NORETHISTERONE AND LEVONORGESTREL ESTERS: A NOVEL SYNTHETIC METHOD

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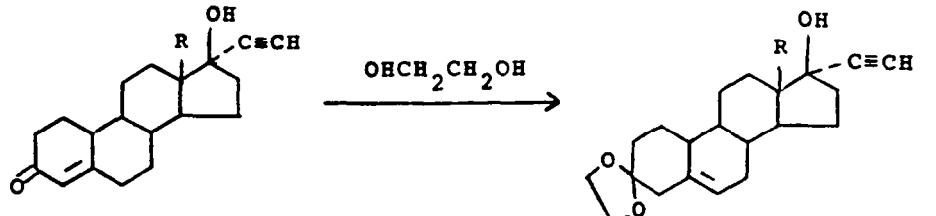
ABSTRACT

Aliphatic, alicyclic and arylcarboxylic esters of norethisterone and levonorgestrel were prepared in a one-step synthesis and in near-quantitative yield using trifluoroacetic anhydride.

INTRODUCTION

The 1975 WHO Programme on steroidal esters as long-acting contraceptive agents prompted the search for efficient methods for the preparation of these compounds (1). More than 200 esters of norethisterone (17α-ethynyl-17β-hydroxyestr-4-en-3-one) and levonorgestrel (13β-ethyl-17α-ethynyl-17β-hydroxygon-4-en-3-one) were synthesized using a variety of methods. One method required protection of the 3-keto function via the ethylenedioxy derivative before esterification of the 17β-alcoholic function [(2), Equation 1]. Others involved the activation of the 17β-hydroxy group by the formation of the lithium [(3), Equation 2] or thallium [(4), Equation 2] salt. The acid for esterification must also be converted to the more reactive corresponding acid chloride [(2-5), Equation 3]. These additional steps generally resulted in poor overall yields of esters.

The most successfully employed method was the thallous ethoxide method of Herz et al (4). Although this method has been employed widely in the synthesis of steroidal esters (mainly norethisterone and levonorgestrel esters), it has certain disadvantages. These are long reaction time, complicated set-up and, most importantly, the presence of thallium in the final product (6), which is not desirable as thallium and its salts are extremely toxic. An alternative method without the use of thallium would therefore be ideal.

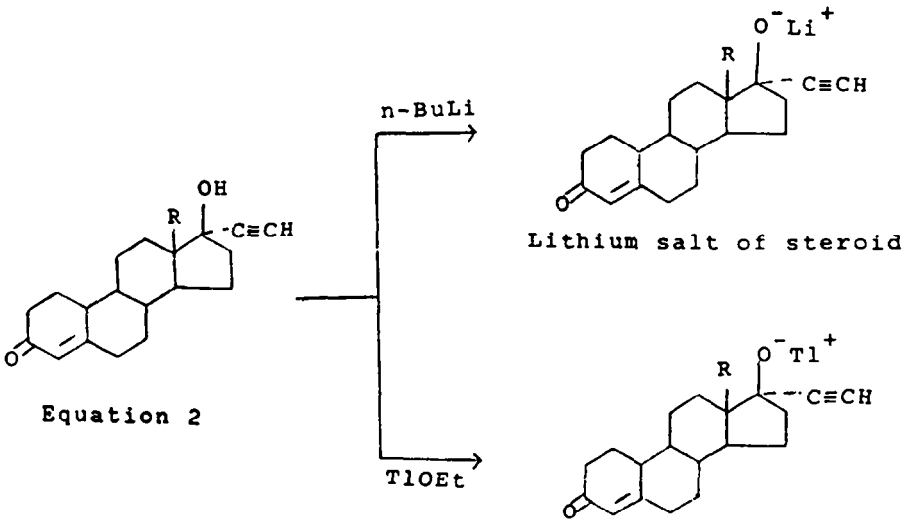


R = $-CH_3$ norethisterone

R = $-C_2H_5$ levonorgestrel

Ethylenedioxy derivative of steroid

Equation 1



Lithium salt of steroid

Thallium salt of steroid

Equation 2

Equation 3 $R'COOH + SOCl_2 \longrightarrow R'COCl$

Although the use of trifluoroacetic anhydride in esterification has been well documented (7), this method has not been applied to the esterification of norethisterone or levonorgestrel. The mechanism involved in this method is shown in Equations 4-6 (8).

$$RCOOH + (CF_3CO)_2O \rightleftharpoons RCOOCOCF_3 \qquad \text{Equation 4}$$

$$RCOOCOCF_3 \rightleftharpoons RCO^+ + CF_3COOH \qquad \text{Equation 5}$$

$$RCO^+ + R'OH \longrightarrow RCOOR' + H^+ \qquad \text{Equation 6}$$

The extraordinary simplicity of this method together with the various advantages quoted in literature (9) has led to a study of its application in the synthesis of norethisterone and levonorgestrel esters.

