LONG-ACTING CONTRACEPTIVE AGENTS: FURYLALKYLCARBOXYLIC ACID ESTERS OF NORETHISTERONE

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ABSTRACT

5-Methyl- and 5-ethyl-furylalkylcarboxylic esters of norethisterone (17α-ethynyl-17β-hydroxyestr-4-en-3-one) were prepared in high yield in the presence of thallous ethoxide. The activities of these compounds as long-acting contraceptive agents have been evaluated.

INTRODUCTION

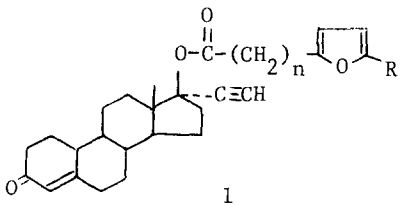
In 1975, the Special Programme of Research, Development and Research Training in Human Reproduction of the World Health Organization initiated a programme for the chemical synthesis and biological evaluation of steroid esters with potential activity as long-acting, injectable progestogens (1).

In the present work, we report the syntheses of five norethisterone esters (1a-e) of furylalkylcarboxylicacids. The acids chosen were from the methyl derivatives of furan, namely: 5-methyl-2-furylethanoic acid (2a),3-(5'-methyl-2'-furyl)propanoic acid (2b) and 4-(5'-methyl-2'-furyl)butanoic acid (2c); and derivatives of ethylfuran: 5-ethyl-2-furyl-ethanoic acid (2d) and 3-(5'-ethyl-2'-furyl)propanoic acid (2e).

CHEMICAL SYNTHESIS

The furylpropanoic acids (2b, 2e) and the butanoic acid derivative (2c) were prepared by standard methods (2,3). A different approach had to be employed for the synthesis of the furylethanoic acids (2a, 2d), due to the instability of some of the intermediates formed via the standard methods (4,5,6). An alternative route involving the use of rhodanine (7) was successfully employed, giving a high overall yield (80%) of the acids (2a,2d).

Esterification of norethisterone with the furylalkyl acid chlorides was achieved in high yield (70-90%) by the use of thallous ethoxide (8,9,10). It was observed that during the initial formation of the thallous salt of norethisterone in refluxing benzene at atmospheric pressure, a side product was also formed which was assigned the structure estr-4-ene-3,17-dione (3) (11). Refluxing under reduced pressure (60-65°) minimised the formation of (3), thereby greatly improving the yield of the esters (1a-e).



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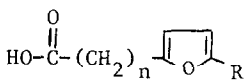

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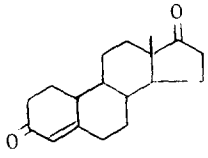
a R = Me n = 1

b R = Me n = 2

c R = Me n = 3

d R = Et n = 1

e R = Et n = 2



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EXPERIMENTAL

All melting points were determined in a Gallenkamp melting point apparatus and are uncorrected. The optical rotations are for chloroform solutions of the compounds, determined in a Leitz polarimeter at the indicated temperatures. The ultraviolet absorption spectra were also determined for chloroform solutions of the compounds, in a Perkin Elmer 551 UV spectrophotometer. The infrared absorption spectra were carried out in pressed KBr discs using a Jasco IRA-1 diffraction grating IR spectrophotometer. The R_f values noted for the norethisterone esters were from spots on standard silica gel plates developed with a mixture of benzene/hexane/methanol (6:3:1). R_f values noted for the furylalkylcarboxylic acids were from spots on standard Kieselgel Type 60 plates developed with a mixture of benzene/ethyl acetate/acetic acid (40:8:2). Spot characterisation in all instances was by exposure to iodine vapour. Elemental analyses were determined on a Perkin Elmer Auto-Analyser 240. NMR spectra were recorded on carbon tetrachloride solution using a Varian instrument. Mass spectra were obtained on a Jeol JMS-100 at 75 eV.

General Method of Preparing the Acid Chlorides

In a dry system, thionyl chloride (1.5 mole) in dry benzene was added dropwise to the acid (1 mole) in dry benzene. The mixture was stirred at 70°C for 1 h. and the excess thionyl chloride and benzene evaporated off at room temperature under vacuum. The desired acid chloride was then purified by vacuum distillation.

The acid chloride was used in a freshly distilled state for the synthesis of the steroidal esters described below.

Preparation of Steroidal Esters

Norethisterone 5-methyl-2-furylethanoate (1a):

To a solution of norethisterone (m.p. 204-6°C; 7 g, 0.023 mole) in dry benzene (300 ml), thallous ethoxide (7 g, 0.028 mole) was added and the solution was refluxed under reduced pressure. The solvent was slowly distilled off and replaced with fresh anhydrous benzene. After distilling a total of 150 ml solvent, the solution was cooled to room temperature. A solution of 5-methyl-2-furylethanoyl chloride (4.44 g, 0.025 mole) in dry benzene (30 ml) was added dropwise over 15 min. with continuous stirring. The reaction mixture was maintained at 30°C for 16 h., then filtered and the filtrate washed with water several times to remove thallous chloride, dried over anhydrous sodium sulphate and evaporated to dryness in vacuo. The yellow product on crystallization from methanol/chloroform yielded the ester (1a), 7.62 g (78%), m.p. 174°.

