4,5-SECOANDROSTANES BY ESCHENMOSER'S REACTION*

Alexander KASAL[a], Ladislav KOHOUT[a] and Jiří FILIP[b]

[a] *Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6 and*
[b] *Institute for the Research, Production and Utilization of Radioisotopes, 102 27 Prague 10*

Received September 13th, 1984

17β-Benzoyloxy-4,5-secoandrost-3-yn-5-one (*V*), accessible from testosterone in three steps, can be converted both to Δ^5-unsaturated alkynes of the type *XXV* (*via* axial hydroxy derivative *XVII*) and to alkynes of the type *XXVI* (by hydrogenolysis of equatorial methanesulfonate *XXIII*). These compounds were hydrated and hydrolysed to 17β-hydroxy-4,5-secoandrost-5-en-3-one and 17β-hydroxy-4,5-secoandrostan-3-one (*XXX* and *I* respectively). Catalytic hydrogenation of compound *XXX* with tritium afforded [5,6-$^3H_2$]-derivative *XXXI*.

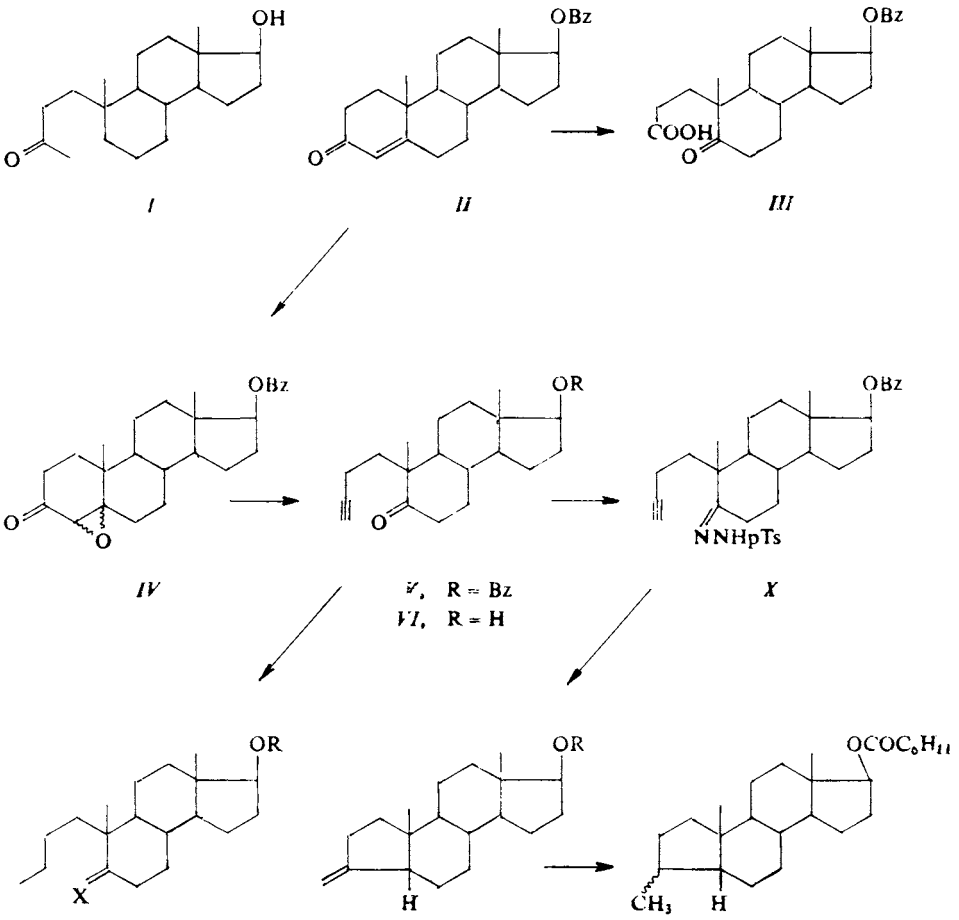
The preparation of physiologically interesting 4,5-secoanalogues of steroid hormones of type *I* has been carried out[1-4] by a sequence comprising several steps, in which the key operation was the oxidation of the testosterone derivative (*II*) to A-nor--secoacid *III*. In this procedure the three-carbon chain in position 10 had to be prolonged to a four-carbon chain after elimination of the keto group in position 5. In this paper we describe the results of the experiments investigating the synthetic potential of Eschenmoser's fragmentation[5] of α,β-epoxy ketones of the type *IV* to 4,5-seco derivatives of the type *V*.

Previous authors used the compounds of the type *V* for the preparation of 5β--hydroxy-A-norsteroids[6] and 3-thiasteroids[7]. From earlier studies it was evident that the utilisability of substances of the type *V* will be restricted by the easy cyclization to A-nor-derivative and the isomerization[8] of the terminal acetylenic group to substances with the triple bond in position 2. A further paper indicated the danger of Wagner–Meerwein rearrangement during the solvolysis of 5β-*p*-toluenesulfonyloxy derivatives[9].

Testosterone benzoate (*II*) was used as the starting material which was converted to a mixture of 4α,5α- and 4β,5β-epoxides (*IV*) in the conventional manner. This mixture was then converted to 17β-benzoyloxy-4,5-secoandrost-3-yn-5-one (*V*) using Eschenmoser's procedure (reaction of *p*-toluenesulfonylhydrazine in the presence of acetic acid). First, experiments were carried out aiming at a direct elimination of the 5-oxo group in compound *V*: reduction of ketone *V* according to Huang–Min-

* Part CCCXIV in the series On Steroids; Part CCCXIII: This Journal *50*, 973 (1985).

lon afforded compound *VII* which did not contain a triple bond (IR spectrum, mass spectroscopy). The preparation of hydrazone of compound *V* under mild conditions took place slowly, while under more vigorous conditions (boiling in hydrazine hydrate under argon) hydrazone *VIII* was formed in which the triple bond was again reduced. The preparation of *p*-toluenesulfonylhydrazone of compound *V* also took place slowly and compound *X* could be obtained in good yield directly during the Eschenmoser reaction, if carried out in the presence of an excess of the reagent. Reduction of compound *X* with sodium borohydride in the presence of acetic acid



