CYCLIZATION OF 17-ETHYLENEDIOXY-3α,5-CYCLO-6,7-SECO-5α--ANDROSTANE-6,7-DIOL*

Helena VELGOVÁ[a], Dietrich ZEIGAN[b], Günther ENGELHARDT[b] and Antonín TRKA[a]

[a] *Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6 and*
[b] *Academy of Sciences of the GDR, Centralinstitute of Physical Chemistry, 1199 Berlin-Adlershof, GDR*

Received May 18th, 1978

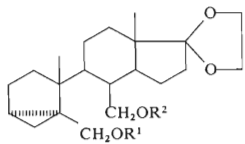
Intramolecular cyclization of 17-ethylenedioxy-3α,5-cyclo-6,7-seco-5α-androstane-6,7-diol (*I*) on treatment with *p*-toluenesulphonyl chloride in pyridine gives 17-ethylenedioxy-3α,5-cyclo--B-homo-7-oxa-5α-androstane (*III*) and 17-ethylenedioxy-3,5-methylene-6-oxaandrostane (*II*). The cyclic ethers *II* and *III* after deketalization and treatment with boron trifluoride etherate in acetic anhydride yield 3β,7-dihydroxy-6,7-secoandrost-5-en-17-one (*XIV*) along with a small quantity of 3β,5-cyclo-A-homo-6-oxa-5β-androstane-17-one (*XIII*). Proof of the structures in question is based on IR, ^{1}H-NMR, ^{13}C-NMR and mass spectrometric data.

In our preceding paper[1] we dealt with the preparation of compounds of the 3α,5--cyclo-6,7-seco-5α-androstane type which appeared of interest from the pharmacological point of view. In view of the presence of a cyclopropylcarbinyl moiety in some of these substances it was desirable to study their behavior under conditions permitting intermediary formation of a cyclopropylcarbinyl cation which is known[2] to easily undergo rearrangement both to homoallylic and cyclobutyl derivatives.

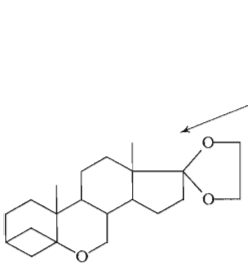
The present paper is concerned with intramolecular cyclization of 17-ethylenedioxy-3α,5-cyclo-6,7-seco-5α-androstane-6,7-diol (*I*) and with some reactions of the cyclization products. When the known intramolecular cyclization of diols on treatment with *p*-toluenesulphonyl chloride in pyridine[3-5] was applied to 17-ethylenedioxy-3α,5-cyclo-6,7-seco-5α-androstane-6,7-diol (*I*, ref.[1]) two cyclic ethers *II* and *III* were obtained in about a 1 : 2 ratio. Mass spectrometry demonstrated the same molecular weight of 332 and the molecular formula $C_{21}H_{32}O_3$ for both compounds *II* and *III*. The IR and ^{1}H-NMR spectroscopic data (Table I) revealed that the cyclopropyl ring was present only in the compound *III*. At the same time, the ^{1}H-NMR spectrum of the ether *III* disclosed the presence of two methylene groups bearing an oxygen atom (Table I). All this evidence proves *III* to be 17-ethylenedioxy-3α,5--cyclo-B-homo-7-oxa-5α-androstane. This structure was further corroborated by the

* Part CCXI in the series On Steroids; Part CCX: This Journal *43*, 3433 (1978).

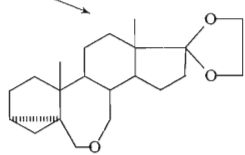
behavior of 17-ethylenedioxy-6,7-dihydroxy-3α,5-cyclo-6,7-seco-5α-androstane 6-acetate 7-*p*-toluenesulphonate (*VI*, ref.[1]) on treatment with potassium hydroxide in methanol. Under these conditions the sole reaction product was the cyclic ether *III*.



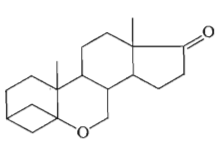
I, $R^1 = R^2 = H$
VI, $R^1 = Ac$, $R^2 = Ts$



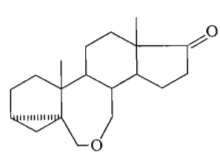
II



III

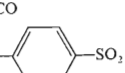


IV



V

Ac = CH_3CO

Ts = 

Removal of the protecting ethylenedioxy group by treatment with *p*-toluenesulphonic acid in methanol converted the cyclic ether *III* into the oxo derivative *V*.

In the minor cyclic ether *II* no evidence for the presence of a cyclopropane ring or a double bond was found in the IR and ^{1}H-NMR spectra (Table I). The presence of proton signals of only one methylene group bearing an oxygen atom in the ^{1}H-NMR spectrum of the compound *II* (Table I) indicates that one of the two carbon atoms, which the ether oxygen is attached to, must be tertiary. Under the reaction

TABLE I

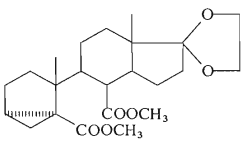
Characteristic Parameters of ^{1}H-NMR and IR Spectra

^{1}H-NMR spectra were measured in deuteriochloroform with tetramethylsilane as internal standard. Chemical shifts are given in δ-scale (ppm); the coupling constants in Hz. Following abbreviations are used for the characterization of the signals: b broad, d doublet, dd doublet of doublets, mt multiplet, s singlet, t triplet. IR spectra were measured in tetrachloromethane. Frequencies are given in cm^{-1}.

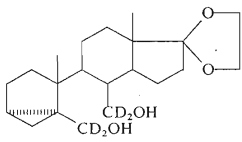
Compound	^{1}H-NMR					IR
	19-H[a]	18-H[a]	H-cyclo-propane	$C_{(6)}$—H	$C_{(7)}$—H	cyclo-propane
III	1·06	0·87	0·11 dd[b] 0·56 t[c]	3·31 dd[d] 3·95 d[d]	3·42 dd[e] 3·83 dd[f]	3 070
II[s]	1·02	0·86	—	—	3·07 t[g] 3·67 dd[h]	—
IV	1·04	0·90	—	—	3·10 t[i] 3·70 dd[j]	—
X	0·995	0·80	0·05 dd[k] 0·50 t[l]	—	—	3 070
IX	1·03	0·88	—	—	—	—
XI	1·04	0·91	—	—	—	—
XIII	0·89	0·85	—	—	3·18 t[m] 3·74 dd[n]	—
XIV[q]	1·10	0·89	—	—	4·00 bd[o] 4·42 bd[p]	—
XVII	0·89	0·84	—	—	—	—
XVIII[r]	1·11	0·90	—	—	—	—

