NEW CLASSES OF ORALLY ACTIVE HORMONAL DERIVATIVES. II. 17-CYCLOALK-1'-ENYL ETHERS OF 17β-HYDROXY-ANDROSTANES AND 19-NORANDROSTANES

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ABSTRACT

Twenty-eight 17β-cycloalk-1'-enyloxy androstanes and 19-nor-androstanes were prepared and assayed for their oral androgenic and myogenic activity in rats.

Several of these compounds, which easily regenerate the parent 17β-hydroxysteroid in vitro and in vivo, displayed higher activity and/or myogenic/androgenic ratio than methyltestosterone.

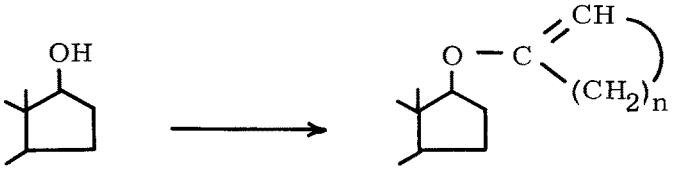
Alkylation in 17α-position has been known for many years as the only effective means to endow 17β-hydroxysteroids, in androstane and 19-norandrostane series, with oral effectiveness.

Research started in our laboratories some years ago (1) showed that labile ether groups at 17β-oxygen may be valuable substitutes for 17α-alkyl groups in promoting oral activity of 17β-hydroxy-steroids by delaying their metabolic inactivation. These results were confirmed by research carried out in other laboratories (2).

In the first paper of this series (3) we presented the alkyl androstan-17β-yl mixed acetals. Here, we wish to report in extenso the data concerning cycloalk-1'-enyl ethers of 17β-hydroxy-androstanes and 19-norandrostanes.

CHEMISTRY

Preparation of cycloalkenyl ethers from hydroxysteroids by reaction with lower alkyl ketals of cyclanones had been already reported (4,5). We prepared steroid-17β-yl enol ethers (II) from 17β-hydroxyandrostanes (I) by various modifications of the same basic procedure.



I II n = 2, 3

The reaction was carried out without diluent and catalyst (Method A), with acid catalyst in dimethylformamide (Method B), or in benzene (Method C). Method A worked satisfactorily only for the preparation of cyclopentenyl ethers. Method B gave satisfactory results also with cyclohexanone derivatives but it could not be used on 3-ketosteroids, except cross-conjugated $\Delta^{1,4}$-3-ketones, since it induced partial enolization. This occurred to a lower extent with Method C, which could be used also on Δ^{1}-3-ketones.

The survival of cycloalkenyl group to metal hydride reduction and acylation allowed to convert compounds prepared according to the above methods into related cycloalkenyl ethers (Method D and E, respectively).

A specific procedure was developed for compound 18, which was obtained by alkaline isomerization of the $\Delta^{5(10)}$-analogue 19 in higher yield than by Method A.

The structure of the new steroidyl enol ethers has been further confirmed on 17β-(cyclopent-1'-enyloxy)-5α-androstan-3-one (1) by hydrogenation to 17β-cyclopentyloxy-5α-androstan-3-one (29),

identical with the compound obtained from 17β-hydroxy-5α-androstan-3-one by direct O-alkylation with cyclopentyl bromide.

The physical constants and the analytical data of the cycloalkenyl ethers prepared are reported in Table I.

BIOLOGY

The experiments have been performed according to Hershberger et al. (6) on castrate albino rats. The steroids, dissolved in sesame oil were orally administered daily at three dose levels, 2,4,8 micromoles, for seven days.

The androgenic activity has been assessed on seminal vesicles and ventral prostate and the myogenic activity on levator ani. The results are presented in Table II as relative potencies versus methyltestosterone (17β-hydroxy-17-methyl-4-androsten-3-one; MT).

Some tested compounds exhibited activity on the androgenic targets of the same order as or higher than MT. Many compounds exhibited higher activity than MT on levator ani.

The highest androgenic activity was displayed by compounds 2 and 20 deriving from 17β-hydroxy-5α-androst-1-en-3-one and by compounds 25,26,27, deriving from 5α-androst-1-ene-3β,17β-diol.

The highest myogenic activity was displayed by compounds 2,12, 13,18,20,25,26, and 27. 19-Norderivative 18, compound 20, and 17β-cyclopentenyloxy-1,4-androstadien-3-one (4, Quinbolone) displayed particularly high myogenic/androgenic ratios.

Quinbolone has been clinically investigated for its anabolic activity (7). The metabolism of this compound (8) and its effect on liver function in man (9) have been also extensively studied. The results of these studies confirmed the complete reversibility in vivo of the ether linkage and the absence of hepatotoxic effects.

