Long-acting contraceptive agents: testosterone esters of unsaturated acids

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The synthesis of 13 new esters of testosterone is described, with the esterifying acids bearing acetylenic, olefinic, or polyunsaturated functions in the chain, for evaluation as long-acting androgens. (*Steroids* **55**:36–39, 1990)

Keywords: testosterone esters; unsaturated acids, long-acting androgens; contraceptions; steroids

Introduction

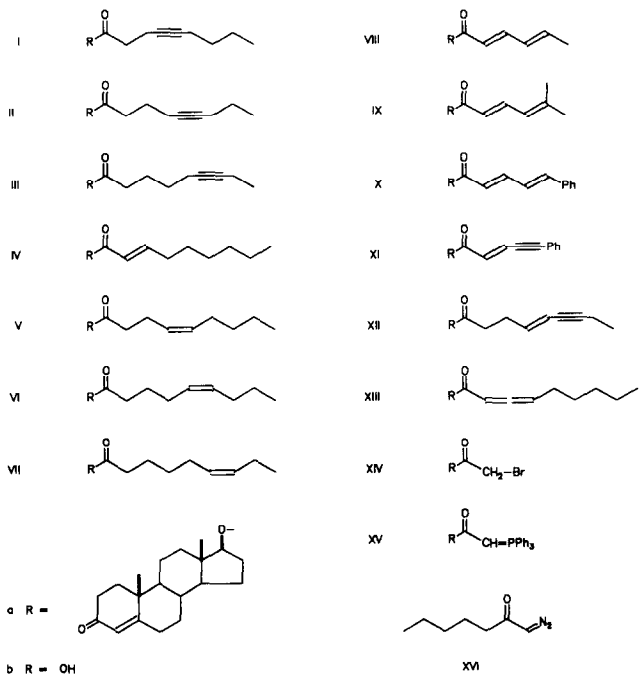
In 1975, the Special Programme of Research, Development and Research Training in Human Reproduction of the World Health Organization established a task force to develop an international chemical synthesis program directed to find new, long-acting contraceptive steroids.[1] The results concerning the works on progestogen esters have already been published in this journal.[2]

It is generally accepted that many of the strategies envisaged for producing infertility in the male will necessitate androgen replacement therapy; hence, the Programme has been interested in developing long-acting esters of testosterone that would exhibit a more constant release rate and maintain testosterone levels in the normal range longer than testosterone enanthate. Eventually, these testosterone esters would be of interest not only for fertility regulation, but also for infertility and gerontology. The evaluation of the biologic activity of these esters in male rats will be reported elsewhere.

Experimental

The ^{13}C-nuclear magnetic resonance (NMR) images were recorded on a Varian CFT-20 NMR spectrometer operating at 20.1 MHz. The samples were recorded in 5-mm outside diameter tubes using $CDCl_3$ as solvent.

The ^1H-NMR spectra were recorded with a Perkin-Elmer R-12B (60 MHz) or R-32 (90 MHz) instrument in $CDCl_3$, with tetramethylsilane as internal reference. Infrared spectra were measured on a Perkin-Elmer 402 spectrometer. Mass spectra were recorded with a Hewlett-Packard 5930A instrument. Thin-layer chromatography was performed on Merck silica gel (0.063 to 0.2 mm), the spray reagent being iodine or vanillin (1 g)/H_2SO_4 (160 ml)/EtOH (40 ml).



Scheme

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Received March 7, 1989; revised July 12, 1989.

General procedure for the esterification of testosterone

To a solution of testosterone (38.5 mmol) in dry benzene (100 ml) and pyridine (4.5 ml) was added, at 0 C, the corresponding acid chloride (40 mmol). The mixture was allowed to go to room temperature and was stirred for 10 to 20 hours. Usual work-up and silica gel medium-pressure chromatography (benzene to acetone ratio, 50 : 1) yielded the pure ester.

Testosterone non-4-ynoate (**Ia**): oil, $[\alpha]_D$ + 112° ($CHCl_3$); λ_{max} 241 nm (EtOH), ε 16,600; ν_{max} (KBr) 1,615, 1,673, 1,733 cm^{-1}; δ ($CDCl_3$) 5.75 (1H, s, 4-H), 4.66 (1H, m, 17-H), 2.48 (4H, s, 2'-H_2 and 3'-H_2), 1.20 (3H, s, 10-Me), 0.89 (3H, t, J = 7 Hz, 8'-Me), 0.85 (3H, s, 13-Me); m/z 424 (M^+), 271. Found: C, 79.43%; H, 9.62%. $C_{28}H_{40}O_3$ requires C, 79.20%; H, 9.50%.