[a] Singlets; [b] $J = 8$ and 5; [c] $J = 5$ and 3·5; [d] $J = 13$; [e] $J_{7,8} = 7{\cdot}5$; $J_{7,7} = 12{\cdot}5$; [f] $J_{7,8} = 4{\cdot}5$; $J_{7,7} = 12{\cdot}5$; [g] $J_{7,8} = J_{7,7} = 10$; [h] $J_{7,8} = 4$; $J_{7,7} = 10{\cdot}5$; [i] $J_{7,8} = J_{7,7} = 11$; [j] $J_{7,8} = 4{\cdot}5$; $J_{7,7} = 11$; [k] $J = 8$ and 5; [l] $J = 4$ and 4·5; [m] $J_{7,8} = J_{7,7} = 11$; [n] $J_{7,8} = 4$; $J_{7,7} = 11$; [o] $J_{7,7} = 11{\cdot}5$; [p] $J_{7,7} = 11{\cdot}5$ with fine splitting c. 1·5; [q] further signals: 2·03 (s, 6 H); 4·62 (bmt, 1 H, $W/2 = 15$ Hz); 4·85 (s, 2 H); [r] further signals: 4·64 (mt, 1 H, $W/2 = 15$ Hz); 4·84 (s, 2 H); [s] ^{1}H-NMR spectra were measured in deuteriochloroform–deuteriobenzene mixture (9 : 1).

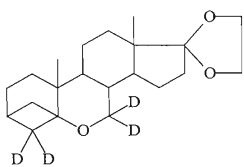
conditions, intermediary formation of cyclopropylcarbinyl cation has to be expected. In view of the above mentioned spectroscopic data it may be assumed that the cyclic ether *II* is a cyclobutyl derivative. Two structures, *A* and *B*, may be envisioned for this compound (Fig.1). Since ^{13}C-NMR spectroscopy appeared to be a suitable tool for making a decision between these structures, we prepared the free ketone *IV* and its deuterated analog *XI*. The ketone *IV* was obtained from *II* by deketalization while



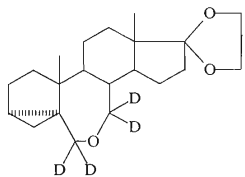
VII



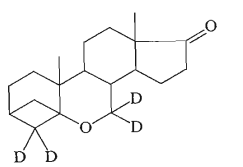
VIII



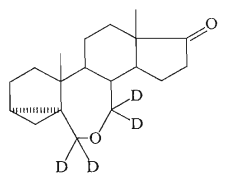
IX



X

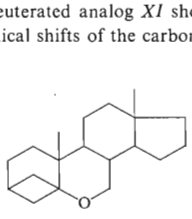


XI



XII

the deutero analog *XI* was prepared from 17-ethylenedioxy-3α,5-cyclo-6,7-seco--5α-androstane-6,7-dioic acid dimethyl ester (*VII*, ref.[1]). Reduction of this compound with lithium aluminum deuteride in boiling dioxane furnished the tetradeuterated diol *VIII* which was subjected to intramolecular cyclization in the same manner as in the preparation of the cyclic ether *II*. The reaction furnished in c. 1 : 2 relation two cyclic ether, *IX* and *X*, which were dekatalized to give the tetradeuterated cyclic ethers *XI* and *XII*. Analysis of the ^{13}C-NMR spectra of the cyclic ether *IV* and of its deuterated analog *XI* showed that in the case of the deuterated analog *XI* the chemical shifts of the carbon atoms in positions 3 and 5 are shifted by about 6 Hz



A *B*

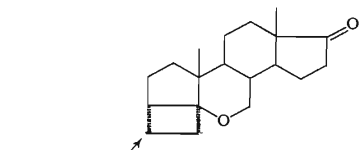
FIG. 1
Possible Structural Types for the Compounds *IV* and *XIII*

to the higher field as compared with shifts of the undeuterated compound *IV*. This isotope β-effect means that the deuterated methylene group must be symmetrically oriented to both the $C_{(3)}$ and $C_{(5)}$ atoms. Since only the structural type *A* fulfils this requirement, it can be concluded that the cyclic ether *IV* has the structure of 3,5--methylene-6-oxaandrostan-17-one (Table II).

TABLE II
Characteristic Relations Between the ^{13}C Chemical Shifts of the Structural Types *A* and *B* and the Compounds *IV* and *XIII*

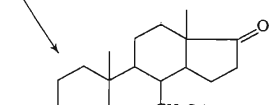
Carbon atom	Predicted[6]		Observed[a]	
	type *A*	type *B*	*IV*	*XIII*
3	$\delta(A) < \delta(B)$		26·8	36·5
4	$\delta(A) > \delta(B)$		33·2	28·4
4a	$\delta(A) > \delta(B)$		31·9	21·7
5	$\delta(A) < \delta(B)$		82·0	91·2

[a] The chemical shifts are given in δ-scale, related to $\delta(TMS) = 0$ ppm.

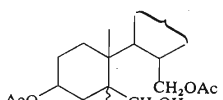


XIII

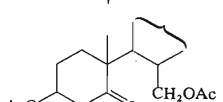
IV, V



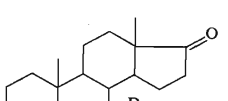
XIV



XV

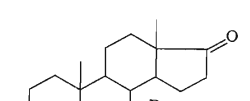


XVI



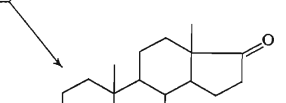
XVIIa

or



XVIIb

XI



XVIII

Ac = CH_3CO

The cyclic ether *IV* is considerably stable toward acids. It was recovered uneffected both on treatment with perchloric acid in dioxane and with boron trifluoride etherate in benzene at room temperature. Cleavage of the ether ring was achieved by treatment with boron trifluoride etherate in acetic anhydride and was accompanied by rearrangement under the formation of two products. The major product was an unsaturated compound *XIV* whereas the minor product has the properties of a cyclic ether. The structure of these compounds was established by means of spectroscopic methods. In the ^{1}H-NMR spectrum of the unsaturated compound *XIV* a singlet of two olefinic protons is present (Table I) This fact is consistant only with exomethylene character of the double bond. In the ^{1}H-NMR spectrum of the compound *XIV* are further present signals of three CHOAc protons (Table I), the signal of one of these protons being a multiplet of a width of 30 Hz which is consistent with its location in the 3α-position. The olefin *XIV* thus has the structure of 3β,7-dihydroxy-6,7-secoandrost--5-en-17-one 3,7-diacetate. The exomethylene character of the double bond in the compound *XIV* was also corroborated by chemical means in the following manner. The olefin *XIV* was subjected to *cis*-hydroxylation with osmium tetroxide and the diol *XV* thus obtained was cleaved by periodic acid oxidation to furnish the dione *XVI* in 65% yield. The ^{1}H-NMR spectrum of the later compound displays signals of two $C_{(4)}$-protons at 2·66 and 3·02 ppm and signals of two CHOAc protons (Table I). The signals of $C_{(4)}$-protons appear as doublets of doublets with identical geminal coupling constants ($J_{4,4}$ = 12 Hz). The value of the vicinal coupling constant of 4α-proton is 5Hz, while the value for the vicinal coupling constant of 4β-proton is 11 Hz which is in agreement with the spatial orientation of the protons at $C_{(4)}$ with respect to 3α-proton.

