STEROID DERIVATIVES. LXXII.*
FORMATION AND REACTIONS OF STEROID 16-SPIRO-2'-OXIRANS

V. SCHWARZ

Research Institute for Pharmacy and Biochemistry, Prague 9

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Under the influence of chromic acid, derivatives of 17α-hydroxy-16-methylene-20-pregnanone, *I—V*, undergo epoxidation at the 16-methylene double band. The reaction is stereospecific, from the α-side, giving rise to (16*S*)-spiro-2'-oxirans of the pregnane series, *VI—X*. Under more energetic conditions the corresponding oxirans of the androstane series, *XII* and *XIII*, are also formed. Monoperphthalic acid reacts in a similar manner. With hydrogen bromide in glacial acetic acid oxirans of the androstane series *XII* and *XIII* open the ring and give 16β-bromomethyl-16α-hydroxy compounds *XX* and *XVI*.

In the course of our experiments with the oxidation of 21-acetoxy-11α,17α-dihydroxy-16-methylene-4-pregnene-3,20-dione (*I*)** to the corresponding 11-keto derivative using Jones reagent[3], *i.e.* 8N chromic acid in 8N-H_2SO_4 in acetone as medium, we found, by means of thin-layer chromatography, that in addition to the expected 3,11,20-trione the by-product *VI* is also formed. The latter two substances differ only little in polarity. If an excess of the oxidant is used, compound *VI* is the main product. From the normal product of oxidation substance *VI* differs by its elemental analysis, which shows that it has one oxygen atom more. In the IR spectrum it lacks the maximum for the 16-methylene double bond, at 895 cm. Similar behaviour during Jones oxidation was also observed in the case of the corresponding 1,4-dien-3-one *II* which gave a prednisone derivative, *VII*. The formation of substances *VI* and *VII* was observed even during the oxidation of 11α-hydroxy compounds *I* and *II* with chromium oxide–pyridine complex (*i.e.* under very mild conditions) although to a lesser extent. Simpler derivatives with a 16-methylene-17α-hydroxy-20-oxo structure *III—V*, also underwent oxidation with Jones reagent under formation of compounds *VIII—X* richer by one oxygen atom. In the IR spectra of these compounds the maximum for the 16-methylene double bond at 895 mc^{-1} also disappeared showing that the oxidation took place on this group; hence, the epoxidation reaction must have taken place on this group under formation of 16-spiro-2'-oxiran derivative.

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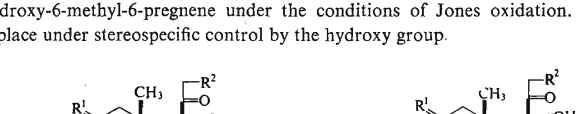
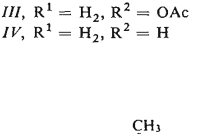
** This compound was prepared by partial acetylation of the corresponding 11α,17α,21-triol[1]; in contrast to earlier results of another group[2], it was isolated in crystalline form, m.p. 214—216°C, $[\alpha]_D^{22}$ +38°.

A direct proof of structure was carried out by an alternative oxidation of 17α-hydroxy-16-methylene-4-pregnene-3,20-dione[2,4,5] (*IV*) with perphthalic acid, giving rise to product *IX*. The by-product formed in this reaction was identified as diepoxide *XI*. This conclusion is based on the absence of the absorption in the UV spectrum and on elemental analysis. It was reduced with chromous chloride[6] to monoepoxide *IX*. It is known[7,8] that the epoxidation of allylic double bonds with peracids is sterically directed by the adjacent hydroxyl, *i.e.* that the epoxide formed has the same configuration as the hydroxy group. Hence, the structure (16*S*)-spiro[17α-hydroxy-4-pregnen-16,2′-oxiran]-3,20-dione follows for substance *IX*, and analogous structures also for compounds *VI* – *VIII* and *X*. The smooth epoxidation of the double bond with chromic acid derivatives is somewhat unexpected. Nevertheless, an analoggous reaction course was also described by Djerassi and coworkers[9] for the derivative 5α-hydroxy-6-methyl-6-pregnene under the conditions of Jones oxidation. It also took place under stereospecific control by the hydroxy group.