I *II* *III*

IV *V*, R = Bz; *VI*, R = H *X*

VII, X = H_2, R = H
VIII, X = NNH_2, R = H
IX, X = H_2, R = $C_6H_{11}CO$

XI, R = Bz
XII, R = H

XIII

Bz = C_6H_5CO, pTs = $CH_3C_6H_4SO_2$, Ac = CH_3CO, Ms = CH_3SO_2

TABLE I

Characteristic parameters of the ^{1}H NMR spectra. The spectra were recorded on a Tesla 60 instrument in deuteriochloroform (concentration between 0·25 and 0·5 mol l^{-1}) with tetramethylsilane as internal reference, chemical shifts are given in the δ-scale (ppm), the half-height width (W) is given in Hz

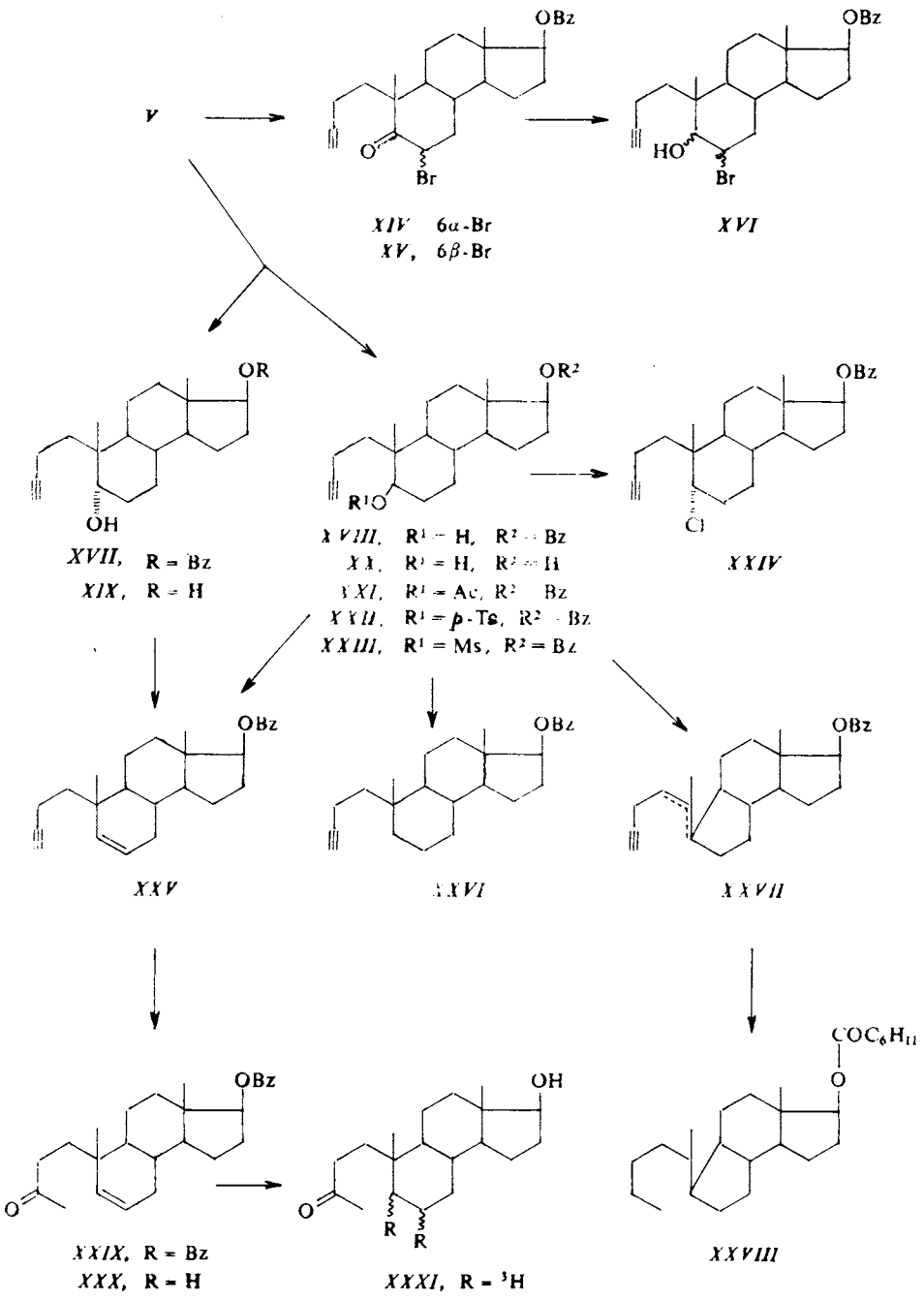
Compound	5-H	17-H[a]	18-H[b]	19-H[b]	Other signals[c]
V	—	4·85	1·00	1·10	—
VI	—	3·66	0·80	1·08	—
VII	—	3·62	0·73	0·83	—
VIII	—	3·63	0·73	0·80	—
IX	—	4·83	0·78	0·83	—
X	—	4·81	0·94	0·96	2·43[d]
XI	—	4·81	0·92	1·03	4·81[e]
XII	—	3·60	0·73	1·02	4·80[e]
XIII	—	4·74	0·79	0·95	0·99[f]
XIV	—	4·85	0·99	1·15	4·92[g]
XV	—	4·85	1·03	1·39	4·46[h]
XVII	3·63[i]	4·84	0·92	0·87	—
XVIII	3·54[j]	4·83	0·93	0·86	—
XIX	3·63[k]	3·57[k]	0·73	0·86	—
XX	3·49[k]	3·59[k]	0·73	0·85	—
XXI	4·65[k]	4·80[k]	0·93	0·93	2·03[l]
XXII	4·41[j]	4·81	0·90	0·90	2·43[m]
XXIII	4·58[j]	4·83	0·93	0·93	3·02[n]
XXIV	4·05[i]	4·87	0·93	1·02	—
XXV	5·29[o]	4·87	0·91	0·94	5·67[p]
XXVI	—	4·86	0·93	0·88	—
XXVII[r]	—	4·84	0·94	1·64	—
XXVIII[r]	—	4·51	0·78	0·86[s]	—
XXIX	5·25[o]	4·84	0·95	0·95	2·13[t], 5·67[p]
XXX	5·22[o]	3·65	0·77	0·93	2·13[t], 5·62[p]

