POTENTIAL LONG-ACTING CONTRACEPTIVE AGENTS: ESTERS AND ETHERS OF TESTOSTERONE WITH α- AND/OR β-CHAIN BRANCHING

J.E.HERZ *,a, J.V.TORRES b,1, A. MURILLO AND S.CRUZ b,2
a)Department of Biotechnology, Institute for Biomedical Research, UNAM, Apdo. Postal 70228, Mexico and (b) Department of Chemistry, CINVESTAV, Mexico 13

A.SHAFIEE * AND M.VOSOOGHI, Department of Chemistry, College of Pharmacy, Tehran University, Tehran, Iran

S.SOTHEESWARAN *,3 AND A.A.L.GUNATILAKA, Department of Chemistry, University of Peradeniya, Peradeniya, Sri Lanka

Received 10-29-85
Revised 5-26-86

ABSTRACT

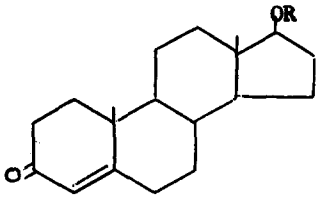
The synthesis of ten esters and two ethers of testosterone (17 β-hydroxyandrost-4-en-3-one) is described. All these possess some form of α - and/or β - substitution in the ester/ether side-chain. The work was undertaken in order to evaluate the long-acting antifertility effect of such compounds in males.

INTRODUCTION

In 1975, the World Health Organisation (W.H.O) as a part of the Special Programme of Research and Training in Human Reproduction established a chemical synthesis programme (4) which was aimed primarily at finding new long-acting steroidal male and female contraceptive agents. This paper covers

---

* Authors to whom any correspondence may be addressed.



1, R= $-COCH(CH_3)_2$

2, R= $-COC(CH_3)_2CH_2CH_2CO_2CH_3$

3, R= $-COC(CH_3)_2CH_3$

4, R= $-COC(CH_3)_2CH_2CH_3$

5, R= $-COC(CH_3)_2CH_2CH_2CH_3$

6, R= $-COC(CH_3)_2CH_2CH_2CH_2CH_3$

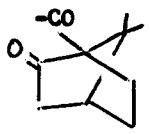
7, R= $-Si(CH_3)_2C(CH_3)_3$

8, R= $-Si(CH_3)_2OSi(CH_3)_3$

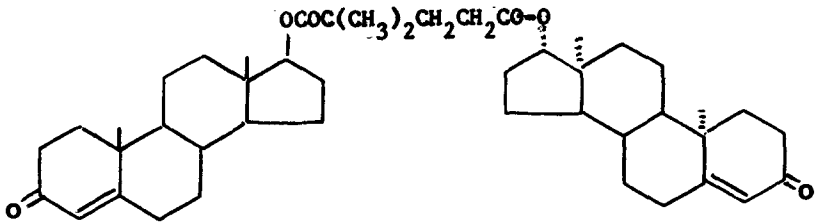
9, R= $-COCH_2C(CH_3)_2CH_3$

10, R= $-COCH(CH_2CH_3)_2$

11, R=



12,



a part of the work carried out by three of the participating laboratories during the period 1977-1980, in which ten related potential long-acting male contraceptive steroidal esters and two steroidal ethers have been synthesised and submitted for evaluation of their biological activities.

CHEMICAL SYNTHESIS

Of the twelve compounds synthesised, all were derivatives of testosterone. Two of them were α -monosubstituted esters, six were α , α'-disubstituted esters and one was a β , β'-disubstituted ester. One was a ditestosterone ester which was both α -monosubstituted and α , α' -disubstituted. Two siloxy ethers of testosterone were also included for comparison among this group, because of their similar alkyl substitution patterns.

Testosterone 2-methyl propanoate (1) was prepared using the conventional method of reacting 2-methyl propanoyl chloride with testosterone in the presence of pyridine. For the esterification of the 17-OH group in testosterone with 3,3-dimethyl butanoic and 2-ethyl butanoic acids, the benzenesulfonyl chloride method of Gunatilaka and Sotheeswaran (5) was employed. The molar ratio

used was benzenesulfonyl chloride : acid : testosterone = 2 : 4 : 1. The benzenesulfonyl chloride method was found to be unsatisfactory for the esterification of the carboxylic acids of the type $R_1R_2R_3CCO_2H$. Hence, for the preparation of the esters at the 17-OH group in testosterone with ketopinic acid to produce the ester, 11, the p-toluenesulfonic acid method of Crabbe' et al (6) was employed. Compounds 2 through 6, 8 and 12 were prepared by the method described by Muller and Herz (7), whereas the siloxy ether, 7, was prepared by treating testosterone with t-butyldimethylsilyl reagent in dimethylformamide.

