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LONG-ACTING CONTRACEPTIVE AGENTS: TESTOSTERONE ESTERS OF CYCLOALKYLCARBOXYLIC ACIDS

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ABSTRACT

The synthesis of twenty five esters of testosterone (17β-hydroxy-androst-4-en-3-one) is described. All esters are derivatives of cycloalkycarboxylic acids. Some of the esters possess α-,β-and/or δ-substitution in the ester side-chain. The work was undertaken in order to evaluate long-acting male antifertility effect of such esters. Most of the compounds, especially compound No. 1, were found to be active. Compound No. 1 is presently under clinical studies.

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INTRODUCTION

There has been a great demand for long-acting, injectable steroid contraceptives. As a part of the World Health Organization's program for the synthesis of long-acting injectable contraceptives,[2] several cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl esters of testosterone were synthesized as candidates for male contraceptive agents.

CHEMICAL SYNTHESIS

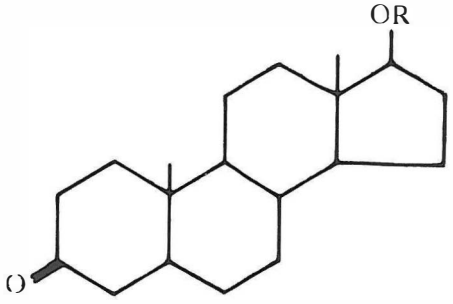
The synthesis of *trans*-cyclopropane-1,2-dicarboxylic acid was accomplished according to the literature.[3] The acid dichloride was prepared following the latter literature using dimethyl formamide (DMF) in catalytic amounts. The acid monochloride was obtained after treatment of the diacid in dry tetrahydrofuran with one mole of thionylchloride and a catalytic amount of DMF.[4] The synthesis of other acids were either previously reported[5] or are commercially available.

EXPERIMENTAL

Melting points were taken on a Kofler hot-stage microscope and are uncorrected. ^{1}H NMR spectra were obtained using Varian T-60, Bruker HFX-90 and WP-80 instruments: chemical shifts are reported as ppm (δ) relative to TMS. UV spectra were taken on Varian Techtron 635 and Jobin Yvon Duospac spectrometers. Infrared spectra were measured on Perkin Elmer 267 and Shimadzu IR-400 instruments. Mass spectra were recorded with a Varian MAT Ch-5 (70eV).

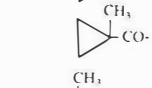
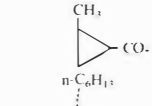
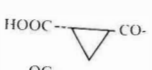
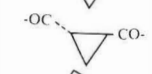
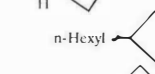
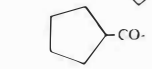
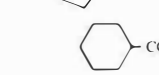
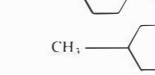
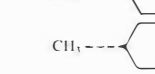
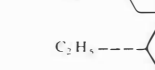
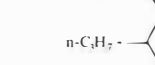
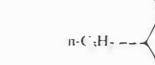
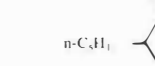
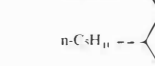
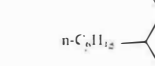
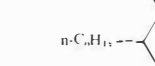
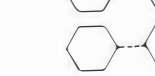
Esterification of Testosterone

To a stirring solution of testosterone (2.88g, 0.01 mol) in pyridine (30 ml)
chloride (0.1 mol) was added. After the addition was complete, the stirring was continued at room temperature for 24 hours. The mixture was added to hydroch-