[a] Doublet of doublets, J = 8 and 9 Hz; [b] singlet unless stated otherwise; [c] in the spectra of all benzoyloxy derivatives signals of aromatic protons appear as multiplets at 7·43 and 8·03 ppm; [d] singlet of the methyl group in $CH_3C_6H_4SO_2$-grouping; [e] broad doublet of two vinylic protons, J = 8 Hz; [f] doublet (J = 7·5 Hz) of the 3ξ-methyl group; [g] the signal of the $C_{(6)}$-proton; [h] multiplet (W = 9 Hz) of the $C_{(6)}$-proton; [i] multiplet, W = 6 Hz; [j] doublet of doublets, J = 4 and 11 Hz; [k] part of overlapping multiplets; [l] singlet of the acetoxy group; [m] singlet of the methyl group in $CH_3C_6H_4SO_3$ grouping; [n] singlet of the methyl group in CH_3SO_3-grouping; [o] broad doublet, J = 10 Hz; [p] doublet of broad doublets, J = 10 and 4·5 Hz; [r] the values given were deduced from the spectrum of an inseparable mixture of isomers; [s] doublet, J = 6 Hz; [t] singlet of the methyl keto group.

afforded a single product, *XI*, in the IR and NMR spectrum of which the signals of the C≡C—H group could not be detected, but the signals of the exomethylene group were evident. The structure of compound *XI* was proposed on the basis of analogies from earlier studies and it was confirmed by the finding that the same substance is also formed during the hydrogenolysis of 5β-methanesulfonyloxy derivative *XXIII* (see below). A chemical proof of the cyclization of the 4,5-seco derivative to A-nor-derivative *XI* was given by catalytic hydrogenation to compound *XIII*: the mass spectrum demonstrated the presence of 4 cycles, the ^{1}H NMR spectrum the presence of a further, this time – however – a secondary methyl group on the skeleton (Table I). The results of these experiments could be interpreted as a consequence of the high reactivity of the terminal triple bond and the low reactivity of the substituent in position 5. A similar situation also appeared in the reduction of the mixture of bromohydrins *XVI* with zinc dust, which led to a mixture of olefins lacking a triple bond (IR spectroscopy, mass spectra).

Further the possibilities of deoxygenation of compound *V via* corresponding 5-hydroxy derivatives were tested. On reaction with sodium borohydride 5β-hydroxy derivative *XVIII* is formed from the ketone, having an equatorial hydroxy group. Meerwein–Pondorf's reduction of ketone *V* afforded a mixture of 5-hydroxy derivatives *XVII* and *XVIII*, but also of 5,17β-dihydroxy derivatives *XIX* and *XX*. The relatively highest yield of the 5α-alcohol *XVII* with the axial hydroxyl group was obtained on reaction with tritert-butoxy lithium aluminium hydride (39%). Both isomers *XVII* and *XVIII* can be separated by careful chromatography on silica gel, but for the preparation of larger batches of these alcohols a method was elaborated making use of the different reactivity of the 5-hydroxy group in the axial and the equatorial position; the mixture of alcohols was acetylated under mild conditions and the product was separated to chromatographically sufficiently differing components: the acetylated product (*XXI*) was identical with the acetylation product of the pure 5β-alcohol *XVIII*, while the non-acetylated fraction was identified as the 5α-alcohol *XVII*. Similarly the reactivity of 5α- and 5β-alcohols could be differentiated with advantage during the esterification with sulfonic acid derivatives: thus, for example, pure 5β-*p*-toluenesulfonyloxy derivative *XXII* and 5β-methanesulfonyloxy derivative *XXIII* could be obtained from a mixture of 5-alcohols in addition to the unreacted 5α-hydroxy derivative *XVII*.

Dehydration of the axial hydroxy derivative *XVII* with thionyl chloride in pyridine afforded 17β-benzoyloxy-4,5-seco-5-androsten-4-yne (*XXV*) in a 77% yield. On dehydration of the equatorial 5β-alcohol *XVIII* with various reagents, mainly the substitution product was formed in the majority of cases, *i.e.* 5α-chloro derivative *XXIV*. The highest yield of olefin *XXV* (44%) was obtained from 5β-hydroxy derivative *XVIII* on reaction with tetrachloromethane and triphenylphosphine, but the product was accompanied by the chromatographically very similar 5α-chloro derivative *XXIV* (13%).


V
OBz
O
Br
XIV 6α-Br
XV, 6β-Br
OBz
HO
Br
XVI
OR
OH
XVII, R = Bz
XIX, R = H
OR²
R¹O
XVIII, R¹ = H, R² = Bz
XX, R¹ = H, R² = H
XXI, R¹ = Ac, R² = Bz
XXII, R¹ = p-Ts, R² = Bz
XXIII, R¹ = Ms, R² = Bz
OBz
Cl
XXIV
OBz
XXV
OBz
XXVI
OBz
XXVII
OBz
O
XXIX, R = Bz
XXX, R = H
OH
O
R
R
XXXI, R = ³H
COC₆H₁₁
O
XXVIII

In the cases of sulfonic acid esters both types of the —S—O—C— grouping cleavage were observed: under the effect of alumina in hot benzene the starting 5β-hydroxy derivative *XVIII* can be regenerated, while under the effect of lithium aluminium hydride the same reaction takes place, accompanied by hydrolysis of the 17β-benzoyloxy group under formation of 5β,17β-dihydroxy-4,5-secoandrost-4-yne (*XX*). The product of a possible hydrogenolysis of the 5β-methanesulfonyloxy group could not be detected. An alternative way of cleavage of the sulfonate was observed during the decomposition of compound *XXIII* in boiling dimethyl sulfoxide: in this case the product of direct elimination (olefin *XXV*, 25%) was accompanied by a product of elimination combined with a rearrangement (*XXVII*, 27%). We propose the tentative structure of the rearrangement product (*XXVII*) in analogy with a previous study[9] and on the basis of an analysis of the ^{1}H NMR spectrum of compound *XXVII* and the corresponding perhydro derivative *XXVIII*, where the $C_{(19)}$-protons appear as a doublet (J = 6 Hz). When methanesulfonate *XXIII* was reacted with zinc dust in the presence of sodium iodide a cleavage between the oxygen atom and the carbon atom in position 5 takes also place. The main product is the product of direct hydrogenolysis (*XXVI*, 75%), while the by-product is a product of cyclization, *i.e.* 17β-benzoyloxy-3-methyleno-A-nor-5β-androstane (*XI*, 22%) (the same reaction was carried out by Pradhan and coworkers[9] on the cholestane skeleton, who observed the same distribution of the products). To sum up, it may be said that among the deoxygenation methods tested two are useful for the synthesis of the required 4,5-seco-analogues from corresponding 5-oxo-3-alkynes of the type *V*: dehydration of 5α-hydroxy derivatives and hydrogenolysis of 5β-methanesulfonyloxy derivatives leading to compounds of the type *XXV* and *XXVI*, respectively, which represent suitable starting compounds of the type *XXX* and also *I*, respectively. Hydration of alkyne *XXV* to methyl ketone *XXIX* was carried out in a 39% yield, under catalysis with mercuric acetate. Hydrogenation of 17β-hydroxy-4,5-secoandrost-5-en-3-one (*XXX*) with gaseous tritium (without a carrier) on palladium (5% palladium on barium sulfate) gave compound *XXXI* with an activity of 1·89 TBq . . mmol^{-1}, which was used for biochemical experiments.

