NEW CLASSES OF ORALLY ACTIVE HORMONAL DERIVATIVES. I. ALKYL ANDROSTAN-17β-YL AND ALKYL 19-NORANDROSTAN-17β-YL MIXED ACETALS

Romano Vitali, Rinaldo Gardi, Giovanni Falconi and Alberto Ercoli
Vister Research Laboratories
Casatenovo (Como), Italy

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ABSTRACT

A series of alkyl steroid-17β-yl mixed acetals of aliphatic and cycloaliphatic ketones have been prepared from several androstane and 19-norandrostane derivatives. By oral administration many of these compounds, which are easily hydrolizable both in vitro and in vivo, have proved to be more potent than methyltestosterone in the usual test for androgenic and myogenic activity.

It is well known that testosterone and related steroids of androstane and 19-norandrostane series bearing a 17β-hydroxyl group and no substituent at the 17α position lack oral effectiveness.

Since the preparation of methyltestosterone in 1935, alkylation at C_{17} has been the only effective means to promote oral activity and has been largely applied to the synthesis of orally active androgenic and anabolic steroids. However, the presence of an alkyl group at C_{17}, irreversibly linked to the steroid molecule, besides affecting its metabolic fate and preventing its elimination as 17-ketosteroid, is known to be responsible for hepatotoxic effects. Jaundice has been reported to occur, although rarely, during treatment with methyl-

testosterone or related 17α-methyl, ethyl or ethynylderivatives; more frequently, elevation of certain blood enzymes, as well as retention of bromosulfalein have been observed [1]. Moreover, 17α-alkylsteroids may present a lesser or greater degree of progestational activity, particularly remarkable in the 19-norandrostane derivatives, which can be considered in many instances as an unwanted side-effect.

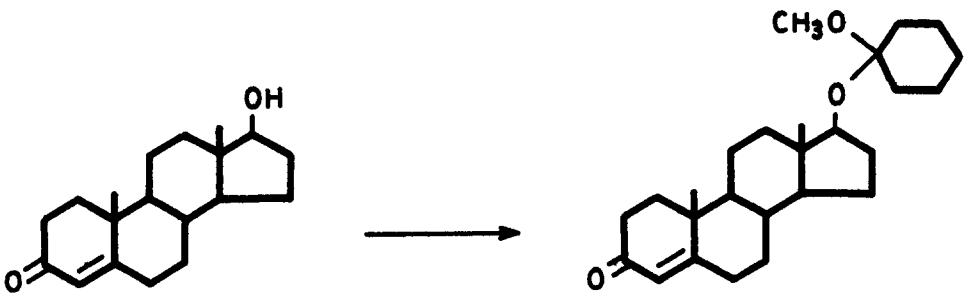
In pursuing our studies of the influence of etherification at the different oxygens of the molecule on the steroid utilization by the body [2], we investigated in the last years the etherification of 17β-hydroxy-androstanes and of 17β-hydroxy-19-norandrostanes as a possible means to endow such compounds with oral activity. Our efforts were chiefly directed to the preparation of ethers bearing the protecting group bonded to the 17β-oxygen by an acid sensitive link.

In 1962 [3] we announced the satisfactory results obtained with steroid-17β-yl acetals and enol ethers of aldehydes and ketones, including derivatives of androgenic, anabolic and estrogenic hormones. In the same preliminary paper mention was also made of the favourable oral activity of testosterone 17-tetrahydropyranil ether prepared some years before by A.C. Ott et al. [4]. Following our studies others have prepared and tested labile ethers of 17β-hydroxy steroids. A.D.Cross et al. prepared tetrahydropyranil ethers of anabolic [5] and estrogenic [6] steroids, 2'-hydroxyethyl ethers of estrogens [7] and substituted tetrahydropyranil ethers [8].

In this paper we wish to report in extenso the data concerning alkyl androstan-17β-yl and alkyl 19-norandrostan-17β-yl mixed acetals of aliphatic and cycloaliphatic ketones.