R=See Table 1

Table I. Physical Constants of Testosterone Esters

No.	R*	m.p.° C**	$[\alpha]_D$ ($CHCl_3$)	λ_{max} (log ε) ***	IR (cm^{-1})	NMR, δ ($CDCl_3$)
1		157-159	+ 84	244 (3.85)	1725, 1660, 1615	5.66 (s, 1H, HC = C), 4.66 (bt,1H,HC-O), 1.18 (s, 3H, CH_3), 0.83 (s,3H,CH)
2		133-135	+ 94	240 (3.91)	1715, 1670	5.63 (s, 1H, HC = C), 4.53 (bt,1H,HC-O), 1.23 (s,3H, CH), 1.17 (s,3H,CH_3), 0.77 (s,3H,CH)
3		98-100	+ 101	239 (3.85)	1720, 1670	5.63 (s, 1H, HC = C), 4.58 (m,1H,HC-O), 1.13 (s, 3H, CH), 1.10 (s,3H,CH_3), 0.80 (s,3H,CH)
4		oil			1730, 1680 1620	5.72 (s,1H,HC = C), 4.58 (t,1H,HC-O), 1.30 (s, 3H,
5		154-156		228 (4.34)	1710, 1660 1610	7.16 (m, 5H, arom), 5.74 (s,1H,HC = C), 4.65 (t, 1H, HC-O), 1.22 (s,3H,CH), 0.90 (s,3H,CH)
6		224-226		236 (4.17)	1700, 1650 1610	5.75 (s, 1H, HC = C), 4.66 (t,1H,HC-O) 1.21 (s, 3H, CH_3), 0.87 (s,3H,CH_3)
7		263-266		236 (4.55)	1700, 1650, 1600	5.72 (s, 2H, HC = C), 4.65 (t,2H,HC-O), 1.23 (s, 6H, Ch), 0.90 (s,6H,CH)
8		114-116	+ 95	240 (4.24)	1715, 1655	5.80 (s, 1H, HC = C), 4.73 (t,1H 1.17 (s, 3H, CH), 0.83 (s,3H
9		116-118	+ 92	241 (4.21)	1720, 1670	5.77 (s, 1H,HC = C), 4.67 (t,1H,HC-O), 1.20 (s, 3H, CH), 0.83 (s,3H,CH)
10		94-96	+ 98	240 (4.25)	1730, 1680	5.76 (s, 1H HC = C), 4.66 (t,1H,HC-O), 1.20 (s, 3H, CH), 0.83
11		oil	+ 80	239 (4.22)	1730, 1678	5.62 (s, 1H, HC = C), 4.60 (t,1H,HC-O), 1.20 (s, 3H, CH_3), 0.80 (s,3H,CH_3)
12		97-98	+ 114	240 (4.14)	1725, 1670	5.63 (s, 1H, HC = C), 4.58 (t,1H,HC-O), 1.18 (s, 3H, Ch_3), 0.80 (s,3
13		130-132	+ 90	246 (3.98)	1730, 1670, 1615	5.70 (s, 1H, HC = C), 4.63 1.19 (s, 3H, CH), 0.80 (s,3H,CH_3)
14		114-116	+ 89	240 (4.25)	1730, 1675,	5.75 (s, 1H, HC = C), 4.67 (t,1H,HC-O), 1.20 (s, 3H, CH_3), 0.85 (s,3H,CH_3)
15		166-167	+ 117	242 (4.22)	1730, 1670	5.80 (s, 1H, HC = C), 4.66 (t,1H,HC-O), 1.20 (s, 3H, CH_3), 0.83 (s,3H,CH_3)
16		139-141	+ 102	240 (4.17)	1730, 1675	5.76 (s, 1H, HC = C), 4.66 (t,1H,HC-O), 1.17 (s, 3H, CH), 0.82 (s,3H,CH_3)
17		74-76	+ 87	240 (4.41)	1730, 1680, 1620	5.76 (s, 1H, HC = C), 4.66 (t,1H,HC-O), 1.20 (s, 3H,CH_3), 0.83 (s,3H
18		140-142	+ 93	241 (4.19)	1725, 1675	5.80 (s, 1H, HC = C), 4.66 (t,1H,HC-O) 1.20 (s, 3H, CH_3), 0.83
19	n-C_4H_9	131-133	+ 88	241 (4.22)	1725, 1685	5.73 (s,1H, HC = C), 4.60 (t,1H,HC-O), 1.18 (s, 3H, CH), 0.82 (s,3H,CH_3)
20		53-55	+ 81	240 (4.24)	1730, 1670	5.76 (s, 1H, HC = C), 4.66 (t,1H,HC-O), 1.20 (s, 3H, CH_3), 0.85 (s,3H,CH_3)
21		125-127	+ 89	240 (4.20)	1720, 1680	5.76 (s, 1H, HC= C), 4.66 (t,1H,HC-O), 1.20 (s, 3H,CH_3).
22		84-87	+ 98	242 (4.16)	1730, 1665	5.76 (s, 1H, HC = C), 4.66 (t,1H,HC-O), 1.20 (s, 3H, CH_3), 0.85 (s,3H,CH_3)
23		95-98	+ 65	242 (4.12)	1728,1689	5.85 (s, 1H, HC = C), 4.40 (t,1H,HC-O), 1.20 (s, 3H,
24		95-97	+ 78	242 (4.19)	1728, 1675	5.73 (s, 1H, HC = C), 4.70 (t,1H,HC-O), 1.20 (s, 3H, CH), 0.85 (s,3H,CH)
25		167-171	+ 64	242 (4.35)	1725, 1680	5.83 (s, 1H, HC = C), 4.70 (t,1H,HC-O), 1.20 (s

