Dieckmann Condensation for Preparation of A-Nor-steroids

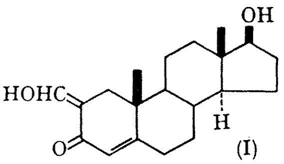
By KITARO OKA and SHOJI HARA*

(*Division of Organic Chemistry, Tokyo College of Pharmacy, Ueno-sakuragi* 1-*chome, Taito-ku, Tokyo* 110, *Japan*)

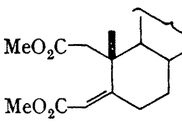
EARLY workers stated that the Dieckmann condensation of an $\alpha\beta$-unsaturated diester such as (II) was not successful for the preparation of A-nor-steroids.[1]

We report an improved Dieckmann condensation applicable to steroidal $\alpha\beta$-unsaturated esters [*e.g.* (II)] and also to the saturated 5β-series, resulting in the corresponding A-nor-steroids in good yields. We used sodium hydride in toluene and methanol to cause cross-conjugation of the diester, and then decarboxylated the resultant 3-methoxycarbonyl-ketone.

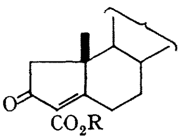
The diester (II)[2] was prepared in 75% yield from 2-hydroxymethylenetestosterone (I)[3] by a modification of Weisenborn's method: the mixture of acetic acid and ethyl acetate used as solvent for the ozonolysis was neutralized with an equimolar amount of sodium hydrogen carbonate after the reaction, and the dicarboxylic acid solution was directly methylated with diazomethane. The dimethyl ester (II) was heated under reflux in toluene with an excess of sodium hydride and methanol for 2 hr. to give compound (IIIa) in 90% yield; m.p. 174—176°. Since no reaction occurred with sodium hydride or sodium powder in the absence of methanol, the mechanism probably involves the methoxy-anion (V) as an intermediate.



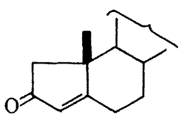
(I)



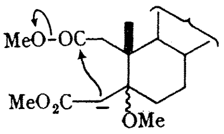
(II)



(III) a, R=Me
b, R=Me



(IV)



(V)

Mild hydrolysis of the ester (IIIa) with an equimolar quantity of sodium hydroxide in 50% aqueous acetone overnight afforded the carboxylic acid (IIIb) in 85% yield. The acid was decarboxylated by heating it at 190° in ethylene glycol for 1 hr. to give A-nor-testosterone (IV), m.p. 175—177°, shown to be identical with an authentic sample[2] by comparison of i.r. and u.v. spectra and mixed m.p.

The same reaction conditions were used for the preparation of a 5β-A-nor-steroid in 80% overall yield. We previously reported the same reaction with 5α-3-oxo-steroids.[4]

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