EXPERIMENTAL

All melting points are uncorrected. Infrared (IR) spectra were determined in chloroform solution unless otherwise stated. Nuclear magnetic resonance (NMR) spectra were obtained in $CDCl_3$ solution using tetramethylsilane as an internal standard.

2-Methylpropanoic acid, 4-methoxycarbonyl-2,2-dimethyl butanoic acid, 2,2-dimethyl propanoic acid, 2,2-dimethyl butanoic acid, 2,2-dimethyl pentanoic acid, 2,2-dimethyl hexanoic acid, 3,3-dimethyl butanoic acid, 2-ethyl butanoic acid and 2,2-dimethyl pentane-1,5-dioic acid were obtained from commercial sources or were synthesised from readily available starting materials (8). Ketopinic acid was synthesised from D-camphor according to the procedure of Bartlett and Knox (9). 1-Chloropentamethyldisiloxane and t-butyldimethylsilylchloride were obtained commercially from Aldrich Chemical Co.

Acid chlorides were prepared as previously

described (8). All samples submitted for bioassay were dried to constant weight at 40°C under vacuum using KOH as the desiccant.

The analytical, physical and spectroscopic data of all the compounds synthesised and submitted for bioassay are given below. The bioassay results will be published elsewhere.

Testosterone 2-methylpropanoate (1): (60%), m.p. 132-134°C, $(\alpha)_D$ +90 ($CHCl_3$); λ_{max} 239 nm, log ε 4.22; ν_{max} 1668(C=O), 1730(ester C=O) cm^{-1}; δ 5.80(1H,s,HC=), 4.67(1H,t,$HCCO_2$-), 1.12(3H,s,CH_3), 0.85(3H,s,CH_3); $C_{23}H_{34}O_3$ requires C, 77.09%; H, 9.50%; Found C, 77.27%; H, 9.31%.

Methyl testosterone 2,2-dimethylpentanedioate (2):oil (65%), $(\alpha)_D$ +76°C($CHCl_3$); λ_{max} 246 nm, log ε 4.43; ν_{max} 1630(C=C), 1690(C=O), 1740(ester C=O) cm^{-1}; δ 5.62(s), 4.55(m),3.6(s),1.2(s),0.8(s); $C_{27}H_{40}O_5$ requires C, 72.94%; H,9.07%; Found C, 72.64%; H, 9.15%.

Testosterone 2,2-dimethylpropanoate (pivaloate) (3): crystals from ether (55%), m.p. 159-60°C, $(\alpha)_D$ +89.8°($CHCl_3$); λ_{max} 245 nm, log ε 4.475; ν_{max} 1625(C=C), 1685(C=O), 1730(ester C=O) cm^{-1}; δ 5.5(s), 4.5(t), 2.2(m), 1.15(s), 0.8(s); $C_{24}H_{36}O_3$ requires C, 77.38%; H,9.74%; Found C,77.16%; H, 9.68%.

Testosterone 2,2-dimethylbutanoate (4): crystals from ether-hexane (75%), m.p. 155-6°C, $(\alpha)_D$ +92.5°($CHCl_3$); λ_{max} 244 nm, log ε 4.49; ν_{max} 1630 (C=C), 1690(C=O), 1735(ester C=O) cm^{-1}; δ 5.63(s), 1.17(s), 0.87(s); $C_{25}H_{38}O_3$ requires C, 77.68%; H, 9.91%; Found C, 77.92%; H, 9.98%.

Testosterone 2,2-dimethylpentanoate (5): crystals from ether-hexane (60%), m.p. 81-3°C, $(\alpha)_D$ +110°($CHCl_3$); λ_{max} 244 nm, log ε 4.54; ν_{max} 1625(C=C), 1670(C=O), 1725(ester C=O) cm^{-1}; δ 5.65(s), 1.1(s), 0.85(s); $C_{26}H_{40}O_3$ requires C, 77.95%; H, 10.06%; Found C, 77.92%; H, 10.21%.

Testosterone 2,2-dimethylhexanoate (6): oil (62%), $(\alpha)_D$ + 78°($CHCl_3$); λ_{max} 244 nm, log ε 4.49; ν_{max} 1630(C=C), 1690(C=O), 1735(ester C=O) cm^{-1}; δ 6.6(s), 4.5(m), 1.15(s), 0.90(s); $C_{27}H_{42}O_3$ requires C, 78.21%; H, 10.21%; Found C, 78.38%; H, 10.13%.