EXPERIMENTAL

The melting points were determined on a Kofler block and they are not corrected. Specific rotations were measured in chloroform solutions, the infrared spectra in tetrachloromethane. The mass spectra were measured on an AEI GS 902 spectrometer. Only the masses of significant peaks are listed, with relative intensities in brackets. The plates for analytical and preparative chromatography were either made from silica gel Woelm G-DC, or commercial Silufol plates (Kavalier) were used. The distribution of activity on the plates was measured on a Berthold TLC Scanner 2, combined with a multichannel Berthold Silena analyzer and a Hewlett-Packard 97 microcomputer. The radioactivity of the samples was determined by means of liquid scintillators (SLD 31, dioxane–naphthalene, Neratovice) using a Packard–Tricarb instrument. The sensitivity

of the detection was determined using the internal standard method and an EK-1 etalon. Gaseous tritium was supplied by the Techsnabexport firm (USSR).

17β-Benzoyloxy-4,5-secoandrost-3-yn-5-one (*V*)

A solution of *p*-toluenesulfonylhydrazine (6·75 g) in 170 ml of dichloromethane and 170 ml of acetic acid was added dropwise at 0°C and under stirring over 1 h to a solution of epoxides *IV* (14 g) in 100 ml of dichloromethane and 100 ml of acetic acid. After one hour of stirring at room temperature the mixture was concentrated in a vacuum to 1/4 of its volume, diluted with chloroform, washed with an aqueous potassium hydrogen carbonate solution and water, dried over sodium sulfate and the residue was purified by column chromatography on silica gel. A mixture of 20% of ether in light petroleum eluted 10·5 g of ketone *V*, m.p. 160—161°C (acetone), $[\alpha]_D^{20}$ +89° (*c* 1·1); IR spectrum: 3 316, 2 120 (C≡CH), 1 720, 1 276 (C_6H_5COO), 1 711 (sh, C=O) cm^{-1}. For $C_{26}H_{32}O_3$ (392·5) calculated: 79·55% C and 8·22% H; found: 79·65% C and 8·11% H.

4,5-Secoandrostan-17β-ol (*VII*)

A solution of ketone *V* (94 mg) in triethylene glycol (5 ml) and hydrazine hydrate (0·8 ml), additioned with 200 mg of potassium hydroxide, was heated at 140°C under a reflux condenser. After 30 min the condenser was eliminated and the mixture was heated to 200°C. After 4 h heating at 200°C under a reflux condenser the mixture was cooled to 0°C, acidified with dilute hydrochloric acid (5%) and allowed to stand in a refrigerator. The substance separated was freed from the supernatant and washed with water. The product was purified by thin-layer chromatography on silica gel (20% ether in benzene) and crystallized. M.p. 88—89°C (heptane, 60 mg), $[\alpha]_D^{20}$ +14° (*c* 1·0). IR spectrum: 3 630, 1 057, 1 025 (OH) cm^{-1}. Mass spectrum, *m/z*: 278 (M^+). For $C_{19}H_{34}O$ (278·5) calculated: 81·95% C, 12·31% H; found: 81·65% C, 12·95% H.

17β-Hydroxy-4,5-secoandrostan-5-one Hydrazone (*VIII*)

Ketone *V* (132 mg) was refluxed in 4 ml hydrazine hydrate under nitrogen. After 3 h the mixture was cooled, the product filtered off under suction (161 mg), washed with ether, water, and again with ether. M.p. 105—110°C (decomp.). IR spectrum (KBr): 3 400, 1 115 (OH), 3 320, 1 610 (C=NNH_2) cm^{-1}. For $C_{19}H_{34}ON_2.N_2H_4$ (338·5) calculated: 67·41% C, 11·31% H, 16·52% N; found: 67·65% C, 11·25% H, 16·09% N.

17β-Hexahydrobenzoyloxy-4,5-secoandrostane (*IX*)

17β-Benzoyloxy-4,5-secoandrost-5-en-3-yne (*XXV*, 84 mg) was hydrogenated in acetic acid (2 ml) on a platinum catalyst (18 mg). After 2 h reaction the mixture was filtered, the filtrate evaporated in a vacuum and the residue purified on a thin layer of silica gel (benzene). The product (74 mg) would not crystallize from common solvents, $[\alpha]_D^{20}$ +12° (*c* 1·2). IR spectrum: 1 731, 1 183 (—COO—) cm^{-1}. Mass spectrum, *m/z*: 388 (4), 331 (30), 260 (56), 203 (100). For $C_{26}H_{44}O_2$ (388·6) calculated: 80·35% C, 11·41% H; found: 80·18% C, 11·51% H.