The crude product was further purified by passing a solution of it in benzene through a column of neutral alumina (Brockmann 2) previously washed with n-hexane followed by a mixture of benzene/hexane (3:7). Eluents showing a single spot on TLC were evaporated to dryness under reduced pressure to yield a crystalline product, m.p. 173-5°C. Recrystallization of this product from methanol/chloroform increased the m.p. to 174-6°C. $[\alpha]_D^{21}$ -9° ; R_{NET} = 2.21;

UV: 241 nm, ε 21067

IR: 1618, 1665, 1755 cm^{-1}

Anal: $C_{27}H_{32}O_4$ requires C: 77.11 H: 7.67
Found C: 77.45 H: 7.87

Norethisterone 3-(5'-methyl-2'-furyl)propanoate (1b):

The general procedure as described for the synthesis of (1a) was followed. Esterification was carried out for 44 h. at 55°C. The crude product (an orange gum) was passed through a neutral alumina column and eluted with benzene/hexane (1:5). Evaporation of eluents in vacuo yielded (1b) as white crystals (70%), m.p. 127-9°C. Recrystallization from methanol raised the m.p. to 130-1°C. $[\alpha]_D^{21}$ -1°; R_{NET} = 2.17;

UV: 241 nm, ε 17201

IR: 1610, 1660, 1740, 3220 cm^{-1}

NMR: 0.91 (3H, s), 2.24 (3H, s), 2.61 (1H, s), 2.85 (4H, m), 5.90 (3H, bs) δ

MS: 434 (M^+)

Anal: $C_{28}H_{34}O_4$ requires C: 77.39 H: 7.89
Found C: 77.45 H: 8.12

Norethisterone 4-(5'methyl-2'-furyl)butanoate (1c):

The general procedure as described for the synthesis of (1a) was followed. Esterification was carried out for 16 h. at 50°C. The crude material was recrystallized from methanol/chloroform to give (1c) (92%), m.p. 160-3°C. The product was passed through a column of neutral alumina eluted with benzene/hexane (3:7). Recrystallization from

methanol/chloroform increased the m.p. to 162-3°C. $[\alpha]_D^{22}$ -6°; R_{NET} = 2.32;

UV: 241 nm, ε 26474
IR: 1610, 1660, 1740, 3215 cm^{-1}
Anal: $C_{29}H_{36}O_4$ requires C: 77.64 H: 8.09
Found C: 77.72 H: 8.20

Norethisterone 5'ethyl-2'-furylethanoate (1d):

The general procedure as described for the synthesis of (1a) was followed. Esterification was carried out for 16 h. at 30°C. The crude product (a gum) was passed through a column of neutral alumina, eluted with benzene/hexane (3:7). Evaporation of the eluents in vacuo yielded a solid, which was recrystallized from methanol/pentane to afford the required ester (1d) (82%), m.p. 73-4°C. $[\alpha]_D^{21}$ -5°; R_{NET} = 2.20;

UV: 241 nm, ε 17968
IR: 1618, 1662, 1755, 3220 cm^{-1}
Anal: $C_{28}H_{34}O_4$ requires C: 77.39 H: 7.89
Found C: 77.48 H: 7.90

Norethisterone 3-(5'ethyl-2'-furyl)propanoate (1e):

The general procedure as described for the synthesis of (1a) was followed. Esterification was carried out for 16 h. at 48°C. The crude product on recrystallization from methanol gave white crystals (70%), m.p. 106-8°C. Chromatography over neutral alumina eluted with benzene/hexane (3:7) and recrystallization from methanol increased the m.p. to 107-8°C. $[\alpha]_D^{22}$ -1°; R_{NET} = 2.28;

UV: 241 nm, ε 26313
IR: 1610, 1660, 1740, 3220 cm^{-1}
Anal: $C_{29}H_{36}O_4$ requires C: 77.64 H: 8.09
Found C: 77.79 H: 8.17

BIOLOGICAL ACTIVITY

The esters were evaluated in an estrus suppression assay in rats, by Dr G. Bialy and co-workers, Contraceptive Development Branch, Center for Population Research, NICHHD, Bethesda, MD, USA. The results of this assay are reported in an accompanying paper in this Journal and indicate that two of the esters, (Ib) and (Ie), show slightly longer duration of action than does norethisterone enanthate, whereas the other compounds appear to be less active.

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