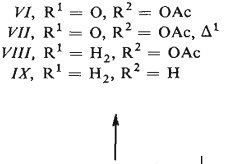


I, R^1 = β-H, α-OH, R^2 = OAc
II, R^1 = β-H, α-OH, R = OAc, Δ^1
III, R^1 = H_2, R^2 = OAc
IV, R^1 = H_2, R^2 = H

VI, R^1 = O, R^2 = OAc
VII, R^1 = O, R^2 = OAc, Δ^1
VIII, R^1 = H_2, R^2 = OAc
IX, R^1 = H_2, R^2 = H



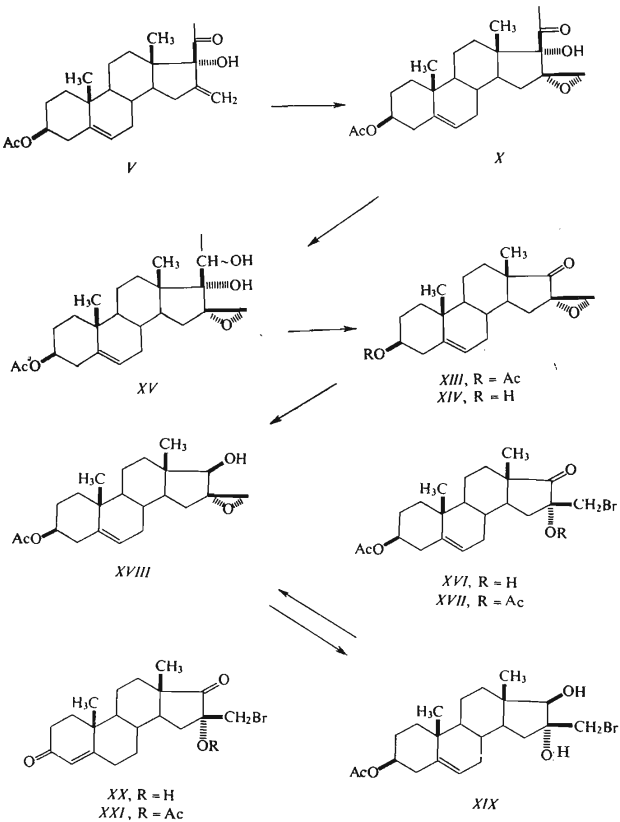
XII



XI

During the oxidation of simple derivatives *IV* and *V*, especially when a large excess of the reagent was used and the reaction was carried out at room temperature instead of the customary 0°C, the formation of by-products *XII* or *XIII* was observed. The latter two compounds were mutually correlated by hydrolysis of the 3β-acetoxy group of substance *XIII* to 3β-hydroxy derivative *XIV*, and Oppenauer oxidation of the latter to a product identical with substance *XII*. In all three compounds the IR spectrum contained a maximum at 1740 – 1748 cm^{-1}, characteristic of the carbo-

nyl group on the five membered ring. The analysis also suggested derivatives of the androstane series. The direct proof of structure was carried out by correlation with an adequately substituted pregnane derivative: 20-keto group of spiro-oxiran *X* was reduced with sodium borohydride under formation of diol *XV* which was oxidised immediately (without further characterisation) with sodium periodate[20] to authentic (16*S*)-spiro[3β-acetoxy-5-androsten-16,2′-oxiran]-17-one identical with compound *XIII*.