N-(*p*-Toluenesulfonyl)-hydrazone of 17β-Benzoyloxy-4,5-secoandrost-3-yne-5-one (*X*)

a) *p*-Toluenesulfonylhydrazine (30 mg) was added to a solution of compound *V* (20 mg) in dioxane (0·6 ml) and the mixture was heated at 100°C for 2 h. It was then diluted with chloroform, washed with potassium carbonate solution and water, dried over sodium sulfate and evaporated. The product was purified by thin layer chromatography on silica gel (with 10% of ether

in toluene). The product (24 mg) does not crystallize from common solvents, $[\alpha]_D^{20}$ +30° (*c* 1·2). IR spectrum: 3 310, 2 120 (C≡CH), 3 220 (NH), 1 167, 1 335 (SO_2), 1 712, 1 280 (C_6H_5COO), 1 631 (C=N) cm^{-1}. For $C_{33}H_{40}N_2O_4S$ (560·7) calculated: 70·68% C, 7·19% H, 5·00% N, 5·72% S; found: 70·27% C, 7·01% H, 4·55% N, 6·13% S.

b) A solution of epoxides *IV* (110 mg) in 2 ml of a mixture of dichloromethane and acetic acid (1 : 1) was added dropwise at 0°C under stirring over 1 h to a solution of *p*-toluenesulfonylhydrazine (500 mg) in 3 ml of the same solvent mixture. After 1 h the mixture was diluted with chloroform, washed with water, a solution of potassium hydrogen carbonate and water, dried over sodium sulfate and concentrated *in vacuo*. The residue was separated on a thin layer of silica gel with 10% of ether in toluene. The lipophilic product (16 mg) was identical with ketone *V*, while the polar product (85 mg) was identical with compound *X* according to its IR and NMR spectra.

17β-Benzoyloxy-3-methyleno-A-nor-5β-androstane (*XI*)

Sodium borohydride (1 g) was added at 20°C and under stirring to a solution of compound *X* (1 g) in acetic acid (10 ml), over 1 h. After another hour of stirring the mixture was heated to 75°C (1 H) and then evaporated in a vacuum. The residue was partitioned between chloroform and an aqueous potassium hydrogen carbonate solution, the organic layer was washed with water, dried over sodium sulfate and chromatographed on a silica gel column. A 1 : 1 mixture of toluene and light petroleum eluted 80 mg of compound *XI*, m.p. 123–125°C (methanol), $[\alpha]_D^{20}$ +94° (*c* 1·2). IR spectrum: 1 721, 1 276 (C_6H_5COO), 3 075, 1 654, 3 015, 879, 882 (C=C) cm^{-1}. Mass spectrum, *m/z*: 378 (97), 363 (31), 256 (100), 241 (52). For $C_{26}H_{34}O_2$ (378·5) calculated: 82·49% C, 9·05% H; found: 82·31% C, 8·89% H.

3-Methyleno-A-nor-5β-androstan-17β-ol (*XII*)

Lithium aluminium hydride was added to a solution of benzoate *XI* (89 mg) in tetrahydrofuran (1 ml) and the solution was allowed to stand at room temperature. After 18 h the excess of the hydride was destroyed by addition of a few drops of water, the mixture was saturated with anhydrous sodium sulfate and the solid material was filtered off under suction and washed with ether. The residue was purified by chromatography on a thin layer of silica gel with 10% ether in benzene and crystallized from acetone at −18°C. M.p. 127–128°C (57 mg), $[\alpha]_D^{20}$ +70° (*c* 1·1). Circular dichroism (methanol): $\Delta\varepsilon_{203}$ +4·9. IR spectrum: 3 625, 1 055 (OH), 3 175, 3·015, 1 655, 879 (C CH_2) cm^{-1}. For $C_{19}H_{30}O$ (274·4) calculated: 83·15% C, 11·02% H; found: 83·06% C, 11·16% H.

17β-Hexahydrobenzoyloxy-3ξ-methyl-A-nor-5β-androstane (*XIII*)

A solution of compound *XI* (45 mg) in acetic acid (1 ml) was shaken under hydrogen in the presence of platinum catalyst (15 mg) for 1 h. The catalyst was filtered off and the filtrate evaporated to dryness in a vacuum. The residue was crystallized from acetone and methanol, m.p. 91–93°C (32 mg). Mass spectrum, *m/z* (% b.p.): 386 (M^+, 12), 371 ($M^+ - CH_3$, 3), 258 ($M^+ - C_6H_{11}COOH$, 100), 243 ($M^+ - C_6H_{11}COOH - CH_3$, 73). For $C_{26}H_{41}O_2$ (386·6) calculated: 80·77% C, 10·95% H; found: 80·54% C, 10·69% H.

17β-Benzoyloxy-6β-bromo-4,5-secoandrost-3-yn-5-one (*XV*)

Pyridinium hydrobromide dibromide (110 mg) was added to a suspension of ketone *V* (80 mg) in 3 ml of acetic acid at room temperature and under stirring. After 10 min the solution was

diluted with ether, washed with water, then an aqueous solution of potassium hydrogen carbonate and water, dried over sodium sulfate and concentrated. The residue was purified by thin-layer chromatography on silica gel (benzene). According to ^{1}H NMR spectroscopy the lipophilic product (86 mg) is a mixture of compounds *XIV* and *XV* in a 5 : 3 ratio. IR spectrum: 3 310, 2 118 (C≡CH), 1 721, 1 274 (C_6H_5COO) cm^{-1}. For $C_{26}H_{31}BrO_3$ (471·4) calculated: 16·93% Br; found: 16·50% Br.

Reduction of the Mixture of Bromo Ketones *XV* and *XIV*

A solution of bromo ketones *XIV* and *XV* (65 mg) in ethyl acetate (0·5 ml) and methanol (0·5 ml) was cooled to 0°C under stirring and sodium borohydride (150 mg) was added to it in several portions. After 3 h stirring the mixture was decomposed by pouring it into dilute hydrochloric acid with ice, the product was extracted with chloroform and the extract washed with an aqueous potassium hydrogen carbonate solution and water, and dried. After evaporation of the solvents the product was reduced with zinc dust (1 g) in boiling ethanol (5 ml). After 3 h zinc was filtered off, the filtrate was concentrated *in vacuo* and separated on silica gel thin layer (benzene). The lipophilic product (10 mg) had an R_F value identical with that of compound *XXVI*, but the mass spectrum demonstrated the presence of two hydrogenation products of compound *XXV* (dihydro- and tetrahydro derivative, in an about 1 : 1 ratio).