As regards the cyclic ether *XIII*, the presence of the molecular ion in its mass spectrum established the same molecular weight as for the cyclic ether *IV*. As was confirmed by IR and ^{1}H-NMR spectroscopy the cyclic ether *XIII* does not contain a cyclopropyl ring or a double bond in its molecule. Its ^{1}H-NMR spectrum displays signals of protons of only one methylene group bearing an oxygen atom. Therefore, we have assumed that the structure of this cyclic ether *XIII* probably corresponds to the structural type *B* (Fig. 1). This assumption was confirmed by ^{13}C-NMR spectroscopy.The compound *XIII* and its deuterated analog *XVII* showed in contrast to the above discussed pair *IV* and *XI* a high field shift of 6 Hz only for the $C_{(5)}$ atom but not for $C_{(3)}$. This unsymmetrical isotope β-effect is not compatible with a structure of the *A* type. For both the structural types *A* and *B* the chemical shifts of the carbon atoms in the positions 3, 4, 4a and 5 were calculated according to Lindemann and Adams[6]. As shown in Table II the relations between these calculated chemical shifts for the both types *A* and *B* are in agreement with the relations between the chemical shifts observed for the compounds *IV* and *XIII*. Therefore it was concluded that the compound *XIII* has the structure corresponding to the structural type *B*. It remains to determine the configuration at positions 3 and 5. In the bicyclo-

[3.2.0]heptyl system the rings may be fused *cis* or *trans*. It is known[7] that the *trans* derivatives with a leaving group at the bridge-head are more reactive then the *cis* compounds, the behavior being attributed to the strain relief on ionization to a *cis* derived ion. The *cis* derivatives are known to be stable toward acids. We have found that the cyclic ether *XIII* is comparatively stable toward perchloric acid in dioxane and toward boron trifluoride etherate in benzene solution at room temperature. When treated with boron trifluoride etherate in acetic anhydride, nearly 90% of the compound *XIII* was recovered unchanged along with a small amount of 3β,7--dihydroxy-6,7-secoandrost-5-en-17-one 3,7-diacetate (*XIV*). Therefore we have

TABLE III

^{13}C Chemical Shifts of Androstan-17-one[9, corr. by 10], 3,5-Methylene-6-oxa-androstan-17-one *IV* and 3β,5-Cyclo-6-oxa-A-homo-5β-androstan-17-one *XIII*

Carbon atom	Compound		
	androstan-17-one	*IV*	*XIII*
1	38·6	40·0	34·5
2	22·1	27·2	28·6
3	26·7	26·8	36·5
4	28·8	33·2	28·4
4_a	—	31·9	21·7
5	47·0	82·0	91·2
6	29·0	—	—
7	31·0	66·8	65·9
8	35·1	34·4	34·1
9	54·9	49·5	43·1
10	36·7	38·3	42·6
11	20·1	20·5	21·0
12	31·7	31·6	31·7
13	47·7	47·5	47·5
14	51·6	47·0	47·2
15	21·7	21·3	21·3
16	35·7	35·7	35·7
17	220·4	220·3	220·2
18	13·8	13·8	13·38
19	12·2	14·4	12·8

The ^{13}C- NMR spectra were measured in deuteriochloroform with hexamethyldisiloxane as standard. The chemical shifts are given in δ-scale, δ(TMS) = 0 ppm.

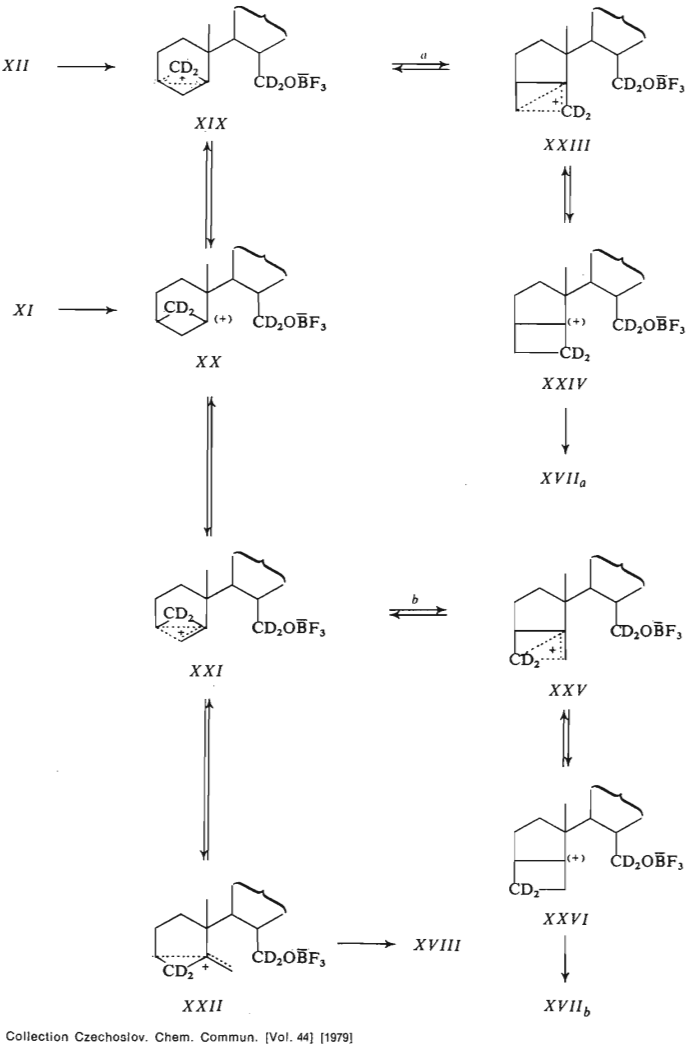
assumed that in the cyclic ether *XIII* the A ring and the four-membered ring are *cis*-fused. Our assumption that this product has the more stable *cis*-configuration is also supported by the analogous case of the solvolysis of bicyclo[3.1.0]hexan-1--methyl *p*-nitrobenzoate where the reaction product, bicyclo[3.2.0]heptan-1-ol is considered[8] to be the *cis* derivative.