Interesting results were obtained from the reactions of the spiro-oxiran ring in hydrogen bromide solution in glacial acetic acid, *i.e.* under the conditions when bromohydrin is formed. This reaction was investigated first on less complex spiro-oxirans of the androstane series: thus, the oxiran derivative of dehydroepiandrosterone acetate *XIII* afforded after 15 minutes reaction at room temperature a mixture of two products. Their mobility on thin layer of silica gel was different. The main, more polar, product was identified as the corresponding bromohydrin *XVI*; the less polar by-product *XVII* was its acetate, as evidenced by its IR spectrum (absence of hydroxy group band at 3400–3600 cm^{-1}), elemental analysis and the formation from bromohydrin *XVI* on acetylation with acetic anhydride in pyridine at very prolonged reaction time (4 days at room temperature). This unwillingness to acetylate indicated a tertiary hydroxy group in bromohydrin *XVI* which was also proved on the basis of the unreactivity of substance *XVI* towards Jones reagent. The absence of a skeletal rearrangement was proved by the smooth conversion of bromohydrin *XVI* back to the starting epoxide *XIII* under the effect of potassium acetate in acetone A quite analogous reaction sequence, starting with dione *XII*, also gave a mixture of bromohydrin *XX* and of its amorphous 16-acetate *XXI*. The product *XXI* was not further characterised; however, on alkaline hydrolysis it gave the starting epoxide *XII*, as the free bromohydrin *XX* also did. The opening of the oxiran ring in compounds *XII* and *XIII* took place in accordance with the expectation that the protonated ring would be attacked preferentially by the bromide anion at a sterically better accessible site, *i.e.* on the methylene $C_{(3')}$ oxiran ring.

On reduction of 17-keto derivative *XIII* with sodium borohydride the corresponding 17β-hydroxy compound *XVIII* was obtained which was then converted with hydrogen bromide to bromohydrin *XIX*. This was also obtained on reduction of the 17-keto group in bromohydrin *XVI* with tri-tert-butoxy lithium aluminium hydride, *i.e.* under conditions which do not attack bromine[11]. The hydroxy groups of *XIX* (16α- and 17β-) are in a special relationship with the bromine which enables both of them to close an oxygen cycle, in the first case a three-membered, and in the second case a four-membered one. Under the effect of potassium acetate in acetone on bromohydrin *XIX* a three-membered oxiran, *XVIII*, was obtained exclusively, which is in agreement with the uneasy formation of four-membered rings by cyclisation reactions although the conditions for the formation of an oxetan ring were favourable[12].

EXPERIMENTAL

Melting points were determined on a Kofler microblock. Optical rotations were measured in chloroform, unless stated otherwise, with a ±3° accuracy. Samples for analysis were dried over phosphorus oxide at 0·1 Torr and 76°C for 8 hours. The UV spectra were measured on a Zeiss VSU-1 spectrophotometer (NaCl prisms, quartz cell 1 cm thick) in methanol. The IR spectra were measured on a two-beam Zeiss UR-10 spectrophotometer, in 6% chloroform solutions. The NMR spectra were measured on a Zeiss ZKR 60 apparatus, at 60 Mc in deuteriochloroform, using tetramethylsilane as the internal standard. The values of chemical shifts are given in p.p.m. on a δ-scale. Thin-layer chromatography was carried out on silica gel CH, Lachema, Brno, in chloroform–methanol mixtures of various ratios. Detection was carried out with conc. sulfuric acid and heating at 110°C. Conjugated ketones were also chromatographed on silica gel layers containing a fluorescent

indicator (Silufol, Kavalier Votice). The same systems as above were used for elution, detection was carried out under ultraviolet light of 254 nm wave-length (Chromatolite).

Oxidation of 21-Acetoxy-11α,17α-dihydroxy-16-methylene-4-pregnene-3,20-dione (*I*) with Jones Reagent