Testosterone non-5-ynoate (**IIa**): oil, $[\alpha]_D$ + 84° ($CHCl_3$); λ_{max} 241 nm (EtOH), ε 15,600; ν_{max} (film), 1,615, 1,670, 1,725 cm^{-1}; δ ($CDCl_3$) 5.75 (1H, s, 4-H), 4.64 (1H, m, 17-H), 1.20 (3H, s, 10-Me), 0.97 (3H, t, J = 7 Hz, 8'-Me), 0.85 (3H, s, 13-Me); m/z 424 (M^+), 271. Found: C, 79.36%; H, 9.62%. $C_{28}H_{40}O_3$ requires C, 79.20%; H, 9.50%.

Testosterone non-6-ynoate (**IIIa**): oil, $[\alpha]_D$ + 77° ($CHCl_3$); λ_{max} 241 nm (EtOH), ε 14,800; ν_{max} (film), 1,620, 1,675, 1,730 cm^{-1}; δ ($CDCl_3$) 5.84 (1H, s, 4-H), 4.67 (1H, m, 17-H), 1.22 (3H, s, 10-Me), 1.11 (3H, t, J = 7 Hz, 8'-Me), 0.86 (3H, s, 13-Me); m/z 424 (M^+), 271. Found: C, 79.12%; H, 9.62%. $C_{28}H_{40}O_3$ requires C, 79.20%; H, 9.50%.

Testosterone trans-non-2-enoate (**IVa**): oil, $[\alpha]_D$ + 102° ($CHCl_3$); λ_{max} 241 nm (EtOH), ε 18,000, 211 nm, ε 20,000; ν_{max} (film) 1,620, 1,655, 1,675, 1,715 cm^{-1}; δ ($CDCl_3$) 6.98 (1H, dt, J = 7, J = 16 *Hz*, 3'-H), 5.82 (1H, dt, J = 16, J = 2 Hz, 2'-H), 5.73 (1H, s, 4-H), 4.70 (1H, m, 17-H), 1.22 (3H, s, 10-Me), 0.89 (3H, t, J = 7 Hz, 8'-Me), 0.88 (3H, s, 13-Me); m/z 426 (M^+), 271. Found: C, 78.61%; H, 10.12%. $C_{28}H_{42}O_3$ requires C, 78.83%; H, 9.92%.

Testosterone cis-non-4-enoate (**Va**): oil, $[\alpha]_D$ + 82° ($CHCl_3$); λ_{max} 241 nm (EtOH), ε 16,700, ε 211 nm, 20,000; ν_{max} (film) 1,620, 1,670, 1,730 cm^{-1}; δ ($CDCl_3$) 5.75 (1H, s, 4-H), 5.41 (2H, m, 4'- and 5'-H), 4.65 (1H, m, 17-H), 1.21 (3H, s, 10-Me), 0.89 (3H, t, J = 7 Hz, 8'-Me), 0.84 (3H, s, 13-Me); m/z 426 (M^+), 328. Found: C, 78.90%; H, 9.69%. $C_{28}H_{42}O_3$ requires C, 78.83%; H, 9.92%.

Testosterone cis-non-5-enoate (**VIa**): oil, $[\alpha]_D$ + 86° ($CHCl_3$); λ_{max} 241 nm (EtOH), ε 17,000; ν_{max} (film) 1,620, 1,670, 1,730 cm^{-1}; δ ($CDCl_3$) 5.75 (1H, s, 4-H), 5.40 (2H, m, 5'- and 6'-H), 4.64 (1H, m, 17-H), 1.20 (3H, s, 10-Me), 0.90 (3H, t, J = 7 Hz, 8'-Me), 0.84 (3H, s, 13-Me); m/z 426 (M^+), 271. Found: C, 78.57%; H, 9.83%. $C_{28}H_{42}O_3$ requires C, 78.83%; H, 9.92%.

