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

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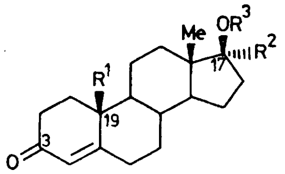
Summary Testosterone and 19-norethisterone are smoothly esterified by some hindered carboxylic acids in pyridine containing benzenesulphonyl chloride.

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.

TABLE

Steroid	Acid	Reaction time/h	Ester	Yield/%[a]	$[\alpha]^{28}$/° (CHCl$_3$)	M.p./°C[b]	
						Ester	2,4-DNP derivative
(**1**)	$\mathrm{Bu^tCH_2CO_2H}$	72	(**4**)	72	+75	135—137	—
(**1**)	$\mathrm{Et_2CHCO_2H}$	72	(**5**)	70	+80	127—129[c]	—
(**2**)	$\mathrm{Bu^tCH_2CO_2H}$	48	(**6**)	55	−45	oil	158—160
(**2**)	$\mathrm{Et_2CHCO_2H}$	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°.

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$_6$H$_6$, 1:1). These esters were characterised as their 2,4-dinitrophenylhydrazone derivatives (see Table).

We thank the World Health Organisation for financial support, and Dr. K. J. Toyne (University of Hull) and Mr. B. M. R. Bandara (Australian National University) for providing mass spectral and microanalytical data.

(*Received, 7th July* 1978; *Com.* 722.)

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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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