It was also necessary to decide whether the four-membered ring has an α- or β-configuration. The data of ^{13}C-NMR spectroscopy permit tentative assignment of 3α,5α-configuration to the cyclobutane ring in the cyclic ether *XIII*. Compared with chemical shifts of the carbon atoms in positions 9 and 1 in androstan-17-one[9,10] (Table III), the values of chemical shifts of these carbon atoms in the compound *XIII* are displaced to the higher field by about 11·8 ppm and 4·1 ppm, respectively. In the case of the $C_{(9)}$ atom in the compound *XIII* the observed shift (which was found to be 5·4 ppm to the higher field in the case of the compound *IV*) should be explained as the sum of shifts evoked by the γ-effect due to substitution of $C_{(6)}$ atom for the oxygen atom and by the γ_{gauche}-effect of the $C_{(4a)}$ atom which would be α-oriented to the plane of the steroid skeleton. Analogically, the change in the ^{13}C chemical shift of the $C_{(1)}$ atom can be explained by the γ_{gauche}-effects due to α-configuration of $C_{(4)}$ and $C_{(4a)}$ atoms. Additional support for the α-orientation of the cyclobutane ring in the compound *XIII* is the fact that no high shift of the $C_{(19)}$ atom signal was observed. If the cyclobutane ring was β-oriented, a marked high field shift should be expected due to the γ_{gauche}-interaction of $C_{(19)}$ with $C_{(4a)}$ atom.

On treatment with boron trifluoride etherate in acetic anhydride the cyclic ether *V* undergoes the same rearrangement as the compound *IV*. Also in this case, the olefin *XIV* is formed as the main product along with a small amount of the cyclic ether *XIII*. However, if the compound *V* is treated with boron trifluoride etherate in benzene solution or with perchloric acid in dioxane at room temperature, the reaction results in the exclusive formation of the cyclic ether *IV*.

On reaction with boron trifluoride etherate in acetic anhydride the deuterated analoga of the compounds *IV* and *V*, *i.e.* both the cyclic ether *X* and *XI*, give the olefin *XVIII* along with a small amount of the compound *XVII*. Mass spectrometry proved the presence of four deuterium atoms in the compound *XVIII* while the fragment of *m/e* 109 indicated the presence of two deuterium atoms in the ring A. Complementary information was gained from the ^{1}H-NMR spectrum of the compound *XVIII* in which a two-proton singlet at 4·84 ppm demonstrated the presence of two olefinic protons. At the same time, the signal of the 3α-proton is present as a multiplet at 4·64 ppm. These facts show that the exomethylene group is not deuterated and the deuterated methylene group is located in the position 4.

The fact that on treatment with boron trifluoride etherate in acetic anhydride the cyclopropyl and cyclobutyl derivatives *V* and *IV* yield the same products *XIII* and *XIV*, respectively, in about the same proportion, is indicative of one or more common


XII
XIX
a
XXIII
XI
XX
XXIV
XVII$_a$
XXI
b
XXV
XXVI
XXII
XVIII
XVII$_b$

intermediates in both cases. In view of the formation of the deuterated olefin *XVIII* both from the cyclopropyl derivative *XII* and from the cyclobutyl derivative *XI* we believe that the reaction of these compounds with boron trifluoride etherate in acetic anhydride may proceed by a mechanism shown in Scheme 4. Ionization of the cyclopropyl derivative *XII* is assumed to lead to the cationic intermediate *XIX* which undergoes rapid degenerate cyclopropylcarbinyl–cyclopropylcarbinyl rearrangement to the cation *XXI*. This rearrangement proceeds more probably *via* the puckered cyclobutyl cation *XX* which could also arise from the cyclobutyl derivative *XI* (ref.[2]) as a primary product of its ionization. Rearrangement of the cation *XXI* to the homoallylic cation *XXII* followed by solvent attack give rise to the olefin *XVIII*.

Two ways may be envisaged for the formation of a small amount of the cyclobutyl derivative *XVII*: either equilibration of a small fraction of the cationic intermediate *XIX* to the cation *XXIII* and further to the *cis*-derived ion *XXIV* yielding by internal return the comparatively stable cyclic ether *XVII* deuterated in the position 4a (pathway *a*)). The second possible pathway *b*) would be rearrangement of the cationic intermediate *XXI* to the cation *XXV* and to the *cis*-derived ion *XXVI* which would give by internal return the cyclic ether *XVII* deuterated in the position 4. The fact that in the absence of a nucleophilic solvent the cyclopropyl derivative *XII* yields the cyclobutyl derivative *XI* as a sole product seems to indicate the transformation occurs by the pathway *b*). However, since the present results do not permit unequivocal location of the deuterated methylene group in the cyclobutyl derivative *XVII*, the pathway *a*) cannot be excluded with certainty.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Unless stated otherwise optical rotations were measured in chloroform. The IR spectra were measured on a Zeiss UR-20 spectrophotometer. The ^{1}H-NMR spectra were measured in deuteriochloroform on a Varian HA-100 apparatus using tetramethylsilane as internal standard. The chemical shifts are given in ppm. The ^{13}C-NMR spectra were recorded at 25·15 MHz using a JEOL-PFT 100-(NICOLET--1085)-spectrometer system operating in the Fourier-transform mode. The proton noise-decoupled and off-resonance spectra were accumulated (3000 to 30000 scans according to the concentration with 8 k FID and 6024 Hz sweep width) at 25°C in dilute solutions of deuteriochloroform with hexamethyldisiloxane as standard. The chemical shifts δ (ppm) are related to δ (TMS) = = 0 ppm, positive signs mean low field shifts. The mass spectra were measured on the double focussing mass spectrometer AEI MS 902 (Associated Electric Industries, Manchester) using the direct inlet system. The resolving power was 1000 and 10000, respectively, the ionization potential 70 eV and the temperature of the ionic source was 120°C. All the precise masses were found within 3 ppm of the calculated value.

The identity of samples prepared by different routes was checked by mixture melting points and by IR spectra. The statement "worked-up as usual" stands for: The solution was washed with 5% hydrochloric acid, 5% potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent evaporated *in vacuo*.