Testosterone cis-non-6-enoate (**VIIa**): oil, $[\alpha]_D$ + 85° ($CHCl_3$); λ_{max} 241 nm (EtOH), ε 16,400; ν_{max} (film) 1,620, 1,670, 1,730 cm^{-1}; δ ($CDCl_3$) 5.75 (1H, s, 4-H), 5.35 (2H, m, 6'- and 7'-H), 4.63 (1H, m, 17-H), 1.20 (3H, s, 10-Me), 0.95 (3H, t, J = 7 Hz, 8'-Me), 0.84 (3H, s, 13-Me); m/z 426 (M^+), 271. Found: C, 78.61%; H, 10.12%. $C_{28}H_{42}O_3$ requires C, 78.83%; H, 9.92%.

Testosterone E,E-hexa-2,4-dienoate (**VIIIa**): melting point (mp), 180 to 182 C, $[\alpha]_D$ + 161° ($CHCl_3$); λ_{max} 253 nm (EtOH), ε 37,000; ν_{max} (KBr) 1,620, 1,645, 1,680, 1,710, 3,020 cm^{-1}; δ ($CDCl_3$) 7.25 (1H, m, 3'-H), 6.16 (2H, m, 4'- and 5'-H), 5.77 (1H, d, J = 16 Hz, 2'-H), 5.73 (1H, s, 4-H), 4.69 (1H, m, 17-H), 1.83 (3H, d, J = 5 Hz, 5'-Me), 1.17 (3H, s, 10-Me), 0.85 (3H, s, 13-Me); m/z 382 (M^+), 287, 271, 228. Found: C, 78.40%; H, 8.79%. $C_{25}H_{34}O_3$ requires C, 78.49%; H, 8.96%.

Testosterone E-5-methylhexa-2,4-dienoate (**IXa**): mp, 139 to 142 C; λ_{max} 246 nm (EtOH), ε 22,000; ν_{max} (KBr) 1,620, 1,640, 1,685, 1,710 cm^{-1}; δ ($CDCl_3$) 7.63 (1H, dd, J = 13, J = 15 Hz, 3'-H), 6.01 (1H, brd, J = 13 Hz, 2'-H), 5.79 (1H, brd, J = 15 Hz, 4'-H), 5.76 (1H, s, 4-H), 4.70 (1H, m, 17-H), 1.88 (6H, s, 5'-Me_2), 1.18 (3H, s, 10-Me), 0.86 (3H, s, 13-Me); m/z 396 (M^+), 271, 109. Found: C, 78.71%; H, 9.05%. $C_{26}H_{36}O_3$ requires C, 78.75%; H, 9.15%.

Testosterone 5-phenylpenta-2,4-dienoate (**Xa**): mp, 143 to 145 C, $[\alpha]_D$ + 211° ($CHCl_3$); λ_{max} 308 nm (MeOH), ε 30,200; ν_{max} (KBr) 1,688, 1,710 cm^{-1}; δ ($CDCl_3$) 7.33 (5H, m, Ar), 7.00 (1H, d, J = 14 Hz, 3'-H), 6.80 (2H, m, 4'- and 5'-H), 6.00 (1H, d, J = 14 Hz, 2'-H), 5.70 (1H, s, 4-H), 4.66 (1H, m, 17-H), 1.18 (3H, s, 10-Me), 0.88 (3H, s, 13-Me). Found: C, 81.21%; H, 8.01%. $C_{30}H_{36}O_3$ requires C, 81.04%; H, 8.16%.

Testosterone 5-phenylpent-2-en-4-ynoate (**XIa**): mp, 136 to 138 C, $[\alpha]_D$ + 218° ($CHCl_3$); λ_{max} 301 nm (MeOH), ε 26,300; ν_{max} (KBr) 1,680, 1,730, 2,195 cm^{-1}; δ ($CDCl_3$) 7.43 (5H, m, Ar), 7.03 (1H, d, J = 16 Hz, 3'-H), 6.33 (1H, d, J = 16, Hz, 2'-H), 5.76 (1H, s, 4-H), 4.76 (1H, m, 17-H), 1.18 (3H, s, 10-Me), 0.86 (3H, s, 13-Me). Found: C, 81.28%; H, 7.75%. $C_{30}H_{34}O_3$ requires C, 81.41%; H, 7.74%.