Reduction of 17β-Benzoyloxy-4,5-secoandrost-3-yn-5-one (*V*)

a) A solution of ketone *V* (99 mg) in tetrahydrofuran (3 ml) was allowed to stand at room temperature after addition of tritert-butoxy lithium aluminium hydride (200 mg). After 18 h standing the mixture was decomposed by pouring it onto ice and dilute hydrochloric acid, the product was extracted with chloroform, the extract washed with water and concentrated in a vacuum. The residue was separated on 2 thin-layer plates with silica gel, using 10% ether in toluene as developing solvent. Detection was carried out by spraying with morine in methanol (0·02%) and inspection under UV light, The non-polar product (17β-benzoyloxy-4,5-secoandrost-3-yn-5α-ol (*XVII*), 33 mg) melted at 175—176°C, $[\alpha]_D^{20}$ + 78° (*c* 1·1). IR spectrum: 3 625 (OH), 3 310, 2 115 (C≡CH), 1 720, 1 176 (C_6H_5COO) cm^{-1}. For $C_{26}H_{34}O_3$ (394·5) calculated: 79·15% C, 8·69% H; found: 78·98% C, 8·63% H. The polar product (17β-benzoyloxy-4,5-secoandrost-3-yn-5β-ol (*XVIII*), 51 mg) melted at 132—133°C, $[\alpha]_D^{20}$ + 54° (*c* 1·2). IR spectrum: 3 310, 2 115 (C≡CH), 3 625 (OH), 1 720, 1 275 (C_6H_5COO) cm^{-1}. For $C_{26}H_{34}O_3$ (394·5) calculated: 79·15% C, 8·69% H; found: 79·04% C, 8·82% H.

b) Sodium borohydride (400 mg) was added at 0°C and under stirring to a solution of ketone *V* (200 mg) in 4 ml of ethanol and 1 ml of ethyl acetate and the mixture was then stirred at room temperature. A similar working up as under *a*) afforded 140 mg of compound *XVIII* and 34 mg of compound *XVII*.

c) 10 ml of toluene were distilled off from the solution of compound *V* (98 mg) in 40 ml of toluene and solid aluminium isopropoxide (0·5 mg) was added to it. The mixture was refluxed and 15 ml distillate were distiled off over 7 h. After cooling the reaction mixture was extracted with dilute hydrochloric acid, water, aqueous potassium hydrogen carbonate solution and water. The solution was dried over sodium sulfate, filtered and evaporated. The residue was applied onto 2 silica gel thin-layer plates which were developed in 10% ether in benzene. Elution of individual zones (indicated according to increasing polarity) gave: *XVII*, 11 mg, *XVIII*, 10 mg, 4,5-secoandrost-3-yne-5α,17β-diol (*XIX*), 8 mg, and 4,5-secoandrost-3-yne-5β,17β-diol (*XX*), 33 mg, The identity of the compounds was demonstrated by comparison of their IR spectra with those of authentic compounds.

17β-Benzoyloxy-4,5-secoandrost-5-en-3-yne (*XXV*)

a) 5α-Hydroxy derivative *XVII* (235 mg) was dried by azeotropic distillation with toluene, the residue was dissolved in pyridine (2 ml) and the solution was allowed to stand at room temperature with 1·2 ml of thionyl chloride for 2 h. The mixture was poured into a mixture of water and ice, the product was extracted with ether, the extract washed with water, dried over sodium sulfate and concentrated. The residue was chromatographed on a thin layer of silica gel. The main product (R_F 0·35 in 40% of toluene in light petroleum) weighed 172 mg, $[\alpha]_D^{20}$ +35° (*c* 1·2). IR spectrum ($CHCl_3$): 3 305, 2 115 (C≡CH), 1 710, 1 280 (C_6H_5COO), 1 639 (C=C) cm^{-1}. For $C_{26}H_{32}O_2$ (376·5) calculated: 82·93% C, 8·57% H; found: 82·77% C, 8·46% H.

b) 5β-Hydroxy derivative *XVIII* (30 mg) was dissolved in acetonitrile (2 ml) and refluxed with triphenylphosphine (300 mg) for 5 min. Tetrachloromethane (0·1 ml) was then added and the mixture refluxed for another 2 h. The mixture was concentrated in a vacuum, partitioned between water and toluene and the toluene layer dried over sodium sulfate. After concentration the residue was applied onto a silica gel thin layer. After development with a mixture of toluene and light petroleum a chromatographically pure compound was isolated (18 mg), which, however represented a mixture of compounds *XXV* and *XXIV* in an about 7 : 3 ratio (according to ^{1}H NMR spectroscopy). Analytically 2·12% of Cl were found in the product.

c) 5β-Methanesulfonyloxy derivative *XXIII* (91 mg) was refluxed with 10 ml of dimethyl sulfoxide. After 2 h the solvent was evaporated in a vacuum and the product partitioned between water and toluene. The toluene extract was washed with an aqueous potassium hydrogen carbonate solution and water, then dried and concentrated and eventually applied onto a layer of silica gel. After development with a mixture of toluene and light petroleum a chromatographically uniform product could be isolated (38 mg) which however was a mixture of olefin *XXV* and the rearrangement product *XXVII* in a 3 : 1 ratio (according to ^{1}H NMR spectroscopy). On hydrogenation this mixture affords a compound the ^{1}H NMR and mass spectrum of which are interpretable as a mixture of compounds *IX* and *XXVIII*.

4,5-Secoandrost-3-yne-5β,17β-diol (*XX*)

5β-Methanesulfonyloxy derivative *XXIII* (76 mg) was refluxed with a solution of lithium aluminium hydride (about 100 mg) in tetrahydrofuran (4 ml) under nitrogen. After 5 h boiling the mixture was cooled, the excess of the hydride decomposed with a sodium sulfate solution and the mixture was filtered through a layer of sodium sulfate. After evaporation of the filtrate the residue was crystallized from acetone and heptane. Diol *XX* (52 mg) melted at 126–127°C, $[\alpha]_D^{20}$ +13° (*c* 0·9). IR spectrum (KBr): 3 315, 2 115 (C≡CH), 3 350, 1 086, 1 043, 1 031, 1 016 (OH) cm^{-1}. For $C_{19}H_{30}O_2$ (290·4) calculated: 78·57% C, 10·41% H, found: 78·71% C, 10·52% H.