17-Ethylenedioxy-3,5-methylene-6-oxaandrostane (*II*)

A solution of the 17-ethylenedioxy-3α,5-cyclo-6,7-seco-5α-androstane-6,7-diol (*I*, ref.[1]) (500 mg) in pyridine (5 ml) was treated with *p*-toluenesulphonyl chloride (500 mg) at 0°C overnight. The mixture was poured into cold water and the product extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (460 mg) was chromatographed on a silica gel column (40 g) in light petroleum–ether–acetone (9 : 0·5 : 0·5). After working-up the less polar fractions afforded 100 mg of the cyclic ether *II* which was crystallized from ligroin, m.p. 186–188°C, $[\alpha]_D^{22} = +16°$ (*c* 0·5). IR spectrum (tetrachloromethane): 1160, 1112, 1043 cm^{-1}. ^{1}H-NMR spectrum (deuteriochloroform–deuteriobenzene): 0·86 (s, 3 H, 18-CH_3); 1·02 (s, 3 H, 19-CH_3); 3·07 (t, 1 H, $C_{(7)}$—H, $J_{7,7} = 10·5$ Hz, $J_{7,8} = 10·5$ Hz); 3·67 (dd, 1 H, $C_{(7)}$—H, $J_{7,7} = 10·5$ Hz, $J_{7,8} = 4$ Hz); 3·62 (s, 4 H, —O—CH_2—CH_2—O—). For $C_{21}H_{32}O_3$ (332·5) calculated: 75·86% C, 9·56% H; found: 76·04%C 9·56% H. Mol. weight (mass spectrometry): 332.

17-Ethylenedioxy-3α,5-cyclo-B-homo-7-oxaandrostane (*III*)

a) Elution of the chromatography after isolation of the compound *II* in the preceding procedure with light petroleum–ether–acetone (8 : 1 : 1) and working up of the corresponding fractions left product *III* (210 mg) which was crystallized from ligroin at 0°C, m.p. 70–73°C. IR spectrum (tetrachloromethane): 1193, 1125, 1165, 1141, 1065, 1043, 3070 cm^{-1}. ^{1}H-NMR spectrum: 0·11 (dd, 1 H, cyclopropane-H, $J = 5 + 8$ Hz); 0·56 (t, 1 H, cyclopropane-H, $J = 5 + 3·5$ Hz); 0·87 (s, 3 H, 18-CH_3); 1·06 (s, 3 H, 19-CH_3); 3·31 (d, 1 H, $C_{(6)}$—H, $J_{6,6} = 13$ Hz); 3·95 (d, 1 H, $C_{(6)}$—H, $J_{6,6} = 13$ Hz); 3·42 (dd, 1 H, $C_{(7)}$—H, $J_{7,7} = 12·5$ Hz, $J_{7,8} = 7·5$ Hz); 3·83 (dd, 1 H, $C_{(7)}$—H, $J_{7,7} = 12·5$, $J_{7,8} = 4·5$ Hz); 3·88 (center of mt, 4 H, —O—CH_2—CH_2—O—). For $C_{21}H_{32}O_3$ (332·5) calculated: 75·86% C, 9·70% H; found: 75·12% C, 9·36% H. Mol. weight (mass spectrometry): 322.

b) A solution of the 17-ethylenedioxy-3α,5-cyclo-6,7-seco-5α-androstane-6,7-diol 6-acetate 7-*p*-toluenesulphonate (*VI*, ref.[1]) (190 mg) in methanol (20 ml) was refluxed with a solution of potassium hydroxide (200 mg) in water (2 ml) for 2 h. The mixture was concentrated to one third of its volume *in vacuo*, poured into water and the product was taken up into ether. The ethereal extract was washed with water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (180 mg) was preparatively chromatographed on three plates of silica gel (20 × 20 cm) in light petroleum–ether–acetone (8 : 1 : 1). The corresponding zones were collected, eluted with ether and the solvent evaporated *in vacuo*. The residue (130 mg) was crystallized from ligroin at 0°C to yield 80 mg of the cyclic ether *III*, m.p. 69–73°C.

3,5-Methylene-6-oxaandrostan-17-one (*IV*)

a) *p*-Toluenesulphonic acid (50 mg) was added to a solution of the ethylenedioxy derivative *II* (50 mg) in methanol and the mixture was allowed to stand at room temperature for 2 h. The mixture was concentrated to one third of the original volume *in vacuo*, poured into water and the product was taken up in ether. The ethereal extract was washed with 5% potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (50 mg) was preparatively chromatographed on one plate of silica gel (20 × 20 cm) in light petroleum–ether–acetone (8 : 1 : 1). The corresponding zone was collected, eluted with ether and solvent evaporated *in vacuo*. The residue (42 mg) was crystallized from ligroin to yield 31 mg of the ketone *IV*, m.p. 157–159°C, $[\alpha]_D^{22} = +122°$ (*c* 0·5). IR spectrum (tetrachloromethane): 1157, 1063, 1027, 1745, 1409 cm^{-1}. ^{1}H-NMR spectrum. 0·90 (s, 3 H, 18-CH_3); 1·04 (s, 3 H,

19-CH_3); 3·10 (t, 1 H, $C_{(7)}$—H, $J_{7,7} = J_{7,8} = 11$ Hz); 3·705 (dd, 1 H, $C_{(7)}$—H, $J_{7,7} = 11$ Hz, $J_{7,8} = 4{\cdot}5$ Hz). For $C_{19}H_{28}O_2$ (288·4) calculated: 79·12% C, 9·78% H; found: 79·12% C, 9·75%H.

b) The ketone *V* (500 mg) in dioxane (20 ml) was treated with perchloric acid (70%, 0·3 ml) and the mixture was allowed to stand at room temperature for 2 h. Water was added and the product was isolated with ether. The ethereal extract was washed with 5% potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (496 mg) was chromatographed on a silica gel column (40 g) in light petroleum–ether–acetone (8 : 1 : 1) to yield 467 mg of the cyclic ether *IV* which was crystallized from ligroin, m.p. 157 to 159°C, $[\alpha]_D^{22} + 122°$ (c 0·5).