Preparation of acetals from 3-hydroxy [9, 10] and 21-hydroxy-steroids [11] by reaction with lower acetals or enolethers of ketones had been already reported. We prepared steroid-17β-yl alkyl acetals, practically by the same procedure. As an example, testosterone 17-

(1'-methoxy)-cyclohexyl ether (3) was prepared by acid catalized addition of testosterone to cyclohexanone methyl enol ether (Method A) or by acid catalized transacetalation between testosterone and cyclohexanone dimethyl acetal (Method B).



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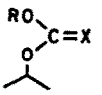
Analytical results, infrared spectra and the chemical behavior strongly supported the attributed structure.

As parent 17β-hydroxysteroids we used, besides testosterone, its reduction or dehydrogenation derivatives, 19-nortestosterone and related compounds. When necessary, the reaction products have been converted in related compounds by performing conventional reactions at C_3. The physical constants and the analytical data of the prepared acetals are reported in Table I.

Further transacetalation may occur on the mixed acetal; thus simple recrystallization from methanol of steroidyl ethyl acetals in the presence of even trace amounts of p.toluenesulphonic acid or pyridine p.toluenesulphonate led to the formation of the corresponding steroidyl methyl acetals [12]. Disteroidyl acetals, which can be also obtained by further transacetalation, will be reported later.