EXPERIMENTAL

Melting points were determined in a Gallenkamp melting point apparatus and are uncorrected. IR spectra were obtained in pressed KBr discs on a Perkin-Elmer 281 IR Spectrophotometer. UV spectra were determined for 0.001% w/v solutions of esters in 95% ethanol on a Perkin-Elmer Model 551 Spectrophotometer. ^1H NMR spectra were performed at the Department of Chemistry, National University of Singapore, using a Perkin-Elmer R32 NMR Spectrometer. Chemical shifts were reported as ppm (δ) relative to the internal standard TMS (tetramethylsilane) for solutions in $CDCl_3$ (s = singlet, m = multiplet, q = quartet). Elemental analyses were also performed at the above establishment using a Perkin-Elmer Auto Analyzer 240. Specific optical rotations were recorded for 1% w/v solutions in $CHCl_3$ on a Leitz Polarimeter at 20°. Thin-layer chromatography was carried out on standard silica gel plates developed by a mixed solvent system of benzene, hexane and methanol (6:3:1) and spot characterization was by exposure to iodine vapour.

All acids were obtained commercially from the following sources : n-valeric acid, n-hexanoic acid, cycloheptane-carboxylic acid, 2,4,6-trimethylbenzoic acid, phenylacetic

acid from Aldrich Chemical Co.; 2-ethyl-n-butyric acid, 3,3-dimethylbutyric acid, cyclopentanecarboxylic acid, cyclohexanecarboxylic acid from Tokyo Kasei Kogyo Co.; cyclopropanecarboxylic acid and cyclobutanecarboxylic acid from Merck. Trifluoroacetic anhydride was obtained from Aldrich Chemical Co., D-Norgestrel from Balpharm AG and Norethisterone from Schering AG.

GENERAL METHOD

In a dry system, a mixture of acid(6.40mM) and trifluoroacetic anhydride (10.62mM) in 40 ml dry benzene was refluxed for 0.5-2 hours. On cooling to room temperature 1.0 g (3.20 mM) of steroid and 0.5 g anhydrous sodium carbonate were added and reflux resumed until esterification was completed as indicated by TLC. Excess acid in the reaction mixture was removed by adding 10% aqueous sodium bicarbonate solution. The benzene layer was then washed with distilled water until neutral, dried with anhydrous magnesium sulphate and the benzene evaporated off under reduced pressure to yield the crude product which was then purified by recrystallizing in methanol/chloroform. In cases where the crude product was a gum, it was chromatographed on a column of silica gel previously washed with hexane and eluted with a mixture of hexane-ether (4:1) to give the corresponding esters on crystallisation.

Accordingly, the following esters were synthesized:
norethisterone acetate(I) m.p. 160-2° (10)
norethisterone 2-ethyl-n-butanoate(II) m.p. 122-4° (11)
norethisterone 3,3-dimethylbutanoate(III) m.p.154-5°(11)
norethisterone benzoate(IV) m.p. 242-4° (12)
norethisterone phenylacetate(V) m.p. 193-5° (12)
levonorgestrel acetate(VI) m.p. 202-3° (13)
levonorgestrel propionate(VII) m.p. 221-3° (13)
levonorgestrel n-butanoate(VIII) m.p. 211-4°(14)
levonorgestrel n-pentanoate(IX) m.p.168-70° (14)
levonorgestrel n-hexanoate(X) m.p 89-90° (14)
levonorgestrel cyclobutanoate(XII) m.p. 227-9° (14)
levonorgestrelcyclopentanoate(XIII) m.p. 210-2° (14)
levonorgestrelcyclohexanoate(XIV) m.p. 176-8°(14)

Levonorgestrel cyclopropionate (XI):

M.p. : 224-5°

$[\alpha]_D^{20}$: -42.2°

UV : λmax = 244 nm; ε = 11 380

IR : 3220; 2105; 1735; 1655; 1610 cm^{-1}

NMR : 5.83 (1H,s); 2.75-2.7 (1H,q); 2.6 (1H,s); 1.7-1.4 (2H,q); 1.15-0.8 (m)δ

Analysis : $C_{25}H_{32}O_3$ requires C : 78.95%; H : 8.42%
Found C : 78.63%; H : 8.45%

Levonorgestrel cycloheptanoate (XV):