To a suspension of acetate *I* (2·96 g) in acetone (150 ml) Jones reagent[3] (6·5 ml) was added dropwise under stirring and cooling with ice and water. After one hour the excess oxidant was decomposed with 2-propanol (3 ml) and the reaction mixture was concentrated *in vacuo* to a small volume and diluted with water. The precipitated product was filtered off, washed with water and dried (2·42 g). The aqueous filtrate was extracted twice with ether. The extract contained another 257 mg of the crude product. The product, which according to thin-layer chromatography contained two components, was chromatographed on a silica gel column (150 g). Elution with a mixture of chloroform and ethanol (99 : 1) gave 906 mg of substance which when crystallised from methanol gave pure (16*S*)-spiro[21-acetoxy-17α-hydroxy-4-pregnen-16,2′-oxiran] -3,11,20-trione (*VI*) (781 mg, 25·5%), m.p. 229—230°C; $[\alpha]_D^{20}$ +166° (*c* 1·0); UV spectrum: λ_{max} 236 nm (log ε 4·21); IR spectrum 3520 (OH), 1750, 1265 (CH_3COO), 1728 ($C_{(20)}$-carbonyl), 1668, 1618 (conjugated carbonyl), 1715 (carbonyl in a hexagonal cycle) cm^{-1}. For $C_{24}H_{30}O_7$ (430·5) calculated: 66·96% C, 7·02% H; found: 66·98% C, 7·19% H. Elution with chloroform–ethanol mixture (97 : 3) gave 21-acetoxy-17α-hydroxy-16-methylene-4-pregnene-3,11,20-trione (1·48 g, 50%), m.p. 219—221°C; $[\alpha]_D^{20}$ +138° (dioxan, *c* 1·6). Literature[2] gives m.p. 213—214°C; $[\alpha]_D^{23}$ +140° (dioxan). If a double amount of Jones reagent was used for the oxidation of the starting compound, the yield of the spiro-oxiran derivative *VI* was 51%.

(16*S*)-Spiro[21-acetoxy-17α-hydroxy-1,4-pregnadien-16,2′-oxiran]-3,11,20-trione (*VII*)

Into a solution of 21-acetoxy-11α,17α-dihydroxy-16-methylene-1,4-pregnadiene-3,20-dione (*II*) (500 mg) in acetone (25 ml) Jones reagent (1·65 ml) was added dropwise under cooling and stirring. After 60 minutes the reaction mixture was worked up as in the above experiment. The crude product was crystallised twice from methanol. The obtained spiro-oxiran derivative *VII* (241 mg) had m.p. 209—212°C. The mother liquors yielded another 35 mg of product, m.p. 207—209°C. Total yield was 276 mg of *VII* (53%). The sample for analysis had m.p. 210—212°C (methanol); $[\alpha]_D^{24}$ +125° (*c* 1·9); UV spectrum: λ_{max} 237 nm (log ε 4·09); IR spectrum: 3520 (OH), 1740 (CH_3COO), 1703 (carbonyl in a six-membered ring), 1722 ($C_{(20)}$-carbonyl), 1600, 1620, 1660, 895 (conjugated carbonyl) cm^{-1}. For $C_{24}H_{28}O_7$ (428·5) calculated: 67·27% C, 6·59% H; found: 67·30% C, 6·58% H.

(16*S*)-Spiro[21-acetoxy-17α-hydroxy-4-pregnen-16,2′-oxiran]-3,20-dione (*VIII*)

21-Acetoxy-17α-hydroxy-16-methylene-4-pregnene-3,20-dione (*III*) (1·9 g) in acetone (100 ml) was oxidised with Jones reagent (2·4 ml) by the above procedure. The working up of the reaction mixture and crystallisation of the crude product from methanol gave derivative *VIII* (0·75 g, 38%), m.p. 183—185°C. The sample for analysis had m.p. 185—187°C; $[\alpha]_D^{20}$ +74° (*c* 1·3); UV spectrum: λ_{max} 240 nm (log ε 4·24); IR spectrum: 3520, 3310 (OH), 1745, 1270 (CH_3COO), 1725 ($C_{(20)}$-carbonyl), 1663, 1618 (conjugated carbonyl) cm^{-1}. For $C_{24}H_{32}O_6$ (416·5) calculated: 69·21% C, 7·74% H; found: 68·93% C, 7·58% H.

(16*S*)-Spiro[17α-hydroxy-4-pregnen-16,2′-oxiran]-3,20-dione (*IX*)

a) Compound *IV* (2·2 g) in acetone (150 ml) was oxidised with Jones reagent (3·2 ml) under the conditions mentioned above. The crude reaction product was chromatographed on a silica gel