Testosterone t-butyldimethylsilylether (7):crystals from ether (55%), m.p. 135°C, (α)$_D$ +94°C($CHCl_3$); λ_{max} 243 nm, log ε 4.25; $C_{25}H_{42}O_2Si$ requires C, 74.57%; H, 10.51%; Found C,74.40%; H,10.57%.

Testosterone pentamethyldisiloxylether (8): oil (42%), (α)$_D$ +91°($CHCl_3$); λ_{max} 238 nm, log ε 4.31; ν_{max} 1630(C=C), 1670(C=O) cm^{-1}; 5.69(s), 3.68(m), 1.2(s), 0.8(s), 0.15(s), 0.1(s); $C_{24}H_{42}O_3Si_2$ requires C, 66.30%; H, 9.74%; Found C, 66.79%; H, 9.60%.

Testosterone 3,3-dimethylbutanoate (9): crystals from ether-hexane (72%), m.p. 135-7°, (α)$_D$ +75°($CHCl_3$); ν_{max} 1610(C=C), 1655(C=O), 1715(ester C=O), 1715(ester C=O) cm^{-1}; δ 5.75(1H,s,4-H), 4.75(1H,m,17-H), 2.25(2H,s,2'-H), 1.25(3H,s,CH_3), 1.07(9H,s, 3 x CH_3), 0.87(3H,s,CH_3), 2.4-1.0(methylene envelope); m/z 386(M^+, 100%), 344(39), 288(100), 271(96), 260(43), 228(100), 147(100),. MW 386.2839; $C_{25}H_{38}O_3$ requires 386.2821.

Testosterone 2-ethylbutanoate (10): crystals from ether-hexane (85%), m.p. 127-9°C [lit.(10) 129-130°].

Testosterone ketopinate (11): crystals from ether-hexane (56%), m.p. 189-190°C, (α)$_D$ +10°($CHCl_3$); ν_{max} 1610(C=C), 1660(C=O), 1720(ester C=O) cm^{-1}; δ 5.6(1H,s,C=CH), 4.6(1H,t, -CH-O), 1.2(3H,s,CH_3), 1.15(3H,s,CH_3), 1.05(3H,s,CH_3), 0.8(3H,s,CH_3), 2.4-1.0(methylene envelope); $C_{29}H_{40}O_4$ requires C, 77.0%; H, 8.85%; Found C,77.06%; H, 8.83%.

1,5-Ditestosterone 2,2-dimethylpentanedioate (12): crystals from hexane (58%), m.p. 237-9°C, (α)$_D$ + 22.54°($CHCl_3$); λ_{max} 246 nm, log ε 4.72; λ_{max} 1630(C=C), 1670(C=O), 1735(ester C=O) cm^{-1}; δ 5.7(s), 4.6(t), 2.2(m), 1.2(s), 0.80(s); $C_{45}H_{64}O_6$ requires C, 77.10%; H, 9.20%; Found C, 77.28%; H, 9.14%.

ACKNOWLEDGMENT

This work received financial support from the World Health Organisation, Special Programme of Research in Human Reproduction.

NOTES AND REFERENCES

1. Present address: Department of Chemistry, CICY, Merida, Yucatan, Mexico.

2. Present address: Department of Biochemistry, Universidad Autonoma Metropolitana, Iztapalapa, D.F.Mexico 10.

3. Present address: Department of Chemistry, School of Pure and Applied Sciences, The University of the South Pacific, Suva, Fiji Islands.

4. Crabbe', P., Diczfalusy, E. and Djerassi, C., SCIENCE, 209, 992 (1980).

5. Gunatilaka, A.A.L. and Sotheeswaran, S., J.CHEM. SOC. (CHEM. COMMUN.), 980 (1978) and CURRENT CHEMICAL REACTIONS, 1, 659 (1979).

6. Crabbe', P., Cruz, A. and Iriarte, J., CANAD. J. CHEM., 46, 349 (1968).

7. Muller, J. and Herz, J.E., STEROIDS, 34, 793 (1979).

8. Watson, T.G., Hosking, M., Herz, J.E., Torres, J.V., Muller, J., Murillo, A., Cruz, S., Shafiee, A., Vossoghi, M., Savabi, F., Sotheeswaran, S. and Puvanesarajah, V., STEROIDS, 41, 255 (1983).

9. Bartlett, P.D. and Knox, L.D., ORGANIC SYNTHESIS, 45, 55 (1965).

10. Gould, D., Finckenor, L., Hershberg, E.B., Cassidy, J. and Pealmann, P.L., J. AM. CHEM.SOC., 79, 4472 (1957).