TABLE I

ALKYL STEROID-17β-YL MIXED ACETALS



No.	Parent 17β-hydroxysteroid	X	R	Method[a]	M.p. °C	$[\alpha]_D$	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	Testosterone	$(CH_2)_4$	CH_3	A, B	188-186	+78	$C_{25}H_{38}O_3$	77.67	9.91	77.67	9.90
2	"	"	C_2H_5	A, B	152-154	+77	$C_{26}H_{40}O_3$	77.95	10.07	78.11	9.99
3	"	$(CH_2)_5$	CH_3	A, B	209-211	+78.5	$C_{26}H_{40}O_3$	77.95	10.07	77.87	9.87
4	"	"	C_2H_5	B	137-139	+80	$C_{27}H_{42}O_3$	78.21	10.21	77.94	10.03
5	"	$(CH_2)_6$	CH_3	A	183-186	+78	$C_{27}H_{42}O_3$	78.21	10.21	78.07	10.17
6	"	$C(CH_3)_2$	CH_3	A	159-161	+91.5	$C_{23}H_{36}O_3$	76.62	10.07	76.40	9.96
7	"	$C(CH_3)_2$	C_2H_5	A, B	134-137	+90	$C_{24}H_{38}O_3$	76.96	10.23	77.16	10.20
8	"	$C(CH_3)(C_2H_5)$	CH_3	A	142-145	+86	$C_{24}H_{38}O_3$	76.96	10.23	77.66	10.20
9	5α-Androstane-17β-ol-3-one	$(CH_2)_4$	CH_3	A, B	176-178	+21.5	$C_{25}H_{40}O_3$	77.27	10.38	77.28	10.29
10	"	"	C_2H_5	B	101-103	+25	$C_{26}H_{42}O_3$	77.56	10.52	77.45	10.47
11	"	$(CH_2)_5$	CH_3	A, B	177-178	+28.5	$C_{26}H_{42}O_3$	77.56	10.52	77.30	10.28
12	Androsta-1,4-diene-17β-ol-3-one	$(CH_2)_5$	CH_3	A	140-142	+39.6	$C_{26}H_{38}O_3$	78.35	9.61		9.69
13	Androsta-4,6-diene-17β-ol-3-one	"	CH_3	A	202-204	+29.5	$C_{26}H_{38}O_3$	78.35	9.61	78.07	9.66
14	4-Hydroxytestosterone	"	CH_3	B	162-164	+72	$C_{26}H_{40}O_4$	74.96	9.68	74.67	9.51
15	5α-Androst-1-ene-17β-ol-3-one	$(CH_2)_4$	CH_3	A	129-131	+42.5	$C_{25}H_{38}O_3$	77.67	9.91	77.82	9.78
16	"	$(CH_2)_5$	CH_3	A	139-141	+49	$C_{26}H_{40}O_3$	77.95	10.07	77.69	10.06
17	5α-Androstan-3β,17β-diol	"	CH_3	C	157-158	+13.5	$C_{26}H_{44}O_3$	77.17	10.96	77.18	10.93
18	" 3-acetate	"	CH_3	D	130-132	+8	$C_{28}H_{46}O_4$	75.29	10.38	75.16	10.27
19	5α-Androstan-3α,17β-diol	$(CH_2)_4$	CH_3	b	133-135	+11	$C_{25}H_{42}O_3$	76.87	10.84	76.93	10.85
20	" 3-acetate	"	CH_3	A, B	161-162	+15	$C_{27}H_{44}O_4$	74.95	10.25	75.15	10.21
21	" "	$(CH_2)_5$	CH_3	A	173-175	+21	$C_{28}H_{46}O_4$	75.29	10.38	75.25	10.45
22	" "	$C(CH_3)_2$	CH_3	A, B	162-164	+20	$C_{25}H_{42}O_4$	73.85	10.41	73.97	10.32
23	Androst-4-ene-3β,17β-diol	$(CH_2)_4$	CH_3	C	152-154	+36	$C_{25}H_{40}O_3$	77.27	10.38	77.23	10.48
24	"	"	C_2H_5	C	86-88	+32	$C_{26}H_{42}O_3 \cdot 1/2\ C_2H_6O$[c]	76.18	10.85	76.02	10.47
25	"	$(CH_2)_5$	CH_3	C	189-191	+42.5	$C_{26}H_{42}O_3$	77.56	10.52	77.53	10.46
26	"	$C(CH_3)_2$	C_2H_5	C	150-152	+48	$C_{24}H_{40}O_3$	76.55	10.71	76.67	10.87
27	" 3-acetate	$(CH_2)_4$	CH_3	D	93-95	0	$C_{27}H_{42}O_4$	75.31	9.83	75.39	10.73
28	" "	$(CH_2)_5$	CH_3	D	103-105	0	$C_{28}H_{44}O_4$	75.63	9.97	75.89	9.78
29	" "	$C(CH_3)_2$	C_2H_5	D	76-79	+8	$C_{26}H_{42}O_4$	74.60	10.11	74.38	10.29
30	" 3-propionate	$(CH_2)_4$	CH_3	D	103-105	-3	$C_{28}H_{44}O_4$	75.63	9.97	75.53	9.96
31	" "	$(CH_2)_5$	CH_3	D	106-107	0	$C_{29}H_{46}O_4$	75.94	10.11	76.05	9.82
32	5α-Androst-1-ene-3β,17β-diol	"	CH_3	C	133-135	+44	$C_{26}H_{42}O_3$	77.56	10.52	77.51	10.53
33	" 3-acetate	"	CH_3	D	127-129	+63	$C_{28}H_{44}O_4$	75.63	9.97	75.64	9.99
34	" 3-propionate	"	CH_3	D	84-86	+58.5	$C_{29}H_{46}O_4$	75.94	10.11	75.99	10.08
35	5α-Androstan-17β-ol	$(CH_2)_4$	CH_3	B	116-118	+10	$C_{25}H_{42}O_2$	80.15	11.30	80.29	11.30
36	5α-Androst-2-ene-17β-ol	$(CH_2)_5$	CH_3	A	158-161	+45	$C_{26}H_{42}O_2$	80.77	10.95	80.57	10.80
37	Estr-5(10)-ene-17β-ol-3-one	"	CH_3	B	154-155	+134	$C_{25}H_{38}O_3$	77.67	9.91	77.74	9.78
38	19-Nortestosterone	"	CH_3	B	155-156	+41	$C_{25}H_{36}O_3$	77.67	9.91	77.43	9.69

a For description of methods, see Experimental Section.
b Preparation described in the Experimental Section.
c Emiethanolate.