column (100 g) with benzene–acetone mixture (95 : 5). Yield: 206 mg (10%) of pure (16*S*)-spiro[4-androsten-16,2′-oxiran]-3,17-dione (*XII*), identical in all respects with substance *XII* prepared by Oppenauer oxidation of the corresponding 3β-hydroxy derivative *XIV*. Further elution with benzene–acetone (9 : 1 and 8 : 2) gave 3,20-dione *IX* (685 mg, 30%), m.p. 217—219°C (methanol). The sample for analysis had m.p. 226—228°C; $[\alpha]_D^{23}$ +63° (*c* 1·1); UV spectrum: λ_{max} 240 nm (log ε 4·24); IR spectrum: 3520, 3280 (OH), 1705 ($C_{(20)}$-carbonyl), 1358 ($COCH_3$), 1660, 1615 (conjugated carbonyl) cm^{-1}: NMR spectrum: 0·85 (18-H), 1·24 (19-H), 2·21 (21-H), 3·09, 3·23, J = 4·0 Hz, doublet (part of an AB quartet) (>C(O)—CH_2), 5·78 (vinyl-H). For $C_{22}H_{30}O_4$ (358·5) calculated: 73·71% C, 8·44% H; found: 73·57% C, 8·53% H.

b) A solution of compound *IV* (33 g) in chloroform (300 ml) was cooled to +4°C and mixed at this temperature with a solution of monoperphthalic acid in ether (400 ml; 78 mg of monoperphthalic acid in 1 ml). The reaction mixture was allowed to stand in a refrigerator for 72 hours and then diluted with ether (500 ml). The precipitate was filtered off and the filtrate washed carefully with a solution of potassium hydrogen carbonate and water. The solution was dried over sodium sulfate and the solvent was evaporated in vacuum to dryness. The residue (30 g) was chromatographed on a silica gel column (870 g). Elution with a benzene–acetone mixture (95 : 5) gave a less polar substance (1·63 g) which after crystallisation from methanol gave (16*S*)-spiro[17α-hydroxy-4ξ,5ξ-oxido-4-pregnen-16,2′-oxiran]-3,20-dione (*XI*) (1·06 g, 3%), m.p. 211 to 213°C; $[\alpha]_D^{22}$ −51° (*c* 2·1) without a maximum in the UV region; IR spectrum: 3500 (OH), 1702 ($C_{(20)}$-carbonyl), 1358 ($COCH_3$) cm^{-1}. For $C_{22}H_{30}O_5$ (374·5) calculated: 70·56% C, 8·08% H; found: 70·06% C, 8·30% H. Elution with a benzene–acetone mixture (9 : 1 and 8 : 2) gave derivative *IX* (12·93 g, 37·5%), m.p. 218—223°C, identical in all respects with compound *IX* prepared as under *a*).

c) 4ξ,5ξ-Oxido derivative *XI* (100 mg) dissolved in a mixture of equal parts of acetic acid and methanol (1·2 ml) was mixed with a solution of chromous chloride in methanol (prepared on reduction of 200 mg of chromic chloride with zinc in hydrochloric acid under a layer of light petroleum) under an inert atmosphere. After 60 minutes the blue solution was diluted with ether and the solution was washed with water, a solution of potassium hydrogen carbonate, and water. After drying over sodium sulfate the solvent was distilled off *in vacuo* to dryness. The oily residue (78 mg) was chromatographed on a silica gel column (6 g). Elution with a benzene–acetone mixture (95 : 5 and 90 : 10) gave derivative *IX*, m.p. 214—216°C, identical with the compound prepared as under *a*) and *b*).

Oxidation of 3β-Acetoxy-17α-hydroxy-16-methylene-5-pregnen-20-one (*V*) with Jones reagent