3α,5-Cyclo-B-homo-7-oxa-5α-androstan-17-one (*V*)

A solution of the ethylenedioxy derivative *III* (50 mg) in methanol (5 ml) was treated with *p*-toluenesulphonic acid (50 mg) in the same manner as in the preceding procedure. The same work-up as in the preceding procedure afforded 50 mg of the crude product which was preparatively chromatographed on one plate of silica gel (20 × 20 cm) in light petroleum–ether–acetone (8 : 1 : 1). The corresponding zone was collected, eluted with ether and the solvent evaporated *in vacuo*. The residue (45 mg) was crystallized from ligroin to yield the ketone *V*, m.p. 80—81°C, $[\alpha]_D^{22} = +124°$ (*c* 0·5). IR spectrum (tetrachloromethane): 3068, 3008, 1745, 1408 cm^{-1}, ^{1}H-NMR spectrum: 0·11 (dd, 1 H, cyclopropane-H, $J = 8 + 5$ Hz); 0·58 (t, 1 H, cyclopropane-H $J = 5 + 3{\cdot}5$ Hz); 0·885 (s, 3 H, 18-CH_3); 1·09 (s, 3 H, 19-CH_3); 3·32 (d, 1 H, $C_{(6)}$—H, $J_{6,6} =$ = 13 Hz); 3·93 (d, 1 H, $C_{(6)}$—H, $J_{6,6} = 13$ Hz); 3·55 (dd, 1 H, $C_{(7)}$—H, $J_{7,7} =$ = 12 Hz, $J_{7,8} = 7$ Hz); 3·90 (dd, 1 H, $C_{(7)}$—H, $J_{7,7} = 12$ Hz, $J_{7,8} = 5$ Hz). For $C_{19}H_{28}O_2$ (288·4) calculated: 79·12% C, 9·78% H; found: 79·12% C, 9·77% H.

17-Ethylenedioxy-6,6,7,7-tetradeuterio-3α,5-cyclo-6,7-seco-5α-androstane-6,7-diol (*VIII*)

A solution of the 17-ethylenedioxy-3α,5-cyclo-6,7-seco-5α-androstane-6,7-dioic acid dimethyl ester (*VII*, ref.[1]) (2·3 g) in dioxane (50 ml) added to a solution of lithium aluminum deuteride (800 mg) in dioxane (25 ml) and the mixture was refluxed for 2 h. The excess deuteride was destroyed with saturated aqueous solution of sodium sulfate and the mixture was passed through a small column of sodium sulfate. The filtrate was concentrated *in vacuo* and the residue (2·25 g) was crystallized from ether–heptane to yield 1·3 g of the diol *VIII*, m.p. 159—161°C. IR spectrum (chloroform): 3625, 3605, 3065, 2135, 2120, 2100 cm^{-1}. For $C_{21}D_4H_{28}O_3$ mol.weight calculated: 354·5; found (mass spectrometry): 354.

17-Ethylenedioxy-4a,4a,7,7-tetradeuterio-3,5-methylene-6-oxaandrostane (*IX*)

The diol *VIII* (1·3 g) in pyridine (10 ml) was treated with *p*-toluenesulphonyl chloride (1·3 g) overnight at 0°C. The mixture was poured into cold water and the product was taken up in ether. The ethereal extract was washed with water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (800 mg) was chromatographed on a silica gel column (80 g) in light petroleum–ether–acetate (8 : 1 : 1). After working up the less polar fractions afforded 400 mg of the cyclic ether *IX* which was crystallized from ligroin, m.p. 180·5—183°C. IR spectrum (tetrachloromethane): 1185, 1159, 1115, 1097, 1038, 2150, 2080 cm^{-1}. ^{1}H-NMR spectrum: 0·88 (s, 3 H, 18-CH_3); 1·03 (s, 3 H, 19-CH_3); 3·86 (center of mt, 4 H, —O—CH_2—CH_2—O—). For $C_{21}D_4H_{28}O_3$ mol.weight calculated: 336·5; found (mass spectrometry): 336.

3,5-Methylene-4a,4a,7,7-tetradeuterio-6-oxaandrostan-17-one (*XI*)

p-Toluenesulphonic acid (100 mg) was added to a solution of the ethylenedioxy derivative *IX* (100 mg) in methanol (10 ml) and the mixture was allowed to stand at room temperature for 15 min. The mixture was concentrated to one third of its volume, poured into water and the product extracted with ether. The ethereal extract was washed with 5% potassium hydrogen carbonate water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (100 mg) was crystallized from ligroin to yield 80 mg of the keton *XI*, m.p. 159–161°C, $[\alpha]_D^{22}$ +106° (*c* 0·5). IR spectrum (tetrachloromethane): 1745, 1410, 1174, 1096, 1055, 2210, 2240, 2080, 2040 cm^{-1}, ^{1}H-NMR spectrum: 0·91 (s, 3 H, 18-CH_3); 1·04 (s, 3 H, 19-CH_3). For $C_{19}D_4H_{24}O_2$ mol.weight calculated: 292·4; found (mass spectrometry): 292.

17-Ethylenedioxy-3α,5-cyclo-4,4,7a,7a-tetradeutrio-B-homo-7-oxa-5α-androstane (*X*)

Elution of the chromatographic column after isolation of the compound *IX* with light petrolcum–ether–acetone (8 : 1 : 1) and working up of the corresponding fractions left product *X* (800 mg) which was crystallized from ligroin, m.p. 59·5–63°C, $[\alpha]_D^{22}$ +24° (*c* 0·5). IR spectrum (tetrachloromethane): 1153, 1125, 1112, 3070, 2205, 2175, 2100, 2085 cm^{-1}. ^{1}H-NMR spectrum; 0·05 (dd, 1 H, cyclopropane-H, J = 8 + 5 Hz); 0·50 (t, 1 H, cyclopropane-H, J = 4 + 4·5 Hz), 0·80 (s, 3 H, 18-CH_3); 0·995 (s, 3 H, 19-CH_3); 3·81 (center of mt, 4 H, —O—CH_2—CH_2—O—). For $C_{21}D_4H_{28}O_3$ mol.weight calculated: 336·5; found (mass spectrometry): 336.

3α,5-Cyclo-6,6,7a,7a-tetradeuterio-B-homo-7-oxa-5α-androstan-17-one (*XII*)

p-Toluenesulphonic acid (100 mg) was added to a solution of the ethylenedioxy derivative *X* (100 mg) in methanol (10 ml) and the mixture was allowed to stand at room temperature for 15 min. The same working up as in the preceding procedure afforded a crude product (100 mg) which was crystallized from ligroin to yield 56 mg of the ketone *XII*, m.p. 81–82°C, $[\alpha]_D^{22}$ = = +115° (*c* 0·5). IR spectrum (tetrachloromethane): 1124, 1748, 3070 cm^{-1}. For $C_{19}D_4H_{24}O_3$ mol.weight calculated: 292·4; found (mass spectrometry): 292.

