POTENTIAL LONG-ACTING CONTRACEPTIVE AGENTS: ESTERS OF TESTOSTERONE WITH ALKOXY- AND HALOGENO-SUBSTITUTED CARBOXYLIC ACIDS

A. Shafiee,[a]* M. Vosooghi,[a] C. G. Francisco,[b]
R. Freire,[b] R. Hernandez,[b] J. A. Salazar,[a]
E. Suarez,[b]* S. Sotheeswaran,[1c]* and A. A. L. Gunatilaka[c]

[a]Department of Chemistry, College of Pharmacy, Tehran University, Tehran, Iran; [b]Instituto de Productos Naturales Organicos del CSIC, Carretara La Esperanza, 2, La Laguna, Tenerife, Canary Islands, Spain; [c]Department of Chemistry, University of Peradeniya, Sri Lanka

Received December 29, 1986
Revised December 2, 1987

ABSTRACT

The chemical synthesis and physical data of several new esters of testosterone (17β-hydroxyandrost-4-en-3-one), which contain either a halogeno or an alkoxy substituent in the acid chain, are reported.

INTRODUCTION

Esters obtained from testosterone with hindered carboxylic acids are potentially useful as long-acting male anti-fertility agents (2,3). Several alkoxylated and α-substituted aliphatic acids were synthesized as reported before (4) and were esterified with testosterone at the 17β-hydroxy function. This was done as a part of the World Health Organisation's program on the synthesis of long-acting injectable contraceptives (5). The syntheses of these esters are reported in this paper. The biological activities of these esters in male rats will be reported elsewhere.

* Authors to whom any correspondence may be addressed.

CHEMICAL SYNTHESIS

Commonly available α-substituted aliphatic acids were purchased. 4-Butoxybutanoic, 5-propoxypentanoic, 7-methoxyheptanoic, and menthyloxyacetic acids were synthesized as before (4). Carvomenthyloxyacetic acid was synthesized using published procedures (6) from l-carvone.

The testosterone esters with chloroacetic and fluoroacetic, 3-pentoxypropanoic, 4-butoxybutanoic, 5-propoxypentanoic, and 7-methoxyheptanoic acids were prepared by reacting their respective acid chlorides with testosterone in the presence of pyridine. During our studies to prepare these steroid esters from the unprotected sterol and hindered carboxylic acids by a simple procedure, we also investigated the role of benzenesulfonyl chloride as the coupling agent (7). For the esterification of the 17β-hydroxy function in testosterone with carboxylic acids of the type $R^1R^2CHCO_2H$ or $R^1CH_2CO_2H$, the satisfactory molar ratio was found to be benzenesulfonyl chloride : acid : sterol = 2 : 4 : 1. When a molar ratio of benzenesulfonyl chloride : acid = 2 : 1 was employed as suggested by Brewster and Ciotti (8), the benzenesulfonate ester was the major product.

Eight esters of testosterone (1) to (8) were synthesized for evaluation of their potential as long-acting male contraceptive agents.

EXPERIMENTAL

Chloroacetic acid and fluoroacetic acid were purchased from Aldrich Chemical Co. Ltd. 3-Pentoxypropanoic acid was supplied by Maybridge Ltd., England, through the World Health Organisation. Menthyloxyacetic acid was synthesized using the procedure of Frankland and O'Sullivan (9). Carvomenthyloxyacetic acid was synthesized using the procedure of Eliel and Schroeter (6). 4-Butoxybutanoic, 5-propoxypentanoic, and 7-methoxyheptanoic acids were synthesized using the procedure described earlier (4).

(a) General procedure for the preparation of testosterone esters:

To a stirred solution of testosterone (0.01 mol) in pyridine (30 mL) at 0°, under nitrogen, the acid chloride (0.01 mol) was added. The mixture was allowed to warm up to room temperature and was stirred further for a few hours. Usual work-up followed by silica gel medium-pressure chromatography gave the pure ester.

(b) Benzenesulfonyl chloride method for the preparation of testosterone esters:

The acid (0.01 mol) was dissolved in dry pyridine and was treated with benzenesulfonyl chloride(0.005 mol). The solution was left at room temperature (if necessary cooled to room temperature) for 1-2 h. Testosterone (0.0025 mol) in dry pyridine was then added and the reaction was monitored by TLC. When the reaction was considered complete, the usual work-up and purification by preparative TLC gave the pure ester.

The data for the new testosterone esters are given below:

Testosterone-3-pentoxypropanoate (1): oil, $(\alpha)_D$ + 28°; λmax240 nm(EtOH), log ε 4.21; νmax (film) 1625, 1670, 1730 cm^{-1}; δ ($CDCl_3$) 5.75(1H,s), 4.68(1H,m), 3.70(2H,t), 3.42(2H,t), 2.57(2H,t), 1.20(3H,s), 0.89(3H,t), 0.84(3H,s); m/z 430(M^+), 388, 307, 271. Found: C,75.20%; H,9.85%. $C_{27}H_{42}O_4$ requires C,75.31%; H,9.83%.

Testosterone-4-butoxybutanoate (2): oil, $(\alpha)_D$ + 80°; λmax 240 nm (EtOH), logε4.20; νmax (film) 1620, 1675, 1730 cm^{-1}; δ($CDCl_3$) 5.75(1H,s), 4.62(1H,m), 3.43(4H,m), 1.18 (3H,s), 0.90(3H,t), 0.82(3H,s); m/z 430(M^+), 373, 358, 330, 272. Found: C,75.25%; H,9.78%. $C_{27}H_{42}O_4$ requires C,75.31%; H,9.83%.