TABLE II

ANDROGENIC AND MYOGENIC ACTIVITY OF ALKYL STEROID-17β-YL MIXED ACETALS

Compound	Molecular weight	Seminal vesicles (control : 5.5 ± 0.3[a])			Ventral prostate (control : 9.9 ± 0.9)			Levator ani (control: 30.1 ± 1.2)			Anabolic index[c]
		1 μmole[b]	3 μmoles	9 μmoles	1 μmole	3 μmoles	9 μmoles	1 μmole	3 μmoles	9 μmoles	
MT	302	10.3±0.3	16.3±1.2	31.4±1.4	46.1±1.2	63.5±3.7	92.1±4.1	32.3±1.0	37.0±1.4	50.1±2.2	0.37
TTHP	373	6.8±1.0	10.1±0.6	16.2±0.9	40.0±3.6	49.1±3.7	69.3±3.3	24.1±1.0	30.5±1.8	41.6±2.4	0.25
1	387	14.9±0.9	29.7±1.2	39.9±1.7	49.8±5.0	85.7±7.2	103.0±8.1	41.5±1.6	51.3±2.5	62.4±5.4	0.47
2	401	12.7±0.3	19.7±1.2	36.3±1.3	52.5±2.1	67.8±3.5	98.3±4.6	33.9±0.9	45.7±3.1	67.0±1.7	0.43
3	401	13.8±1.7	31.5±1.9	24.6±1.8	49.0±2.7	84.7±6.6	82.9±8.3	31.1±1.1	44.5±1.8	49.6±3.2	0.33
4	415	11.8±0.6	31.6±0.8	38.3±2.3	49.2±3.9	73.4±4.9	94.9±5.1	34.4±2.2	54.5±2.3	65.2±3.4	0.49
5	415	9.1±0.7	16.8±0.8	30.6±2.0	48.4±3.7	63.4±4.7	99.7±6.5	32.2±3.0	44.8±1.6	56.3±2.3	0.39
6	361	12.1±0.7	16.1±0.5	28.0±2.1	31.6±2.9	67.6±5.7	87.4±6.0	36.5±1.5	46.3±1.6	57.3±4.4	0.44
7	375	10.9±0.4	16.8±0.8	31.0±1.9	44.5±2.8	65.8±4.1	85.8±4.4	31.8±1.4	40.6±1.9	61.4±1.9	0.41
8	375	9.3±0.4	17.2±0.9	31.6±2.4	42.6±4.0	65.2±4.3	88.0±7.2	30.6±1.7	47.1±1.4	58.9±2.8	0.43
9	389	13.5±0.5	33.1±3.4	49.3±3.8	54.7±2.4	94.5±7.7	114.1± 10	38.0±2.3	59.9±3.4	74.8±4.1	0.46
10	403	6.7±0.3	8.9±0.5	15.9±1.5	30.5±2.5	42.1±2.5	65.1±7.1	26.6±0.7	36.8±1.4	38.2±3.0	0.29
11	403	10.0±0.5	18.8±1.5	33.6±3.2	49.9±3.2	79.1±5.6	111.9±7.0	27.6±2.1	51.9±2.8	68.3±3.5	0.37
12	399	6.3±0.4	9.6±0.8	16.9±1.3	29.5±3.1	40.9±2.5	69.1±4.6	25.5±1.0	30.3±1.4	41.9±2.8	0.33
13	399	6.3±0.2	5.9±0.3	6.9±1.0	20.0±1.1	24.7±1.8	27.8±2.7	20.3±1.7	24.6±1.4	22.4±0.9	0.16
14	417	5.9±0.3	5.9±0.1	7.0±0.6	18.3±1.1	16.4±1.9	27.4±2.0	24.8±1.6	25.6±1.4	35.6±1.4	0.78
