B-nor-5β-androstan-6-one (*XXVII*)

To a solution of acetate *XXVI* (0·5 g) in 2 ml of chloroform and methanol (30 ml) hydrochloric acid (0·5 ml) was added and the mixture was allowed to stand at 37°C for 20 hours. The reaction mixture was concentrated *in vacuo*, diluted with water, and the separated product was extracted with methylene chloride. The extract was washed with a solution of potassium hydrogen carbonate and water, and dried over sodium sulfate and evaporated to dryness under reduced pressure. Yield 320 mg, m.p. 194–196°C; $[\alpha]_D^{20}$ +6° (*c* 1·0). For $C_{19}H_{30}O_3$ (306·4) calculated: 74·47% C, 9·87% H; found: 74·38% C, 9·79% H.

3β-Acetoxy-17β-hydroxy-17-methyl-B-nor-5β-androstan-6-one (*XXVIII*)

Acetylation of diol *XXVII* (110 mg) in a mixture of acetic anhydride (0·3 ml) and 1 ml of pyridine at room temperature for 18 hours gave monoacetate *XXVIII*. Yield 86 mg, m.p. 136–137°C;

$[\alpha]_D^{20}$ +17° (*c* 1·3); The IR spectrum (3610, 1730, 1254, and 1038 cm^{-1}) was different from that of substance *XXVI*. For $C_{21}H_{32}O_4$ (384·5) calculated: 72·38% C, 9·26% H; found: 72·47% C, 9·25% H.

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