Testosterone-5-propoxypentanoate (3): oil, $(\alpha)_D$ + 86°; λ max 240 nm (EtOH), log ε 4.20; ν max (film) 1625, 1670, 1730 cm^{-1}; δ($CDCl_3$) 5.73(1H,s), 4.60(1H, m), 3.35(4H,m), 1.18(3H,s), 0.90(3H,t), 0.82(3H,s); m/z 430(M^+), 387, 288, 272. Found: C,75.30%; H,9.78%. $C_{27}H_{42}O_4$ requires C, 75.31%; H,9.83%.

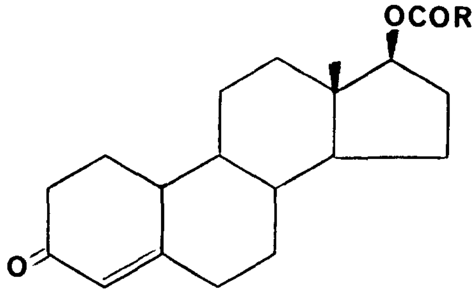
Testosterone-7-methoxyheptanoate (4): m.p. 42–44°, $(\alpha)_D$ + 84°; λmax 240 nm(EtOH), log ε 4.22; ν max (KBr) 1625, 1670, 1730 cm^{-1}; δ($CDCl_3$) 5.75(1H,s), 4.65(1H,m), 3.32 (3H,s), 1.19(3H,s), 0.84(3H,s); m/z 430(M^+), 415, 398, 307, 288, 271. Found: C,75.30%; H,9.75%. $C_{27}H_{42}O_4$ requires C,75.31%; H,9.83%.

Testosterone menthyloxyacetate (5): oil, $(\alpha)_D$ + 15°; δ($CDCl_3$) 5.70(1H,s), 4.09(2H,s), 4.60(1H,m), 3.25(1H,m), 1.15(3H,s), 0.95(3H,d), 0.8(3H,d), 0.8(3H,s); m/z M^+ was not observed, 346, 329, 287(100%), 245, 228. 2,4-Dinitrophenylhydrazone derivative of 5 had m.p. 151–152°.

Testosterone carvomenthyloxyacetate (6): oil, $(\alpha)_D$ + 50°; λ max (film) 1735, 1660, 1610 cm^{-1}; δ(CCl_4) 5.58(1H,s), 4.6(1H,m), 3.95(2H,s), 1.13(3H,s), 0.87(3H,s), 1.0 and 0.8(9H,d), 2.4–0.7 (methylene envelope). m/z M^+ was not observed, 364, 347, 330, 322, 271, 155, 147. 2,4-Dinitrophenylhydrazone derivative of 6 had m.p. 120°.

Testosterone chloroacetate (7): m.p. 125–127°, $(\alpha)_D$ + 114°; λ max 240 nm, log ε 4.16; ν max 1755, 1665 cm^{-1}; δ ($CDCl_3$) 5.75(1H,s), 4.71(1H,t), 4.06(2H,s), 1.16(3H,s), 0.85(3H,s); Found: C,69.01%; H,7.78%. $C_{21}H_{29}O_3Cl$ requires C,69.14%; H,7.96%.

Testosterone fluoroacetate (8): m.p. 144–146°, $(\alpha)_D$ + 85.5°; λmax 239 nm, logε4.19; νmax 1740, 1670 cm^{-1}; δ($CDCl_3$) 5.77(1H,s), 4.83(2H,s), 4.77(1H,t), 1.20(3H,s), 0.85(1H,s). Found : C,72.24%; H,8.15%. $C_{21}H_{29}O_3F$ requires C,72.41%; H,8.33%.



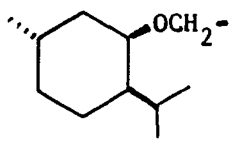
1 R = $-CH_2CH_2O(CH_2)_4CH_3$

2 R = $-CH_2(CH_2)_2O(CH_2)_3CH_3$

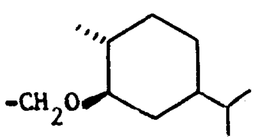
3 R = $-CH_2(CH_2)_3O(CH_2)_2CH_3$

4 R = $-CH_2(CH_2)_5OCH_3$

5 R =



6 R =



7 R = $-CH_2Cl$

8 R = $-CH_2F$

ACKNOWLEDGMENT

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

NOTES AND REFERENCES

1. Present address: School of Pure and Applied Sciences, University of the South Pacific, Suva, Fiji.

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

3. Herz, J.E., Cruz, S.M., Torres, J.V., and Murillo, A., SYNTH COMMUN 7, 383 (1977).

4. Shafiee, A., Vosooghi, M., Francisco, C.G., Freire, R., Hernandez, R., Salazar, J.A., Suarez, E., and Sotheeswaran, S., STEROIDS 41, 285 (1983).

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

6. Eliel, E.L. and Schroeter, S.H., J ORG CHEM 30, 3 (1965).

7. Gunatilaka, A.A.L. and Sotheeswaran, S., J. CHEM. SOC. CHEM. COMMUN , 980 (1978).

8. Brewster, J.H. and Ciotti, C.J., Jr., J AM CHEM SOC 77, 6214 (1955).

9. Frankland, P.F. and O'Sullivan, H.H., J CHEM SOC , 2329 (1911).