15	387	17.0±1.0	36.1±2.0	54.0±2.5	65.5±2.9	93.7±3.7	114.3±7.2	32.3±3.0	72.5±2.4	82.2±2.4	0.60
16	401	22.7±1.8	38.6±1.2	60.9±3.8	65.0±5.9	90.7±5.8	111.7±8.8	32.5±3.1	72.2±3.1	77.5±3.6	0.60
18	447	8.5±0.4	13.7±1.5	28.0±2.4	37.4±3.5	54.5±5.2	86.6±5.5	23.2±1.2	34.6±3.3	51.0±2.4	0.28
20	433	10.8±0.7	19.7±1.9	33.1±1.3	53.7±3.6	69.7±5.4	102.1±8.1	35.2±2.5	49.4±2.9	71.9±2.0	0.46
21	447	11.4±0.7	25.5±1.9	38.7±1.6	48.3±2.4	95.1±7.5	103.2±4.8	34.0±1.2	52.6±3.7	75.8±3.0	0.44
23	389	15.9±0.8	31.8±1.9	43.0±2.6	62.0±2.9	96.8±5.9	139.6±6.8	36.3±2.2	50.6±3.7	64.9±3.4	0.34
24	426	14.2±0.8	26.5±1.4	39.9±1.7	57.2±2.8	77.7±4.4	103.5±4.4	33.5±1.7	49.1±1.9	62.6±2.7	0.38
25	403	15.9±1.6	26.1±2.3	37.7±1.5	59.8±7.4	83.5±8.2	111.6±6.7	35.4±2.3	55.9±2.1	69.6±2.6	0.42
26	377	6.9±0.8	8.6±0.4	25.3±1.1	36.8±2.1	41.4±2.3	82.1±4.2	33.9±1.0	30.3±1.5	52.6±1.8	0.30
27	431	13.5±1.2	25.9±1.9	43.9±2.2	53.0±2.7	74.8±4.3	113.0±4.6	37.6±2.3	56.5±2.9	69.8±1.8	0.48
28	445	14.1±0.9	26.8±1.5	43.8±2.1	57.4±4.2	89.1±6.1	112.3±8.8	37.9±1.4	56.1±2.0	74.7±4.3	0.45
30	445	13.9±0.4	24.1±1.4	42.8±2.0	58.0±1.6	82.7±4.0	106.0±4.8	33.7±1.4	55.5±3.8	70.6±1.8	0.43
31	459	13.6±0.8	21.2±0.7	38.0±1.4	60.7±3.0	76.3±2.3	99.7±6.1	35.9±1.5	51.2±1.3	68.9±2.0	0.44
32	403	22.9±1.6	47.8±3.6	61.0±4.2	72.7±6.2	116.1±11	122.3±8.5	50.5±3.0	76.8±2.6	80.4±3.7	0.51
33	445	25.4±1.8	41.9±2.8	68.2±5.0	71.2±4.8	97.3±4.8	138.4±8.9	57.2±2.8	72.4±3.0	84.6±3.4	0.57
34	459	27.5±1.2	49.1±4.4	79.8±5.4	73.4±5.4	105.7±8.1	141.1± 11	57.1±1.8	69.1±2.0	84.1±3.7	0.52
35	375	6.0±0.3	7.8±0.3	10.9±0.6	21.5±1.6	31.2±2.5	41.3±3.2	23.7±1.5	29.4±1.8	37.3±2.3	0.43
36	387	7.3±0.2	10.8±0.3	23.8±1.4	27.1±1.4	36.6±1.8	60.4±3.3	27.5±1.2	37.5±1.3	61.1±1.9	0.63
37	387	15.2±1.3	19.3±1.2	22.2±0.9	23.2±1.3	35.0±2.8	47.5±2.4	30.5±1.5	37.3±1.8	57.7±1.3	0.83
38	387	7.7±0.3	13.9±1.1	27.2±1.9	30.6±2.3	55.5±5.2	73.9±5.4	30.1±1.3	52.5±2.3	69.7±3.5	0.66