To a solution of acetate *V* (7 g) in acetone (200 ml) Jones reagent (12 ml) was added dropwise under cooling and the mixture was allowed to stand for 30 minutes. Then the excess reagent was decomposed with 2-propanol (3 ml) and the reaction mixture was worked up in the manner described above. The crude product was chromatographed on a silica gel column (400 g). Elution with a mixture of benzene and chloroform (5 : 1) gave (16*S*)-spiro[3β-acetoxy-5-androsten-16,2′-oxiran]-17-one (*XIII*) (1·34 g, 21%), m.p. 189—191°C (methanol); $[\alpha]_D^{22}$ −4·6° (*c* 2·5); IR spectrum: OH absent, 1748 (five-membered cyclic ketone), 1725, 1255, 1032 (CH_3COO), 1670 (Δ5-double bond), 815, 832 (trisubstituted double bond) cm^{-1}. For $C_{22}H_{30}O_4$ (358·5) calculated: 73·71% C, 8·44% H; found: 73·59% C, 8·68% H. On elution with benzene–chloroform mixture (1 : 1) (16*S*)-spiro-[3β-acetoxy-17α-hydroxy-5-pregnen-16,2′-oxiran]-20-one (*X*) (1·29 g, 18%) was obtained, m.p. 205—207°C (methanol); $[\alpha]_D^{22}$ −83° (*c* 1·6); IR spectrum: 3520, 3610 (OH), 1726, 1255, 1035 (CH_3COO), 1710 ($C_{(20)}$-carbonyl), 1356 ($COCH_3$), 1670 (5-double bond), 810, 839 (trisubstituted double bond) cm^{-1}. For $C_{24}H_{34}O_5$ (402·5) calculated: 71·61% C, 8·51% H; found: 71·32% C, 8·61% H.

(16*S*)-Spiro[3β-acetoxy-5-androsten-16,2′-oxiran]-17-one (*XIII*)

a) To a solution of ketone *X* (100 mg) in dioxan (2 ml) methanol (5 ml) and a solution of sodium boro-hydride (50 mg) in methanol (2 ml) were added and allowed to react for 10 minutes. After dilution with water (60 ml) the product was extracted with ether and the organic fraction was washed with water, dried over sodium sulfate, and evaporated under reduced pressure to dryness. The crude 20-hydroxy derivative *XV* (98 mg) was dissolved in methanol (20 ml) and additioned with sodium periodate (150 mg) in water (6 ml). The reaction mixture was allowed to stand at room temperature for 4 days and then evaporated *in vacuo* to a small volume. This was diluted with water and the products filtered off under suction, washed with water, dried and crystallised from methanol. Yield 65 mg (73%) of a substance m.p. 185—188°C identical with the 17-keto derivative *XIII* prepared by Jones oxidation of derivative *V*.

b) Bromohydrin *XVI* (170 mg) was refluxed for 5 hours with potassium acetate (500 mg) in acetone (10 ml). The reaction mixture was concentrated to a small volume, diluted with water, and the separated product filtered off with suction, washed, dried and crystallised from methanol. Yield 89 mg (64%) of a substance melting at 186—189°C, which was identical with the 17-keto derivative *XIII*. The mother liquors yielded another 15 mg of compound *XIII*, m.p. 181—184°C.

(16*S*)-Spiro[3β-hydroxy-5-androsten-16,2′-oxiran]-17-one (*XIV*)

A solution of 3β-acetate *XIII* (1 g) and potassium carbonate (1 g) in methanol (20 ml) was allowed to stand overnight at room temperature. The reaction mixture was concentrated *in vacuo* to a small volume, diluted with water, and the product filtered off, washed with water, dried, and crystallised from acetone; m.p. 203—205°C; $[\alpha]_D^{20}$ +9·5° (*c* 1·6); IR spectrum: 3600 (OH), 1745 (five-membered cyclic ketone) cm^{-1}. For $C_{20}H_{28}O_3$ (316·4) calculated: 75·91% C, 8·92% H; found: 75·67% C, 8·66% H.

(16*S*)-Spiro[4-androsten-16,2′-oxiran]-3,17-dione (*XII*)

a) 3β-Hydroxy derivative *XIV* (560 mg) was dissolved in toluene (20 ml) and a part of the solvent was distilled off. Cyclohexanone (6 ml) was then added followed by aluminum isopropylate (600 mg) in toluene (2·7 ml). After one hour's reflux the volatile material was steam-distilled and the product was filtered off, washed with water and dried. The crude product (516 mg) was chromatographed on a silica gel column (30 g). Elution with benzene–acetone (95 : 5) gave 326 mg (59%) of substance *XII*, m.p. 193—195°C; $[\alpha]_D^{20}$ +163° (*c* 2·4); UV spectrum: λ_{max} 238 nm (log ε 4·32); IR spectrum: 1620, 1670 (conjugated ketone), 1740 (carbonyl in five-membered ring) cm^{-1}. For $C_{20}H_{26}O_3$ (314·4) calculated: 76·40% C, 8·34% H; found: 76·16% C, 8·25% H.