Table I

CYCLOALKENYL ETHERS OF 17β-HYDROXYSTEROIDS

No.	Parent 17β-hydroxysteroid	R	Method*	M.p. °C	$[\alpha]_D$	Formula	Calcd. % C	Calcd. % H	Found % C	Found % H
1	17β-Hydroxy-5α-androstan-3-one		A	100-102	+ 51	$C_{24}H_{36}O_2$	80.85	10.18	80.69	10.22
2	17β-Hydroxy-5α-androst-1-en-3-one	"	A,C	116-119	+ 75.5	$C_{24}H_{34}O_2$	81.31	9.67	81.46	9.72
3	Testosterone	"	A	128-130	+100	$C_{24}H_{34}O_2$	81.31	9.67	81.35	9.64
4	17β-Hydroxy-1,4-androstadien-3-one	"	A,C	134-136	+ 53.5	$C_{24}H_{32}O_2$	81.77	9.15	81.76	9.19
5	17β-Hydroxy-4,6-androstadien-3-one	"	C	142-144	+ 23	$C_{24}H_{32}O_2$	81.77	9.15	81.87	9.32
6	17β-Hydroxy-2α-methyl-4-androsten-3-one	"	C	154-155	+106	$C_{25}H_{36}O_2$	81.47	9.85	81.67	9.84
7	4,17β-Dihydroxy-4-androsten-3-one	"	C	160-162	+ 87	$C_{24}H_{34}O_3$	77.80	9.25	77.65	9.26
8	5α-Androstane-3α,17β-diol	"	**	145-147	+ 30	$C_{24}H_{38}O_2$	80.39	10.68	80.09	10.63
9	" 3-acetate	"	C	134-136	+ 32	$C_{26}H_{40}O_3$	77.95	10.07	77.65	9.98
10	" 3-propionate	"	B,C	91-92	+ 35	$C_{27}H_{42}O_3$	78.21	10.21	78.11	10.08
11	3α-Isopropyloxy-5α-androstan-17β-ol	"	C	54-56	+ 24.5	$C_{27}H_{44}O_2$	80.94	11.07	80.66	10.99
12	5α-Androst-1-ene-3β,17β-diol	"	D	134-137	+ 66	$C_{24}H_{36}O_2$	80.85	10.18	80.67	10.13
13	" 3-acetate	"	E	106-108	+ 85.5	$C_{26}H_{38}O_3$	78.35	9.61	78.57	9.77
14	4-Androstene-3β,17β-diol	"	D	153-155	+ 54.4	$C_{24}H_{36}O_2 \cdot 1/2CH_4O$ §	78.98	10.28	78.98	10.27
15	" 3-propionate	"	E	120-123	+ 12	$C_{27}H_{40}O_3$	78.59	9.77	78.60	9.84
16	5-Androstene-3β,17β-diol 3-propionate	"	B	77-79	- 34.5	$C_{27}H_{40}O_3$	78.59	9.77	78.25	9.49
17	3β-Isopropyloxy-5-androsten-17β-ol	"	C	139-140	- 30	$C_{27}H_{42}O_2$	81.35	10.62	81.40	10.81
18	17β-Hydroxy-4-estren-3-one	"	**	108-110	+ 50	$C_{23}H_{32}O_2 \cdot 1/2CH_4O$ §	79.17	9.61	79.17	9.37
19	17β-Hydroxy-5(10)-estren-3-one	"	A	152-154	+163	$C_{23}H_{32}O_2$	81.13	9.47	81.28	9.51
20	17β-Hydroxy-5α-androst-1-en-3-one		C	137-139	+ 81.5	$C_{25}H_{36}O_2$	81.47	9.85	81.22	9.84
21	17β-Hydroxy-1,4-androstadien-3-one	"	B	128-130	+ 55	$C_{25}H_{34}O_2$	81.92	9.35	81.76	9.37
22	5α-Androstane-3α,17β-diol 3-acetate	"	C	137-139	+ 40	$C_{27}H_{42}O_3$	78.21	10.21	78.44	10.34
23	" 3-propionate	"	B	138-139	+ 37	$C_{28}H_{44}O_3$	78.45	10.35	78.69	10.34
24	5α-Androstane-3β,17β-diol 3-acetate	"	B	102-105	+ 24	$C_{27}H_{42}O_3$	78.21	10.21	78.49	10.41
25	5α-Androst-1-ene-3β,17β-diol 3-acetate	"	E	108-110	+ 93	$C_{27}H_{40}O_3$	78.59	9.77	78.26	9.68
26	" 3-trimethylacetate	"	E	145-147	+ 86.2	$C_{30}H_{46}O_3$	79.24	10.20	79.17	10.26
27	" 3-benzoate	"	E	132-135	+115	$C_{32}H_{42}O_3$	80.97	8.92	80.60	9.13
28	5-Androstene-3β,17β-diol 3-acetate	"	B	142-144	- 26.5	$C_{27}H_{40}O_3$	78.59	9.77	78.68	9.60