3β,5-Cyclo-A-homo-6-oxa-5β-androstan-17-one (*XIII*)

a) Boron trifluoride etherate (0·05 ml) was added to a solution of the cyclobutyl derivative *IV* (360 mg) in acetic anhydride (10 ml) and the mixture was allowed to stand at room temperature for 2 h. The mixture was poured into water and the product was taken up in ether. The ethereal extract was washed with 5% potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (400 mg) was chromatographed on a silica gel column (30 g) in light petroleum–ether–acetone (8 : 1 : 1). After working up the less polar fractions afforded 50 mg of the cyclic ether *XIII* which was crystallized from ligroin, m.p. 156 to 157°C, $[\alpha]_D^{22}$ = +142° (*c* 0·5). IR spectrum (tetrachloromethane): 1130, 1113, 1105, 1092, 1744 cm^{-1}. ^{1}H-NMR spectrum: 0·85 (s, 3 H, 18-CH_3); 0·89 (s, 3 H, 19-CH_3); 3·18 (t, 1 H $C_{(7)}$—H, $J_{7,7} = J_{7,8}$ = 11 Hz); 3·74 (dd, 1 H, $C_{(7)}$—H, $J_{7,7}$ = 11 Hz, $J_{7,8}$ = 4 Hz). For $C_{19}H_{28}O_2$ (288·4) calculated: 79·12% C, 9·78% H; found: 78·79% C, 9·53% H.

b) The cyclopropyl derivative *V* (300 mg) in acetic anhydride (10 ml) was treated with boron trifluoride etherate (0·05 ml) in the same manner as in the preceding procedure. The crude product (300 mg) obtained after working up was chromatographed on a silica gel column (30 g) in light petroleum–ether–acetone (8 : 1 : 1). After working up the less polar fractions afforded 30 mg of the cyclic ether *XIII* which was crystallized from ligroin, m.p. 156–157°C, $[\alpha]_D^{22}$ +141° (*c* 0·5).

3β,7-Dihydroxy-6,7-secoandrost-5-en-17-one 3,7-Diacetate (*XIV*)

a) Elution of the chromatographic column after isolation of the compound *XIII* in the preceding procedure under *a*) with light petroleum–ether–acetone (8 : 1 : 1) and working up of the corresponding fractions left product *XIV* (270 mg) which was crystallized from ligroin, m.p. 140—141·5°C, $[\alpha]_D^{22}$ +118° (*c* 0·5). IR spectrum (tetrachloromethane): 1742, 1242, 1035, 1639, 3050, 3090, 907 cm^{-1}. ^{1}H-NMR spectrum: 0·89 (s, 3 H, 18-CH_3); 1·10 (s, 3 H, 19-CH_3); 2·03 (s, 6 H, two —O—CO—CH_3); 4·00 (broad d, 1 H, $C_{(7)}$—H, $J_{7,7}$ = 11·5 Hz); 4·42 (broad d, 1 H, $C_{(7)}$—H, $J_{7,7}$ = 11·5 Hz with fine splitting *c.* 1·5 Hz); 4·62 (broad mt, 1 H, $C_{(3)}$—H, $W/2$ = 15 Hz); 4·85 (s, 2 H, C=CH_2). For $C_{23}H_{34}O_5$ (390·5) calculated: 70·74% C, 8·78% H; found: 70·95% C, 8·77% H.

b) Elution of the chromatographic column after isolation of the compound *XIII* in the preceding procedure under *b*) with light petroleum–ether–acetone (8 : 1 : 1) and working up of the corresponding fractions left *XIV* which was crystallized from ligroin, m.p. 140—141·5°C, $[\alpha]_D^{22}$ = = +118° (*c* 0·5).

3β,7-Dihydroxy-6,7-secoandrostane-5,17-dione 3,7-Diacetate (*XVI*)

Osmium tetroxide (1 g) was added to a solution of the olefine *XIV* (550 mg) in pyridine (5 ml) and the mixture was allowed to stand at room temperature 10 days in darkness. Water (15 ml), sodium sulfite (2 g) and pyridine (15 ml) were added and the mixture was allowed to stand at room temperature for 30 min. The mixture was poured into water, the product was extracted with chloroform and the extract was worked up as usual. The residue (900 mg) was chromatographed on a silica gel column (80 g) in light petroleum–ether–acetone (5 : 2·5 : 2·5). After working up the corresponding fractions afforded 200 mg of the crude diol *XV*. IR spectrum (chloroform): 1748, 1253, 1030, 3520 cm^{-1}.

The crude diol *XV* (90 mg) was dissolved in dioxane (10 ml), a solution of periodic acid (180 mg) in water (0·5 ml) was added and the mixture was allowed to stand at room temperature overnight. A solid sodium hydrogen carbonate (200 mg) was added, the mixture was concentrated to one third of its volume *in vacuo* and the product was extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (90 mg) was preparatively chromatographed on two plates of silica gel (20 × 20 cm) in light petroleum–ether–acetone (6 : 2 : 2). Working up of the corresponding zones left the dione *XVI* (45 mg) which was crystallized from ether, m.p. 195—196°C, $[\alpha]_D^{22}$ +60° (*c* 0·5). IR spectrum (tetrachloromethane): 1714, 1748, 1235, 1040 cm^{-1}. ^{1}H-NMR spectrum: 0·93 (s, 3 H, 18-CH_3); 1·08 (s, 3 H, 19-CH_3); 2·07 (s, 3 H, —O—CO—CH_3); 2·09 (s, 3 H, —O—CO—CH_3); 3·80 (dd, 1 H, $C_{(7)}$—H, $J_{7,7}$ = 12 Hz, $J_{7,8}$ = 1·5 Hz); 4·295 (dd, 1 H, $C_{(7)}$—H, $J_{7,7}$ = 12 Hz, $J_{7,8}$ = 1·5 Hz); 2·66 (dd, 1 H, $C_{(4\alpha)}$—H, $J_{4,4}$ = 12 Hz, $J_{4\alpha,3\alpha}$ = 5 Hz); 3·02 (dd, 1 H, $C_{(4\beta)}$—H, $J_{4,4}$ = 12 Hz, $J_{4\beta,3\alpha}$ = 11 Hz); 4·86 (center of mt, 1 H, $C_{(3)}$—H, $W/2$ = 16 Hz). For $C_{22}H_{32}O_6$ mol.weight calculated: 392·5; found (mass spectrometry): 392.