Testosterone non-4-en-6-ynoate (**XIIa**): oil, $[\alpha]_D$ + 79° (CCl_4); λ_{max} 238 nm (MeOH) ε 27,800; ν_{max} (film): 960, 1,187, 1,617, 1,677, 1,732, 2,215 cm^{-1}; δ ($CDCl_3$) 6.06 (1H, m, 4'-H), 5.67 (1H, s, 4-H), 5.47 (1H, d, J = 16 Hz, 5'-H), 4.65 (1H, m, 17-H), 1.22 (3H, s, 10-Me), 1.18 (3H, t, J = 7, Hz, 8'-Me), 0.87 (3H, s, 13-Me); m/z 422 (M^+). Found: C, 79.31%; H, 8.91%; $C_{28}H_{38}O_3$ requires C, 79.58%; H, 9.06%.

Testosterone bromoacetate (**XIVa**): testosterone (10 g) was dissolved in dry dioxane (60 ml), N,N-dimethylaniline (10 ml) was added, and the solution was treated dropwise, while cooling in the ice bath, with bromoacetyl chloride (10 g). The reaction was stirred for 2 hours. Water (50 ml) was then added and the crystalline product was filtered off after cooling in a refrigerator, yielding 12.71 g (89%) with a mp of 133 to 140 C.

Testosterone triphenylphosphoranylideneacetate (**XVa**): Testosterone bromoacetate (**XIVa**) (12.61 g) was dissolved in benzene (30 ml), and a solution of triphenylphosphine (8.1 g) in benzene (30 ml) was added. After stirring for 24 hours, the oily product was separated by decantation, then triturated with petroleum ether. The solid phosphonium salt was dissolved

Table 1 Carbon-13 chemical shift data of acids IB-VIIB

Carbon	Ib	IIb	IIIb	IVb	Vb	VIb	VIIb
1′	178.8	180.1	180.2	172.3	180.0	180.5	180.5
2′	34.1	33.0	33.7	120.8	34.3	33.6	34.1
3′	14.6	24.1	23.9	152.4	22.6[a]	24.7	24.4
4′	81.4	18.3	28.5	32.4	131.9	26.4	29.2
5′	77.8	81.4	18.5	27.9	127.0	128.5	26.7
6′	18.4	78.8	82.3	28.9	27.0	131.2	128.5
7′	31.1	20.8	78.7	31.7	31.9	29.4	132.2
8′	21.9	22.5	12.4	22.6	22.4[a]	22.9	20.6
9′	13.6	13.5	14.3	14.0	14.0	13.8	14.3

[a] Assignments may be reversed.

Table 2 Carbon-13 data of testosterone esters Ia-VIIa

Carbon	Ia	IIa	IIIa	IVa	Va	VIa	VIIa
1	35.8	35.8	35.8	35.8	35.8	35.8	35.8
2	33.9	33.9	33.9	33.9	33.9	34.0	33.9
3	197.7	197.8	197.7	197.7	197.8	197.6	197.7
4	124.0	124.0	124.0	124.0	124.0	124.0	124.0
5	170.7	170.6	170.6	170.6	170.6	170.6	170.6
6	32.7	32.7	32.8	32.8	32.7	32.8	32.8
7	31.6	31.6	31.6	31.6	31.5[a]	31.6	31.6
8	35.5	35.5	35.5	35.5	35.5	35.5	35.5
9	53.8	53.8	53.8	53.8	53.8	53.8	53.8
10	38.6	38.6	38.6	38.6	38.6	38.7	38.6
11	20.6	20.6	20.6	20.6	20.6	20.6	20.6
12	36.7	36.7	36.7	36.7	36.7	36.8	36.7
13	42.6	42.6	42.6	42.7	42.5	42.6	42.6
14	50.3	50.3	50.3	50.4	50.3	50.4	50.3
15	23.5	23.5	23.5	23.5	23.5	23.5	23.5
16	27.5	27.6	27.6	27.6	27.5	27.6	27.6
17	82.5	82.3	82.3	82.1	82.3	82.2	82.2
18	12.0	12.0	12.1	12.1	12.1	12.1	12.1
19	17.4	17.4	17.4	17.4	17.4	17.4	17.4
1′	172.0	173.1	173.4	166.6	173.1	173.5	173.5
2′	34.4	33.3	34.1	121.5	34.6	34.0	34.4
3′	15.0	24.5	24.3	149.1	22.9[b]	25.1	24.7
4′	81.0	18.3	28.5	32.2	131.4	26.6	29.2
5′	78.1	81.0	18.4	28.0	127.4	128.7	26.7
6′	18.4	78.9	82.0	28.8	26.9	130.8	128.6
7′	31.0	20.7	78.8	31.6	31.8[a]	29.3	132.0
8′	21.9	22.5	12.4	22.5	22.3[b]	22.8	20.6
9′	13.6	13.4	14.3	14.0	14.0	13.8	14.3