[a] mg/100 g body weight (mean ± S.E.).

[b] Daily dose/ animal (oral route)

[c] Calculated as the ratio of the increase in levator ani weight (mg over the control) to the increase in ventral prostate weight. The average of the ratios calculated on each dose level is presented.

Underlined figures are at least 10% higher than those given by MT at the same dose.

BIOLOGICAL ACTIVITY AND DISCUSSION

The experiments have been performed according to Hershberger et al.[13] on castrate male albino rats, weighing about 50 g. Ten animals for each dose level were employed. The steroids, dissolved in 0.2 ml. of sesame oil, were orally administered daily for seven days, starting on the day following castration. The substances to be compared were administered in equimolar doses. On the 8th day autopsies were performed. Seminal vesicles, ventral prostate and levator ani were weighed on torsion balance. The organ weight are reported in mg/100 g. body weight. Owing to the great number of compounds to be tested, the experiments have been necessarily performed on different days. However the two groups of controls employed in each assay (i.e. untreated and MT-treated animals) were satisfactorily homogeneous.

The biological data of 34 acetals are presented in Table II along with those obtained by methyltestosterone (MT) and testosterone tetrahydropyranil ether (TTHP). Owing to the lack of parallelism among the dose-response curves, relative potencies have been not calculated. The figures of the average organ weight which resulted at least 10% higher than those given by MT at the same dose, have been underlined. The increase at each dose level in levator ani weight was divided by the corresponding increase in ventral prostate weight and the means of the ratios obtained at 3 dose-levels gave the "anabolic index" presented in Table II.

In the series of testosterone derivatives (compounds 1-8) all the new acetals prepared and tested by us are more active than TTHP[14]. Among those compounds, the acetals of cyclopentanone and cyclohexanone (1-4) are the most active, being at several dose-levels more active than MT itself.

Among the androstanolone derivatives (9-11), methoxycyclopentyl ether (9) is about 3 times more active than MT. A still more evident enhancement of activity, among other 3-keto derivatives (12-16), is displayed by the derivatives of 5α-androst-1-ene-17β-ol-3-one (15-16) which present also a remarkably high anabolic index. If, in the above compounds, the 3-keto group is replaced by a hydroxyl group,

either α or β oriented, either free or esterified (18-34), a further increase of activity can be observed in many cases. Especially active are the derivatives of 5α-androst-1-ene-3β,17β-diol (32-34).

3-Deoxocompounds (35-36) and 19-norderivatives (37-38) are less active than the aforementioned acetals, but display a favourable anabolic index. This is specially marked for the nortestosterone derivative (37).

From the data of the present experiments it results that the preparation of mixed acetals from 17β-hydroxyandrostanes allows to obtain compounds many of which are endowed with a very remarkable oral androgenic and/or anabolic activity. The reversibility of the acetal linkage in vivo, and the metabolization of these compounds through physiological pathways have been widely proved [15] and justify the assumption that the class of compounds here described is devoid of liver toxicity as it has been earlier demonstrated for other labile 17-ethers, i.e. steroid-17-yl enol ethers [16].

EXPERIMENTAL SECTION [17]

The following examples are given to illustrate the methods used to prepare the compounds listed in Table I.

METHOD A. - A suspension of testosterone (20 g.) in t.-butyl alcohol (200 ml.) was treated with pyridine p.toluenesulphonate (200 mg.) and cyclohexanone methyl enolether (15 ml.) and stirred while heating with an external bath at 40-45°. As soon as testosterone was completely dissolved (about 3 min.) a solid began to separate giving a heavy bulk of crystalline material. The mixture was kept at room temperature for 2 hours, then a few drops of pyridine was added. The product, taken up in methanol, filtered and recrystallized from methylene chloride-methanol, yielded 3 (23 g.), m.p. 208-211°. Recrystallization gave the analytical sample (see Table I), m.p. 209-211°; $[\alpha]_D$ +78.5°; λ_{max} 241 mμ (ε 15,700); ν_{max}^{Nujol} 1671, 1617, 1184, 1160, 1094 and 1040 cm^{-1}. CH_3O : calcd., 7.75; found, 7.89.

Hydrolysis. - A suspension of 3 (1 g.) in methanol (15 ml.) was treated with 2N oxalic acid solution (0.5 ml.) and heated on the water bath for 5 min. After concentration under reduced pressure, water was added and the solid collected by filtration, washed and dried to give 0.710 g. of testosterone, m.p. 154-156°.