4,5-Secoandrost-3-yne-5α,17β-diol (*XIX*)

Compound *XVII* (96 mg) was dissolved in a solution of lithium aluminium hydride (about 100 mg) in tetrahydrofuran (5 ml) and allowed to stand at room temperature for 18 h. The excess of the hydride was decomposed by careful addition of an aqueous sodium sulfate solution. The mixture was saturated with anhydrous sodium sulfate, the inorganic material was filtered off and the filtrate concentrated *in vacuo*. Crystallization of the residue from ether and heptane afforded compound *XIX* (46 mg), m.p. 137–139°C, $[\alpha]_D^{20}$ +39° (*c* 1·0). IR spectrum (chloroform): 3 620, 1 051 (OH), 3 310, 2 115 (C≡CH) cm^{-1}. For $C_{19}H_{30}O_2$ (290·4) calculated: 78·57% C, 10·41% H, found: 78·30% C, 10·19% H.

Reaction of *XVIII* with Thionyl Chloride

a) Thionyl chloride (0·5 ml) was added to a solution of compound *XVIII* (100 mg) in pyridine (0·5 ml) and the mixture was allowed to stand at room temperature for 100 min. The mixture was poured onto a mixture of ice and water, the product was extracted with chloroform, washed with water, dried over sodium sulfate and concentrated. The residue was applied onto a silica gel thin layer and developed twice with 50% benzene in light petroleum. The less polar product (24 mg) represented a mixture of 20% of monochloro derivative (analysis, found: 1·95% Cl) and 80% of a mixture of olefins in which olefin *XXV* is not present in a detectable amount (^{1}H NMR spectra). Further development of the residue of the plate with 10% ether in benzene and extraction of two further fractions gave 32 mg of the starting alcohol *XVIII* (R_F 0·25) and 29 mg of a more lipophilic compound, probably sulfite of the starting compound. IR spectrum: 3 305, 2 115, 1 710, 1 280 cm^{-1}; ^{1}H NMR spectrum: 0·93 (s, 6 H), 4·30 (m, W = 22 Hz), 4·83 (t, J = 8 Hz, 1 H) ppm. Mass spectrum: 394 *m/z*; analysis: found: 3·62% S).

b) A solution of *XVIII* (90 mg) in 15 ml tetrachloromethane was heated to boiling and when 2 ml of the distillate were condensed the mixture was cooled. Thionyl chloride (0·2 ml) and a solution of Aliquat (10 mg) in tetrachloromethane (1 ml) were added and the mixture was stirred at 65°C for 20 h. After cooling the solution was washed with water and ice, then with an aqueous potassium hydrogen carbonate solution and dried over sodium sulfate. The product was purified by thin-layer chromatography on silica gel. Compound *XXIV* (77 mg), m.p. 158–158°C (ethanol), $[\alpha]_D^{20}$ +61° (*c* 1·1). Mass spectrum, *m/z*: 412 (9), 376 (21), 361 (13), 290 (100), 275 (72), 255 (80), 239 (79). IR spectrum: 3 315, 2 120 (C≡CH), 1 721, 1 275 (C_6H_5COO) cm^{-1}. For $C_{26}H_{33}ClO_2$ (413·0) calculated: 75·61% C, 8·05% H, 8·59% Cl; found: 75·12% C, 8·49% H, 8·11% Cl.

17β-Benzoyloxy-5β-*p*-toluenesulfonyloxy-4,5-secoandrost-3-yne (*XXII*)

p-Toluenesulfonyl chloride (550 mg) was added to a solution of 5β-hydroxy derivative *XVIII* (230 mg) in pyridine (2 ml) and allowed to stand at room temperature for 20 h. The mixture was poured into water, extracted with chloroform, the extract washed with dilute hydrochloric acid, water, aqueous potassium hydrogen carbonate solution and water, and dried over sodium sulfate. The residue was crystallized from a mixture of chloroform and ether, m.p. 144–147°C (decomp.), $[\alpha]_D^{20}$ +22° (*c* 1·0). For $C_{33}H_{40}O_5S$ (548·7) calculated: 72·23% C, 7·35% H, 5·84% S; found: 72·49% C, 7·51% H, 5·51% S.

17β-Benzoyloxy-5β-methanesulfonyloxy-4,5-secoandrost-3-yne (*XXIII*)

A solution of a mixture of the alcohols after reduction of ketone *V* with tritert-butoxy lithium aluminium hydride (902 mg) in toluene (20 ml) was submitted to distillation. When 11 ml of an azeotropic mixture were distilled off the mixture was cooled and pyridine (4·5 ml) and methanesulfonyl chloride (0·45 ml) were added. After 6 h standing at 20°C the solution was poured onto ice, the product was extracted with chloroform, the extract washed with dilute hydrochloric acid, water, aqueous potassium hydrogen carbonate and water, and dried over sodium sulfate. The product was separated chromatographically to afford the more polar components (compound *XVII*, 299 mg) and methanesulfonate *XXIII* (590 mg) which were crystallized from a mixture of chloroform and ether, m.p. 147–148°C, $[\alpha]_D^{20}$ +32° (*c* 1·5). IR spectrum: 3 315, 2 120 (C≡CH), 1 723, 1 277 (C_6H_5COO), 1 343, 1 180, 936 (SO_2O) cm^{-1}. For $C_{27}H_{36}O_5S$ (472·6) calculated: 68·61% C, 7·68% H, 6·79% S; found: 69·09% C, 7·48% H, 6·70% S.

5β-Acetoxy-17β-benzoyloxy-4,5-secoandrost-3-yne (*XXI*)

27 ml of an azeotropic mixture were distilled off from a solution of the mixture of alcohols *XVII* and *XVIII* (189 mg) in toluene (34 ml) and pyridine (2 ml) and acetic anhydride (2 ml) were added to the cooled residue. After 9 h standing at 20°C the mixture was worked up in the conventional manner and the product separated chromatographically to compounds *XVII* (88 mg) and *XXI* (111 mg), m.p. 156–157°C (methanol), $[\alpha]_D^{20}$ +41° (*c* 1·1). IR spectrum: 3 315, 2 125 (C≡CH), 1 736, 1 248 (CH_3COO), 1 723, 1 277 (C_6H_5COO) cm^{-1}. For $C_{28}H_{36}O_4$ (436·6) calculated: 77·03% C, 8·31% H; found: 76·94% C, 8·42% H.