M.p. : 197-9°

$[\alpha]_D^{20}$: -25.3°

UV : λmax = 244.5 nm; ε = 11 001

IR : 3290; 1740; 1665; 1615 cm^{-1}

NMR : 5.84 (1H,s); 2.58 (1H,s); 1.55 (m); 1.10-0.9 (3H,t)δ

Analysis : $C_{29}H_{40}O_3$ requires C : 79.82%; H : 9.17%
Found C : 79.67%; H : 9.31%

Levonorgestrel 2,4,6-trimethylbenzoate (XVI):

M.p. : 177-9°

$[\alpha]_D^{20}$: +61.9°

UV : λmax = 243 nm; ε = 19 469

IR : 3230; 2100; 1730; 1665; 1620 cm^{-1}

NMR : 7.25 (2H,s); 6.8 (2H,s); 5.84 (1H,s); 2.68 (1H,s); 2.32 (6H,s); 2.28 (3H,s); 0.95-0.78 (3H,t)δ

Analysis : $C_{31}H_{38}O_3$ requires C : 81.22%; H : 8.30%
Found C : 79.91%; H : 8.46%

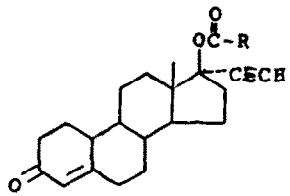
RESULTS AND DISCUSSION

The procedure for esterification was similar to that employed by Solo and Gardner (15) and Parish and Stock (9). The addition of anhydrous sodium carbonate to the reaction mixture (15) proved to be essential because in its absence, the reaction products were usually gummy on work-up.

Table 1 : Reaction times and yields of esters

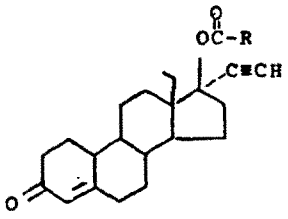
Ester	Esterification time (hours)	Yield (%)
I	0.5	96.5
II	2.5	80.0
III	2.5	74.5
IV	3.0	90.5
V	2.25	82.0
VI	0.5	91.6
VII	1.0	92.4
VIII	1.5	98.4
IX	1.5	98.4
X	2.0	96.2
XI	1.0	95.9
XII	1.5	95.4
XIII	1.75	80.0
XIV	2.0	75.0
XV	2.0	98.7
XVI	3.0	78.0

Esterification was extremely fast in the presence of trifluoroacetic anhydride with most reactions completed within 3 hours (Table 1). Unlike the methods mentioned previously which often required more than 24 hours, this procedure significantly reduced the reaction time. In

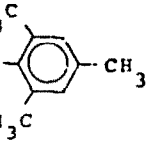


Norethisterone esters

I	R = $-CH_3$	acetate
II	R = $-CH(C_2H_5)_2$	2-ethylbutanoate
III	R = $-CH_2C(CH_3)_3$	3,3-dimethylbutanoate
IV	R = 	benzoate
V	R = $-CH_2-$ 	phenylacetate



Levonorgestrel esters

VI	R = $-CH_3$	acetate
VII	R = $-CH_2CH_3$	propionate
VIII	R = $-(CH_2)_2CH_3$	n-butanoate
IX	R = $-(CH_2)_3CH_3$	n-pentanoate
X	R = $-(CH_2)_4CH_3$	n-hexanoate
XI	R = 	cyclopropionate
XII	R = 	cyclobutanoate
XIII	R = 	cyclopentanoate
XIV	R = 	cyclohexanoate
XV	R = 	cycloheptanoate
XVI	R = 	2,4,6-trimethyl-benzoate (mesitoate)

addition, the yields obtained were generally high, ranging from 75 to 98%. This can be attributed to the fact that the method is a one-step synthesis and that all reactions under investigation went to completion.

Esterification of norethisterone and levonorgestrel was particularly successful with this method. A total of sixteen esters (I-XVI) were synthesized. This was so despite the fact that both steroidal alcohols were tertiary in nature and the steric environment at the 17β position would be expected to be highly non-conducive to esterification.

The acids used in esterification varied widely in nature. They range from the simple straight chain aliphatic acids (I,VI-X) to branched (II,III) and cyclic carboxylic acids (XI-XV). Arylcarboxylic acids with different degrees of substitution were represented by benzoic acid (IV), phenylacetic acid (V) and mesitoic acid (XVI). We have therefore demonstrated that this method works well for both hindered and unhindered acids. It is concluded that this procedure is the method of choice for the esterification of norethisterone and levonorgestrel because of its simplicity, yield and convenience.

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