METHOD B. - a) A solution of testosterone (10 g.) in methylene chloride (300 ml.) containing pyridine p.toluenesulphonate (20 mg.) was treated with cyclohexanone dimethyl acetal, then distilled for about 40 min. After addition of a few drops of pyridine, the solvent was completely evaporated. The residue was taken up in methanol, filtered and recrystallized yielding 3 (8.5 g.), m.p.204-207°.

b) Testosterone (20 g.) was allowed to react with cyclopentanone diethyl acetal (12 ml.) as in the preceding example. The reaction mixture was then made alkaline by addition of a 5% ethanol solution of potassium hydroxyde and worked up as usually. Recrystallization of the product from ethanol yielded 2 (7 g.), m.p. 151-153°. The analytical sample (see Table I) showed m.p. 152-154°; $[\alpha]_D$ +77°; λ_{max} 241-242 mμ (ε 16,250); ν_{max}^{Nujol} 1668, 1612, 1193, 1116 and 1046 cm^{-1}. C_2H_5O: calcd., 11.2; found, 11.42.

c) At the end of a quite identical reaction a few drops of pyridine was added, instead of potassium hydroxyde, and the solvent was completely evaporated under reduced pressure. The oily residue was then flushed several times with methanol until crystallization occurred. The crystals were collected by filtration and recrystallized from methylene chloride-methanol to give a product (6.5 g.), m.p. 175-180°. A further recrystallization gave testosterone 17-(1'methoxy)-cyclopentyl ether (1), m.p. 182-184°; $[\alpha]_D$ +78°; λ_{max} 241 mμ (ε 16,200); ν_{max}^{Nujol} 1668, 1616, 1192, 1153, 1115 and 1048 cm^{-1}; identical with that prepared by reaction with cyclopentanone methyl enolether (see Table I).

METHOD C. - To a solution of 11 (10 g.) in methanol (100 ml.) and tetrahydrofurane (100 ml.) $NaBH_4$ (1.5 g.) in water (10 ml.) was added. The mixture was heated on a boiling water bath (3-4 hours) then kept at room temperature overnight. After removal of the solvent under reduced pressure, water was added and the solid collected by filtration. Crystallization from ether-methanol yielded 17 (8.1 g.), m.p. 156-158°. The analytical sample (see Table I) showed m.p. 157-158°; $[\alpha]_D$ +13.5°; ν_{max}^{Nujol} 3300, 1189, 1158, 1096 and 1047 cm^{-1}.

By reduction of 16 (14 g.) with $LiAlH_4$ [18] (7 g.) in ether (400 ml.) the Δ^1-derivative 32 (10.7 g.) was obtained, m.p. 131-134°. The analytical sample (see Table I) showed m.p. 133-135°; $[\alpha]_D$ +44°; ν_{max}^{Nujol} 3280, 1186, 1157, 1095 and 1044 cm^{-1}.

METHOD D. - To a solution of a 3β-hydroxy derivative (1 g.) in pyridine (10 ml.) acetic or propionic anhydride (5 ml.) was added. The mixture was kept at room temperature overnight then poured into ice-water. The products were isolated and recrystallized as usually.

5α-Androstan-3α,17β-diol 17-(1'-methoxy)-cyclopentyl ether (19). - To a suspension of the acetate 20 (1 g.) in methanol (75 ml.) a 10% K_2CO_3 solution (7 ml.) was added. The mixture was heated to refluxing for 3 hours after the complete solution of the starting product, then concentrated under reduced pressure. The residue, taken up in water, filtered and recrystallized from methanol yielded crude 19 (0.870 g.), m.p. 126-130°. The analytical sample (see Table I) showed m.p. 133-135°; $[\alpha]_D$ +11°; ν_{max}^{Nujol} 3340, 1200, 1153, 1120, 1045 and 1030 cm^{-1}.

REAGENTS. - All alkyl ketals required for the preparation of the compounds in Table I were obtained from the corresponding ketones by reaction with orthoformic esters [19] with the exception of 2,2-dimethoxy and 2,2-diethoxypropanes which were obtained by way of isopropenyl acetate [20]. From the ketals the corresponding enol ethers were prepared following the procedure of H.P.Crocker and R.H. Hall [21] (aliphatic) or by pyrolysis in the presence p.toluenesulphonic acid [22] (cycloaliphatic).