*. Satisfactory microanalyses and/or accurate masses were obtained for all compounds. The yield of the esters was 60-90%.

**. Recrystallized from ether, except for 1 (chloroform-pet. ether), 15,16,19 and 25 (acetone), 20,21,23 and 24 (acetonitrile).

*** UV of all compounds is methanol. except for 5,6 and 7 (in acetonitrile).

Table I. Continued

No. Compound	C% Calcd.	C% Found	H% Calcd.	H% Found	Molecular formula
1	77.53	77.72	8.99	9.12	$C_{23}H_{32}O_3$
2	77.84	77.99	9.19	9.37	$C_{24}H_{34}O_3$
3	77.84	77.65	9.19	9.01	$C_{24}H_{34}O_3$
4	a				
5	a				
6	a				
7	a				
8	77.84	77.63	9.19	9.35	$C_{24}H_{34}O_3$
9	78.39	78.58	9.55	9.74	$C_{25}H_{36}O_3$
10	79.30	79.58	10.13	10.01	$C_{30}H_{46}O_3$
11	79.30	79.48	10.13	10.05	$C_{30}H_{46}O_3$
12	78.13	78.28	9.38	9.19	$C_{25}H_{36}O_3$
13	78.39	78.19	9.55	9.75	$C_{26}H_{38}O_3$
14	78.64	78.83	9.71	9.94	$C_{27}H_{40}O_3$
15	78.69	78.85	9.71	9.50	$C_{27}H_{40}O_3$
16	78.87	78.99	9.86	9.63	$C_{28}H_{42}O_3$
17	79.09	79.31	10.00	9.83	$C_{29}H_{44}O_3$
18	79.09	79.26	10.00	10.18	$C_{29}H_{44}O_3$
19	79.30	79.14	10.13	9.95	$C_{30}H_{46}O_3$
20	79.49	79.68	10.26	10.08	$C_{31}H_{48}O_3$
21	79.49	79.71	10.26	10.44	$C_{31}H_{48}O_3$
22	79.67	79.85	10.37	10.15	$C_{32}H_{50}O_3$
23	79.83	79.66	10.19	10.32	$C_{33}H_{48}O_3$
25	80.00	79.85	10.00	10.19	$C_{33}H_{48}O_3$
25	80.00	80.18	10.00	10.04	$C_{33}H_{48}O_3$

a- Accurate mass was obtained for this compound

loric acid ice solution and extracted with chloroform. The chloroform was washed with water, dried and filtered. The solvent was evaporated and the residue was purified by tlc (silica gel, chloroform/ethyl acetate 90:10) to give the desired compound.

The physical data of the esters prepared are summarized in Table I.

The biological activities of these compounds will be reported in a separate paper by Bailey, et al.*

ACKNOWLEDGMENT

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* Animal Screening tests were performed under the direction of Dr. G. Bailey, Chief, Contraceptive Development Branch, National Institute of Child Health and Human Development, Bethesda, Maryland, USA.