* For description of methods, see Experimental Section

** Preparation described in the Experimental Section

§ Hemimethanolate

Table II

ANDROGENIC AND MYOGENIC ACTIVITY OF CYCLOALKENYL ETHERS OF 17β-HYDROXYSTEROIDS

Compound	Relative Potencies (MT = 100)		
	Seminal vesicles	Ventral prostate	Levator ani
1	75 (66-85)*	59 (48-73)	75 (64-89)
2	208 (189-229)	134 (110-162)	333 (281-394)
3	87 (77-99)	62 (48-79)	106 (94-119)
4	24 (20-29)	8 (7-13)	50 (43-59)
5	6 (4-9)	4 (2-6)	5 (3-8)
6	18 (14-22)	8 (5-13)	23 (18-29)
7	7 (5-10)	4 (2-8)	46 (36-59)
8	37 (30-47)	24 (14-40)	50 (40-63)
9	22 (17-28)	19 (14-27)	33 (25-45)
10	27 (22-34)	28 (16-47)	44 (34-56)
11	73 (63-86)	68 (48-95)	112 (110-114)
12	139 (121-157)	75 (61-92)	234 (181-303)
13	130 (110-153)	81 (58-111)	208 (156-279)
14	119 (105-135)	95 (76-118)	109 (89-133)
15	78 (64-94)	66 (49-88)	67 (56-81)
16	16 (13-20)	7 (4-11)	15 (9-24)
18	32 (26-40)	15 (9-28)	188 (156-228)
19	61 (52-71)	5 (3-9)	105 (87-128)
20	269 (215-336)	178 (134-238)	954 (488-1865)
21	25 (20-31)	16 (11-24)	109 (92-129)
22	49 (41-58)	36 (26-50)	56 (46-68)
23	32 (26-40)	29 (19-45)	46 (36-59)
24	20 (16-25)	9 (6-14)	18 (13-26)
25	246 (207-292)	187 (139-252)	495 (373-656)
26	250 (184-340)	131 (88-195)	604 (376-970)
27	263 (217-320)	179 (145-221)	503 (365-692)
28	20 (16-26)	12 (7-21)	17 (10-30)

*0.95 confidence limits

EXPERIMENTAL SECTION (10)

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

Method A. - A mixture of 17β-hydroxy-1,4-androstadien-3-one (10 g) and cyclopentanone diethyl ketal (15 ml) was heated with an external oil bath at 140-150° for 30 minutes, then at 180-190° for about 45 minutes. In the meantime the alcohol developed in the reaction was allowed to distil off. After addition of a few drops of pyridine, the excess reagent was completely removed under vacuum, the residue was taken up with methanol, allowed to crystallize, and filtered. Recrystallization from methanol gave 17β-(cyclopent-1'-enyloxy)-1,4-androstadien-3-one, 4 (7.92 g), m.p.130-133°. A further recrystallization gave the analytical sample (see Table I), m.p.134-136°; $[\alpha]_D$ +53.5°; λ_{max} 244 mμ, $E^{1\%}_{1cm}$ = 452; ν^{Nujol}_{max} 1670, 1651, 1630, 1607, 1242, 1177, 1018, 883 and 766 cm^{-1}.

Hydrolysis. - A solution of 4 (0.5 g) in methanol (10 ml) was treated with 1N hydrochloric acid 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 17β-hydroxy-1,4-androstadien-3-one (0.39 g), m.p. 170-172°.

Method B. - A mixture of 5-androstene-3β,17β-diol 3-acetate (3 g), cyclohexanone diethyl ketal (6 ml), and N-dimethylformamide (6 ml), was treated with p.toluenesulphonic acid (15 mg) and heated with an external oil bath as above described for Method A. Isolation of the product with the usual procedure and recrystallization from methylene chloride-methanol gave 17β-(cyclohex-1'-enyloxy)-5-androsten-3β-ol acetate, 28 (2.96 g), m.p.142-144°; $[\alpha]_D$ -26.5°; ν^{Nujol}_{max} 1736, 1672, 1240, 1187, 1026 and 777 cm^{-1}.