The cyclopentanone dimethyl acetal (b.p. 139-141°/745 mm., ν_{max} 1193, 1142, 1116 and 1053 cm^{-1}) and methyl enolether (b.p. 120-125°/745 mm., ν_{max} 1654 cm^{-1}) and the cycloheptanone methyl enolether (b.p. 158-163°/735 mm., ν_{max} 1668 cm^{-1}), undescribed until now, where employed without further characterization.

REFERENCES

1. For a literature review on the matter see Falconi, G., HORMONAL STEROIDS, Biochemistry, Pharmacology and Therapeutics, Vol.2, Editors L. Martini and A. Pecile, Academic Press, New York, 1965, p.143.
2. Ercoli, A., Gardi, R., and Bruni, G., RESEARCH PROGRESS IN ORGANIC-BIOLOGICAL AND MEDICINAL CHEMISTRY, Editors U. Gallo and L. Santamaria, North-Holland Publishing Company, Amsterdam, 1964, p.155.
3. Ercoli, A., Gardi, R., and Vitali, R., CHEM. IND. (London) 1284 (1962).
4. Ott, A.C., Murray, M.F., and Pederson, R.L., J. AM.CHEM. SOC. 74, 1239 (1952).
5. Cross, A.D., Harrison, I.T., Crabbé, P., Kincl, F.A., and Dorfman, R.I., STEROIDS 4, 229 (1964).
6. Cross, A.D., Harrison, I.T., Kincl, F.A., Forkes, E., Kray, R., and Dorfman, R.I., STEROIDS 4, 423 (1964).
7. Cross, A.D., Denot, E., Carpio, H., Acevedo, R., and Crabbé, P., STEROIDS 5, 557 (1965).

8. Cross, A.D., and Harrison, I.T., STEROIDS 6, 397 (1965).

9. Kereszty and Wolf, Hung.Patent 131, 346 (March 1, 1943); CHEM. ABS. 43, 3980 (1949). See also Gerecs, A., and Kollonitsch., J., ACTA CHIM. ACAD. SCI. HUNG. 1, 281 (1951); CHEM. ABS. 49, 2470 (1955).

10. Gardi, R., Vitali, R., and Ercoli, A., GAZZ. CHIM. ITAL. 92, 632 (1962).

11. Gardi, R., Vitali, R., and Ercoli, A., GAZZ. CHIM. ITAL. 93, 1642 (1963).

12. For this reason the ethyl acetals reported in the preliminar communication [3], were later found to be largely compounded of the corresponding methyl acetals.

13. Hershberger, L.G., Shipley, E.G., and Meyer, R.K., PROC. SOC. EXP. BIOL. & MED. 83, 175 (1953).

14. For a preliminary communication of some of these results see ref. 1.

15. Ercoli, A., ANDROGENS IN NORMAL AND PATHOLOGICAL CONDITIONS, Editor A. Vermeulen, Excerpta Medica, International Congress Series No. 101, 1965, p.213, and unpublished results.

16. See, among others, Pyörälä, K., Kekki, M., and Eisalo, A., ANN. MED. INT. FENN. 53, 61 (1964); Finardi, G., and Pedini, G., RASS. FISIO. CLIN. TERAP. 37, 165 (1965).

17. Melting points are corrected. Optical rotations were taken in 0.5% dioxane solution at 24± 1. UV spectra were determined in 95% ethanol with an Optical CF_4 spectrophotometer. IR spectra were measured on the Perkin-Elmer 21 instrument. The Authors are indebted to Dr. Sergio Cairoli for the mycroanalyses and to Dr. Cesare Pedrali for the IR spectra.

18. Reduction of 16 with $NaBH_4$ gave a mixture of 32 and 17.

19. Cf. Claisen, L., BER. 31, 1010 (1898).

20. Croxall, W.J., Glavis, F.J., and Neher, H.T., J.AM.CHEM. SOC. 70, 2805 (1948).

21. J. CHEM. SOC., 2052 (1955). Cf. Claisen, L., BER. 31, 1019 (1898).

22. Cf. MacKenzie, C.A., and Stocker, J.H., J. ORG. CHEM. 20, 1695 (1955).