Convenient Preparation of Esters of Testosterone and 19-Norethisterone with Hindered Acids

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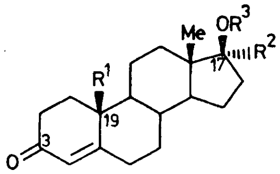
Summary Testosterone and 19-norethisterone are smoothly esterified by some hindered carboxylic acids in pyridine containing benzenesulphonyl chloride.

Esters obtained from testosterone (**1**) and 19-norethisterone (**2**) and hindered carboxylic acids are potentially useful as long-acting antifertility agents.[1,2] Several methods available for their preparation require protection of the 3-keto function,[3] activation of the 17-hydroxy group *via* the lithium[4] or thallium[2] salt, and conversion of the carboxylic acid into the more reactive acid chloride[1,2,4] or anhydride,[5] thus increasing the number of steps and giving poor overall yields of esters.



(**1**) $R^1 = Me, R^2 = R^3 = H$
(**2**) $R^1 = R^3 = H, R^2 = C{\equiv}CH$
(**3**) $R^1 = Me, R^2 = H, R^3 = SO_2Ph$
(**4**) $R^1 = Me, R^2 = H, R^3 = COCH_2Bu^t$
(**5**) $R^1 = Me, R^2 = H, R^3 = COCHEt_2$
(**6**) $R^1 = H, R^2 = C{\equiv}CH, R^3 = COCH_2Bu^t$
(**7**) $R^1 = H, R^2 = C\ CH, R^3 = COCHEt_2$

During our studies to prepare these esters from the unprotected sterol and hindered carboxylic acids by a simple procedure, we investigated the use of benzenesulphonyl chloride as the coupling agent.[6] When esterification of testosterone was attempted with 3,3-dimethylbutyric acid employing the molar ratios recommended by Brewster *et al.*[6] the benzenesulphonate ester (**3**, m.p. 152 °C)† was the major product. However, by changing the molar proportions the desired ester (**4**), uncontaminated with (**3**), was obtained.

When benzenesulphonyl chloride (0·025 mol) was added to the carboxylic acid (0·050 mol) in anhydrous pyridine (15 ml) and left at room temperature for 1 h a heavy anhydride layer separated out. Testosterone (0·0125 mol) in pyridine (15 ml) was then added. After the reaction was complete (t.l.c. control) the product was obtained by the usual work-up procedure. Under these conditions (**2**) was esterified only slowly. However, when the amount of benzenesulphonyl chloride was doubled, under otherwise the same conditions as above, the desired esters were obtained after purification by chromatography (silica–$CHCl_3$; C_6H_6, 1 : 1). These esters were characterised as their 2,4-dinitrophenylhydrazone derivatives (see Table).

TABLE

Steroid	Acid	Reaction time/h	Ester	Yield/%[a]	$[\alpha]^{28}$/° ($CHCl_3$)	M.p./°C[b] Ester	M.p./°C[b] 2,4-DNP derivative
(**1**)	$Bu^tCH_2CO_2H$	72	(**4**)	72	+75	135—137	—
(**1**)	Et_2CHCO_2H	72	(**5**)	70	+80	127—129[c]	—
(**2**)	$Bu^tCH_2CO_2H$	48	(**6**)	55	−45	oil	158—160
(**2**)	Et_2CHCO_2H	48	(**7**)	50	−38	oil	159—161

[a] Isolated yield. [b] 2,4-DNP = 2,4-dinitrophenylhydrazone. [c] lit. (ref. 1), m.p. 129—130 °C; $[\alpha]_D$ +78°.

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† The composition of all new compounds was confirmed by elemental analysis and/or by mass spectrometry. Structural assignments are based upon i.r. and n.m.r. spectroscopic evidence.

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