Partial Hydrolysis of *XXI*

Hydrochloric acid (0·1 ml) was added to a solution of compound *XXI* (70 mg) in 0·5 ml of chloroform and 5 ml methanol and the mixture was allowed to stand at 50°C. After 16 h it was diluted with chloroform, washed with water, dried over sodium sulfate and concentrated. After chromatography on a thin layer of silica gel 52 mg of a substance were obtained which was identical with authentic *XVIII*. The by-product *XX* (8 mg) was identified on the basis of its IR spectrum.

17β-Benzoyloxy-4,5-secoandrost-3-yne (*XXVI*)

A suspension of *XXIII* (47 mg) and zinc dust (400 mg) in dioxane (2 ml) was stirred with a solution of sodium iodide (200 mg) in water (0·2 ml) at 100°C. After 36 h TLC indicated that the starting compound *XXIII* has been consumed. The mixture was diluted with toluene, filtered and washed with water, then dried over sodium sulfate and separated by thin layer chromatography on silica gel. The main fraction (*XXVI*, 28 mg) would not crystallize from common solvents, $[\alpha]_D^{20}$ +21° (*c* 1·1). IR spectrum: 3 315, 2 120 (C≡CH), 1 721, 1 274 (C_6H_5COO) cm^{-1}. For $C_{26}H_{34}O_2$ (378·5) calculated: 82·49% C, 9·05% H; found: 82·74% C, 8·94% H. The lipophilic product (6 mg) was identical with A-norderivative *XI* prepared by another route.

17β-Benzoyloxy-4,5-secoandrost-5-en-3-one (*XXIX*)

Mercuric acetate (1·2 g) was added to a solution of unsaturated compound *XXV* (236 mg) in acetic acid (10 ml) and the mixture was heated at 70°C under stirring. After 2 h acetic acid was evaporated in a vacuum, the residue was extracted with 20 ml of chloroform and the extract was shaken with hydrochloric acid (15%, 10 ml). After 2 h the chloroform layer was washed with water, aqueous potassium hydrogen carbonate and water, then dried and chromatographed on a thin layer of silica gel with 20% ether in light petroleum. Compound *XXIX* (102 mg) would not crystallize from common solvents, $[\alpha]_D^{20}$ +51° (*c* 0·9). IR spectrum: 1 722, 1 275 (C_6H_5COO), 1 722, 1 356 (CH_3CO), 1 675 (C=C) cm^{-1}. For $C_{26}H_{34}O_3$ (394·5) calculated: 79·15% C, 8·69% H; found: 78·98% C, 8·82% H.

17β-Hydroxy-4,5-secoandrost-5-en-3-one (*XXX*)

Benzoate *XXIX* (800 mg) was refluxed with a 1% solution of potassium hydroxide in methanol (70 ml) under argon and exclusion of light. After 90 min the solution was concentrated in a vacuum, the product was precipitated with a saturated sodium chloride solution in water and extracted with chloroform. After washing with water and drying with sodium sulfate the product was purified by thin layer chromatography on silica gel (using 50% ether in benzene for development). The product *XXX* (503 mg) was identical (IR spectrum) with a sample prepared by a different route[3].

[5,6-^{3}H]-17β-Hydroxy-4,5-secoandrostan-3-one (*XXXI*)

a) *Tracing experiment*: A solution of 10 mg of unsaturated ketone *XXX* in 0·5 ml of methanol was mixed with the catalyst (5% palladium on barium sulfate, 5 mg) and put into a hydrogenation apparatus[10], where hydrogenation was carried out at 22°C under magnetic stirring using a tritium-containing hydrogen gas of 0·2 GBq ml^{-1} activity. Samples of the mixture were withdrawn after each 0·2 ml hydrogen absorption and analysed by TLC. The distribution of the activity on the thin-layer plate indicated that under the conditions applied 3,17-dihydroxy derivative is not formed to any considerable extent.

b) *Preparative experiment*: Unsaturated ketone *XXX* (5 mg), palladium catalyst (3 mg) and methanol (0·1 ml) were placed in a 0·8 ml flask. After degassing of the mixture 148 GBq of carrier-free tritium were introduced into the flask with a Toepler pump and the mixture was stirred at 23°C. After 50 min 66 GBq of tritium were consumed and the mixture was chromatographed on a Silufol plate (50% of ether in benzene). In the zone corresponding to compound *I* there was 84% of the total radioactivity of the reaction mixture. Elution of this zone with ethanol gave 22·17 GBq of compound *XXXI* of molar activity 1·89 TBq mmol^{-1}. Radiochemical purity checked on TLC (50% of ether in benzene) was 97·4%.

The authors thank Mrs J. Jelínková and Mrs M. Snopková for the measurement of the ^{1}H NMR *spectra and Dr J. Smolíková for the interpretation of the* IR *spectra. For the measurement of the mass spectra we thank Mrs P. Loudová and for technical assistance Mrs M. Bárová.*

REFERENCES

1. Kasal A.: This Journal *45*, 2541 (1980).
2. Kasal A., Kohout L.: This Journal *47*, 130 (1982).
3. Kasal A., Stárka L., Hampl R., Kohout L.: This Journal *48*, 2040 (1983).
4. Stárka L., Kasal A., Bičíková M., Hampl R.: This Journal, in press.
5. Scheiber J., Felix D., Eschenmoser A., Winter M., Gautschi F., Schulte-Elte K. H., Sundt E., Ohloff G., Kalvoda J., Kaufmann H., Wieland P., Anner G.: Helv. Chim. Acta *50*, 2101 (1967).
6. Pradhan S. K., Kadam S. R., Kolhe J. N.: J. Org. Chem. *46*, 2633 (1981).
7. Flynn G. A.: J. Org. Chem. *48*, 4125 (1983).
8. Boar R. B., Jones S. L., Patel A. C.: J. Chem. Soc., Perkin Trans. 1, *1983*, 513.
9. Pradhan S. K., Kolhe J. N., Mistry J. S.: Tetrahedron Lett. *23*, 4481 (1982).
10. Filip J., Šťastný J., Veřmiřovský J.: Jad. Energ. *13*, 432 (1967).

Translated by Ž. Procházka.