3β,5-Cyclo-4a,4a,7,7-tetradeuterio-A-homo-6-oxa-5β-androstan-17-one (*XVII*)

Boron trifluoride etherate (0·05 ml) was added to a solution of the cyclobutane derivative *XI* (300 mg) in acetic anhydride (10 ml) and the mixture was allowed to stand at room temperature for one hour. The same working up as in the case of the preparation of the cyclic ether *XIII* afforded the crude product (300 mg) which was chromatographed on a silica gel column (30 g) in light petroleum–ether–acetone (8 : 1 : 1). After working up the less polar fractions afforded 30 mg of the deuterated cyclic ether *XVII* which was crystallized from ligroin, m.p. 158—160°C.

IR spectrum (tetrachloromethane): 1745, 1097, 2250, 2210, 2195, 2080, 2055 cm^{-1}. For $C_{19}D_4H_{24}O_2$ mol.weight calculated: 292·4; found (mass spectrometry): 292.

3β,7-Dihydroxy-4,4,7,7-tetradeuterio-6,7-secoandrost-5-en-17-one 3,7-Diacetate (*XVIII*)

After isolation of the compound *XVII* the column was eluted with light petroleum–ether–acetone (8 : 1 : 1) to give product *XVIII* which was crystallized from ether–ligroin, m.p. 143—145°C, $[\alpha]_D^{22}$ +60° (*c* 0·5). IR spectrum (tetrachloromethane): 1744, 1261, 1245, 1238, 905, 1635, 3090. 2258, 2215, 2195, 2178, 2135, 2118 cm^{-1}. ^{1}H-NMR spectrum: 0·90 (s, 3 H, 18-CH_3); 1·11 (s, 3 H, 19-CH_3); 2·03 (s, 3 H, O—CO—OH_3); 2·04 (s, 3 H, —O—CO—CH_3); 4·64 (mt, 1 H, $C_{(3)}$—H); 4·84 (s, 2 H, C=CH_2). For $C_{23}D_4H_{30}O_5$ mol.weight calculated: 394·5; found: 394 ($[M-61]^+$ = 333).

Treatment of the Cyclobutyl Derivatives *IV* and *XIII* with Perchloric Acid

Perchloric acid (0·08 ml) was added to a solution of the cyclobutyl derivative *IV* (60 mg) in dioxane (5 ml) and the mixture was allowed to stand at room temperature for 2 h. Water was added and the product was extracted with ether. The ethereal extract was washed with 5% potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (60 mg) was preparatively chromatographed on one plate of silica gel (20 × 20 cm) in light petroleum–ether–acetone (8 : 1 : 1). The corresponding zone was collected, eluted with ether and the solvent evaporated *in vacuo*. The residue (52 mg) was crystallized from ligroin to yield 38 mg of the cyclobutyl derivative *IV*, m.p. 157—159°C, $[\alpha]_D^{22}$ +122° (*c* 0·5).

The same procedure was applied to the cyclobutyl derivative *XIII* (60 mg) to give 50 mg of the cyclobutyl derivative *XIII* which was crystallized from ligroin, m.p. 156—157°C, $[\alpha]_D^{22}$ +141° (*c* 0·5).

Treatment of the Cyclobutyl Derivatives *IV* and *XIII* with Boron Trifluoride Etherate in Benzene

To a solution of the cyclobutyl derivative *IV* (34 mg) in benzene (4 ml) two drops of boron trifluoride etherate were added and the mixture was allowed to stand at room temperature for 2 hours. Water was added and the product was extracted with ether. The ethereal extract was washed with 5% potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (33 mg) was preparatively chromatographed on plate of silica gel (20 × 20 cm) in light petroleum–ether–acetone (8 : 1 : 1). The corresponding zone was collected, eluted with ether and the solvent evaporated *in vacuo*. The residue (29 mg) was crystallized from ligroin to yield 20 mg of the cyclic ether *IV*, m.p. 157—159°C, $[\alpha]_D^{22}$ +122° (*c* 0·5).

The same procedure was applied to the cyclobutyl derivative *XIII* (30 mg) to give the cyclic ether *XIII* (21 mg) which was crystallized from ligroin, m.p. 156—157°C, $[\alpha]_D^{2}$ +141° (*c* 0·5).

Treatment of the 3β,5-Cyclo-A-homo-6-oxa-5β-androstan-17-one (*XIII*) with Boron Trifluoride Etherate in Acetic Anhydride

To a solution of the cyclobutyl derivative *XIII* (30 mg) in acetic anhydride (1 ml) two drops of boron trifluoride etherate were added and the mixture was allowed to stand at room temperature for 2 h. Water was added and the product was taken up in ether. The ethereal extract was washed with 5% potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue (30 mg) was preparatively chromatographed on one plate

of silica gel (20 × 20 cm) in light petroleum–ether acetone (8 : 1 : 1). The working up of the less polar zone afforded the cyclic ether *XIII* (24 mg) which was crystallized from ligroin, m.p. 156—157°C, $[\alpha]_D^{22}$ +141 (*c* 0·5). After working up the more polar zone afforded the olefine *XIV* (5 mg), which was crystallized from ligroin, m.p. 140—142°C.

The same procedure was applied to the deuterated analog *XVII* to give the products *XVII* and *XVIII* in the ratio 5 : 1.

The analyses were carried out in the analytical laboratories of the Institute by Mr V. Štěrba, Mrs V. Rusová and Mrs E. Sýkorová (under direction of Dr J. Horáček). The IR *spectra were recorded by Mr P. Formánek (under direction of Dr J. Smolíková), the mass spectra by Dr A. Trka, the* ^{1}H-NMR *spectra by Dr M. Buděšinský.*

REFERENCES

1. Velgová H., Černý V.: This Journal *41*, 2630 (1976).
2. Olah G. A., Schleyer P. von R.: *Carbonium Ions*, Vol. III, Chapters 25 and 26. Willey-Interscience, New York 1972.
3. Reynolds D. D., Kenyon W. O.: J. Amer. Chem. Soc. *72*, 1593 (1950).
4. Hesse R. H., Pechet M. M.: J. Org. Chem. *30*, 2759 (1965).
5. Kasal A., Černý V.: This Journal *31*, 2759 (1966).
6. Lindemann L. P., Adams J. Q.: Anal. Chem. *43*, 1245 (1971).
7. Olah G. A., Schleyer P. von R.: *Carbonium Ions*, Vol. III, p. 1330. Willey-Interscience, New York 1972.
8. Closson W. D., Kwiatkowski G. T.: Tetrahedron *21*, 2779 (1965).
9. Eggert H., Djerassi C.: J. Org. Chem. *38*, 3788 (1973).
10. ApSimon J. W., Beierbeck H., Saunders J. K.: Can. J. Chem. *51*, 3874 (1973).

Translated by V. Černý.