Method C. - To a solution of 17β-hydroxy-4,6-androstadien-3-one (1.6 g) in anhydrous benzene (800 ml) containing p.toluenesulphonic acid (20 mg), cyclopentanone diethyl ketal (5 ml) was added, and the mixture was heated with rapid distillation of the solvent for about 40 minutes. After addition of a few drops of pyridine, the solvent was completely removed under reduced pressure. The residue was taken up with methanol, filtered and recrystallized from methanol to give 5 (1.55 g), m.p.139-141°. A further recrystallization gave the analytical sample (see Table I), m.p.142-144°; $[\alpha]_D$ +23°; λ_{max} 283 mμ, $E^{1\%}_{1cm}$ = 680; ν^{Nujol}_{max} 1658, 1640, 1609, 1576, 1242, 1020, 873 and 784 cm^{-1}.

Benzene was substituted by toluene in some instances (e.g. for compound 22) with comparable results.

Method D. - To a suspension of $LiAlH_4$ (1.5 g) in anhydrous ether (50 ml) a solution of 2 (3 g) in ether (50 ml) was added. The mixture was refluxed under stirring for 5 hours. After decomposition of the excess hydride with acetone, saturated Na_2SO_4 solution was added, and the organic layer was separated and washed with water. After removal of the solvent under reduced pressure, water was added and the solid collected by filtration. Crystallization from methanol yielded 12 (2.5 g), m.p. 134-137°; $[\alpha]_D$ +66°; ν_{max}^{Nujol} 3260, 1644, 1247, 1030, 765 and 752 cm^{-1}.

Method E. - The relevant 3β-hydroxyderivatives (see Table I) were acylated in pyridine at room temperature by treatment with the proper acid chloride or anhydride. The products were isolated and recrystallized as usually.

17β-(Cyclopent-1'-enyloxy)-5α-androstan-3α-ol (8). - To a suspension of the propionate 10 (1.5 g) in methanol (75 ml) a 10% K_2CO_3 solution (10 ml) was added. The mixture was heated to refluxing for 4 hours after the complete solution of the starting product, then concentrated under reduced pressure. The residue, taken up in water and filtered, yielded a product (1.4 g), m.p. 143-147°. Cristallization from methanol gave pure 8 (0.92 g), m.p. 145-147°; $[\alpha]_D$ +30°; ν_{max}^{Nujol} 3400, 1648, 1251, 1035, 1007 and 764 cm^{-1}.

17β-(Cyclopent-1'-enyloxy)-4-estren-3-one (18). - A suspension of 19 (1.5 g) in methanol (50 ml) and ether (5 ml) was treated under nitrogen with a 8% KOH methanolic solution (2.5 ml) and kept under vigorous stirring until complete solution (about 10'). After concentration under reduced pressure, water was added and the solid collected by filtration. Crystallization from methanol yielded 18 (1.3 g), m.p. 102-105°. The analytical sample (see Table I) showed m.p. 108-110°; $[\alpha]_D$ +50°, λ_{max} 240-241 mμ, $E_{1cm}^{1\%}$ = 477; ν_{max}^{Nujol} 3460, 1675, 1649, 1620, 1256, 1049, 1022 and 762 cm^{-1}.

17β-Cyclopentyloxy-5α-androstan-3-one (29). - a) To a solution of 17β-hydroxy-5α-androstan-3-one (4 g) in toluene anhydrous (350 ml), cyclopentyl bromide (16 ml) and Ag_2CO_3 (16 g) were added. The mixture was refluxed under stirring for 20 hours, then filtered and submitted to steam distillation until complete removal of toluene and excess cyclopentyl bromide. Ether extraction followed by recrystallization from methanol gave the cyclopentyl ether 29 (3.14 g), m.p. 130-132°. A further recrystallization gave the analytical sample, m.p. 133-134°, $[\alpha]_D$ +34°; ν_{max}^{Nujol} 1719, 1110 and 1084 cm^{-1}.

Anal. Calcd. for $C_{24}H_{38}O_2$: C 80.39 ; H 10.68 ;
Found : 80.16 ; 10.67 .

b) A solution of the cyclopentenyl ether 1 (1 g) in tetrahydrofuran (5 ml) and methanol (45 ml) was catalytically hydrogenated on 10% Pd/C (0.4 g). After filtration of the catalyst, and removal of the solvents under reduced pressure, the residue was crystallized from methanol to afford 29 (0.5 g), m.p. 130-132°, identical with the product obtained according to a).

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10. Melting points are uncorrected. 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. Absorption bands of spectra (UV, IR) were as expected for all of the compounds listed in Table I.