b) A solution of bromohydrin *XX* (20 mg) in methanol (1 ml) was refluxed with potassium hydrogen carbonate (50 mg) for 5 minutes. The reaction mixture was evaporated almost to dryness, then diluted with water, and the product filtered off under suction, washed with water, dried, and crystallised from methanol. Derivative *XII* was obtained (10 mg, 63%), m.p. 193—196°C identical with substance *XII* prepared as above *a*).

c) To a solution of acetate *XXI* (22 mg) in methanol (1 ml) potassium carbonate (20 mg) was added and the mixture was allowed to stand overnight at room temperature. It was then concentrated to a small volume, diluted with water, and the product filtered off, washed, and crystallised from methanol. Yield 11 mg (70%) of a substance, m.p. 191—194°C, identical with derivative *XII* obtained by procedure *a*).

3β-Acetoxy-16β-bromomethyl-16α-hydroxy-5-androsten-17-one (*XVI*)

To a solution of spiro-oxiran derivative *XIII* (562 mg) in glacial acetic acid (5 ml) cooled with icy water a solution of hydrogen bromide in glacial acetic acid (1·74 ml; 73 mg of hydrogen bromide per 1 ml solution) was added and the reaction mixture allowed to stand for 15 minutes. It was then diluted with water and allowed to stand overnight. The product was filtered off, washed thoroughly with water, dried at room temperature, and chromatographed on a silica gel column (30 g). Elution with light petroleum–benzene (2 : 1 and 1 : 1) gave 24 mg (3%) of 3β,16α-diacetoxy-16-bromomethyl-5-androsten-17-one (*XVII*), m.p. 199—201°C (methanol), identical with substance *XVII* obtained on acetylation of bromohydrin *XVI*. On elution with a mixture of benzene and dichloromethane (4 : 1) 333 mg (48%) of substance *XVI* were obtained, m.p. 144—145°C (methanol); $[\alpha]_D^{25}$ +44·4° (*c* 1·5); IR spectrum: 3550 (OH), 1730, 1255, 1031 (CH_3COO), 1728 (carbonyl in a five-membered ring) cm^{-1}. For $C_{22}H_{31}BrO_4$ (439·4) calculated: 18·19% Br; found: 18·11% Br.

3β,16α-Diacetoxy-16β-bromomethyl-5-androsten-17-one (*XVII*)

A mixture of bromohydrin *XVI* (75 mg), pyridine (0·3 ml), and acetic anhydride (0·2 ml) was allowed to stand at room temperature for 4 days. It was then poured onto ice and the product was extracted with ether. The organic layer was washed with dilute hydrochloric acid, water, potassium hydrogen carbonate solution, and again with water. It was then dried over sodium sulfate and the solvent was evaporated in vacuum to dryness. The residue was crystallised from methanol, yielding 66 mg (80%) of diacetate *XVII*, m.p. 207—209°C; $[\alpha]_D^{21}$ +30° (*c* 0·8); IR spectrum: OH absent, 1730, 1255, 1031 (CH_3COO) cm^{-1}. For $C_{24}H_{33}BrO_5$ (481·4) calculated: 59·87% C, 6·91% H, found: 59·70% C, 7·16% H.

(16*S*)-Spiro[3β-acetoxy-17β-hydroxy-5-androsten-16,2′-oxiran] (*XVIII*)

a) An ice-cooled solution of 17-keto derivative *XIII* (200 mg) in dioxan (3 ml) and methanol (6 ml) was mixed with a solution of sodium borohydride (50 mg) in methanol (5 ml). After 10 minutes standing the mixture was diluted with ether (60 ml), washed with water, dried over sodium sulfate, and evaporated to dryness. The residue (198 mg) was crystallised from a mixture of acetone and light petroleum. 17β-Hydroxy derivative *XVIII* was obtained (163 mg), m.p. 152—154°C, which after further crystallisation from the same solvent mixture gave a product melting at 155—156°C. Further slow crystallisation of the substance from a dilute solution (in the same solvent mixture) gave 112 mg (56%) of product, m.p. 173—176°C; $[\alpha]_D^{25}$ −106° (*c* 0·9); IR spectrum: 3450, 3620 (OH), 1720, 1260, 1031 (CH_3COO), 1665 (5-double bond) cm^{-1}. For $C_{22}H_{32}O_4$ (360·5) calculated: 73·30% C, 8·95% H; found: 73·02% C, 8·85% H.