[a] and [b] Assignments of chemical shifts for close-lying peaks marked with the same letter may be reversed.

in methanol (90 ml) and the solution was alkalinized with 1 N NaOH. The oily phosphorane was dissolved in diethyl ether and the solution was washed with water, dried over $MgSO_4$, and concentrated to give the phosphorane (XVa), 16.5 g (91%), oil, δ ($CDCl_3$) 7.0 to 8.0 (15H, m, Ar), 5.76 (1H, s, 4-H), 4.96 (1H, m, 17-H), 0.70 (6H, s).

Testosterone nona-2,3-dienoate (**XIIIa**): a solution of the phosphorane **XVa** (0.15 mol) in tetrahydrofuran (THF) (500 ml) was added at −20 C to a solution of 1-diazoheptan-2-one (**XVI**) (0.18 mol), prepared from pentanoyl chloride and diazomethane, in THF (100 ml). This mixture was further treated with silver benzoate (0.037 mol) in dry dimethyl sulfoxide (70 ml). The reaction was allowed to warm up to room temperature overnight, and after concentration under reduced pressure, the mixture was extracted with diethyl ether. The organic extract was washed with water, dried, and evaporated, and the crude product was purified by column chromatography on silica gel, eluted with benzene/ethyl acetate, 50:1, yielding the ester XIIIa (6%), oil, $[\alpha]_D$ + 97° (CCl_4); λ_{max} 230 nm (heptane), ε 18,700; ν_{max} (film) 862, 1,160, 1,260, 1,620, 1,683, 1,718, 1,965 cm^{-1}; δ (CCl_4) 5.70 (1H, s, 4-H), 5.5 to 5.7 (2H, m, 2′-H and 4′-H), 4.65 (1H, m, 17-H), 1.20 (3H, s, 10-Me), 0.82 (3H, s, 13-Me); m/z 424 (M^+). Found: C, 79.06%; H, 9.61%. $C_{28}H_{40}O_3$ requires C, 79.20%; H, 9.50%.

Results

In this report, we describe the synthesis and physical properties of some esters of testosterone with unsaturated carboxylic acids (**Ia-XIIIa**). The syntheses of the nonynoic (**Ib-IIIb**) and nonenoic acids (**IVb-VIIb**) have been described previously.[3]

E-E-Hexa-2,4-dienoic acid (**VIIIb**) is commercially available (Aldrich Chemical Company) and the other acids required for this work, namely, E-5-methylhexa-2,4-dienoic (**IXb**),[4] 5-phenylpenta-2,4-dienoic (**Xb**),[5] 5-phenyl-4-yn-pent-2-enoic (**XIb**),[6] and non-4-en-6-ynoic acid (**XIIb**),[4] were prepared as previously reported. Esterification of testosterone with each of the first 12 unsaturated acids was performed by reaction with the corresponding acid chlorides in pyridine.

Although the nona-2,3-dienoic acid ethyl ester was easily obtained,[4] this compound could not be hydrolyzed to the acid (**XIIIb**). Hence, we tried an alternative procedure for the synthesis of the ester **XIIIa**, by reaction of bromoacetate of testosterone (**XIVa**) with triphenylphosphine to give the phosphorane (**XVa**). Reaction of this phosphorane (**XVa**) with 1-diazoheptan-2-one (**XVI**) led to the allenic ester (**XIIIa**).

In Tables 1 and 2 are complied the ^{13}C-NMR chemical shifts corresponding to the free monoalkenyl and monoalkynnyl acids (**Ib-VIIb**) and their esters (**Ia-VIIa**), respectively. The carbon resonance assignments were deduced from the proton-noise decoupled and off-resonance decoupled spectra. The values assigned for the acids are in good agreement with the calculated ones.[7]

Acknowledgments

We thank the World Health Organization for financial support of this work.

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