b) A solution of crude bromohydrin *XIX* (200 mg) in acetone (4 ml) was refluxed with potassium acetate (200 mg) for 6 hours. The mixture was concentrated to a small volume and worked up in the conventional manner. The crude product (128 mg) was crystallised from acetone–light petroleum. Yield 108 mg (66%) of a substance, m.p. 165—168°C, identical with hydroxy derivative *XVIII* obtained as under *a*).

3β-Acetoxy-16β-bromomethyl-16α,17β-dihydroxy-5-androstene (*XIX*)

a) To a solution of bromohydrin *XVI* (150 mg) in tetrahydrofuran (2·5 ml) a solution of tri-tert-butoxy lithium aluminum hydride (93 mg) in the same solvent (2·5 ml) was added dropwise and under cooling with ice and stirring. After 5 minutes the reaction mixture was diluted with ether (25 ml), washed with water, dried, and concentrated to dryness. The crude residue (176 mg) was chromatographed on a column of silica gel (5 g). Elution with chloroform gave 98 mg

of chromatographically pure substance which could not be brought to crystallisation. IR spectrum: 3440 (OH), 1720 (CH_3COO) cm^{-1}. For $C_{22}H_{33}BrO_4$ (441·4) calculated: 18·11% Br; found: 17·76% Br.

b) A solution of hydrogen bromide in ethyl acetate (0·14 ml; 350 mg of HBr/1 ml) was added under cooling with ice and stirring to a solution of derivative *XVIII* (142 mg) in ethyl acetate (2 ml) and the reaction mixture was diluted after five minutes with ether and then worked up in the conventional manner. The crude product (170 mg, 98%) would not crystallise. According to thin-layer chromatography the substance was pure and, according to its IR spectrum, identical with bromohydrin *XIX* prepared under *a*).

16β-Bromomethyl-16α-hydroxy-4-androstene-3,17-dione (*XIX*)

To a solution of spiro-oxiran derivative *XII* (150 mg) in glacial acetic acid (1 ml) a solution of hydrogen bromide in glacial acetic acid (0·18 ml; 205 mg of HBr/1 ml) was added under cooling with ice and stirring. After five minutes the mixture was diluted with ether (50 ml) and the ethereal phase was washed with dilute potassium hydrogen carbonate and water. It was then dried over sodium sulfate and the solvent distilled off to dryness *in vacuo*. The residue was chromatographed on a silica gel column (12 g). Elution with benzene–acetone (95 : 5) gave a less polar 16α-acetoxy derivative *XXI* (48 mg) which would not crystallise. IR spectrum: 1740 (carbonyl in five-membered cycle), 1620, 1665 (conjugated ketone), 1728, 1255, 1030 (CH_3COO) cm^{-1}, OH absent. For $C_{22}H_{29}BrO_4$ (437·5) calculated: 18·27% Br; found: 17·56% Br. An identical non-crystalline product was also prepared by four days acetylation of bromohydrin *XX* (20 mg) in acetic anhydride (0·02 ml) and pyridine (0·1 ml) at room temperature.

Elution with benzene–acetone (9 : 1) gave 143 mg of bromohydrin *XX*. Crystallisation from methanol gave an analytically pure product (97 mg, 51%), m.p. 203—205°C (decomp.); $[\alpha]_D^{22}$ +186° (*c* 2·2); UV spectrum: λ_{max} 240 nm (log ε 4·29); IR spectrum: 3540, 3400 (OH), 1740 (five-membered ketone), 1611, 1660 (conjugated ketone) cm^{-1}, α-position to the carbonyl group is substituted. For $C_{20}H_{27}BrO_3$ (395·3) calculated: 60·76% C, 6·88% H; found: 60·26% C, 6·71% H.

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