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Review

Synthesis and chemical reactions of the steroidal hormone 17α-methyltestosterone

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ABSTRACT

Structural modifications of natural products with complex structures like steroids require great synthetic effort. A review of literature is presented on the chemistry of the steroidal hormone 17α-methyltestosterone that is approved by Food and Drug Administration (FDA) in the United States as an androgen for estrogen–androgen hormone replacement therapy treatment. The analog also offers special possibilities for the prevention/treatment of hormone-sensitive cancers. The testosterone skeleton has important functionalities in the molecule that can act as a carbonyl component, an active methylene compound, α, β-unsaturated enone and tertiary hydroxyl group in various chemical reactions to access stereoisomeric steroidal compounds with potent activity. In addition, microbiological methods of synthesis and transformation of this hormone are presented.

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1. Introduction

Steroid nucleus consists of four fused rings, most often one five-membered and three six-membered carbocycles with a total of 17 carbon atoms. Among steroid molecules, there are great variations in structures encompassing compounds of vital importance to life which involve sterols, bile acids, vitamin D group, adrenocortical hormones, sex hormones, cardenolides, bufadienolides, sapogenins, insect molting hormones and antibiotics. They are associated with a variety of physiological functions in the cells. Sterols are modulators of cell membrane fluidity. Cholesterol, as an example, is the parent molecule of steroid metabolism. Bile acids are essential for lipid digestion and cholesterol elimination. Mineralocorticoids are regulators of blood volume and renal excretion, whereas glucocorticoids are regulators of metabolism and immune functions. Androgens and estrogens are sex hormones [1].

Until recently, the synthesis of steroidal compounds is of noticeable scientific interest. Synthetic steroidal enantiomers were thought for a long time to be devoid of biological activity, yet late publications have recommended that enantiomers may be active though not via the typical steroid receptor route [2]. Estradiol, androgens and progesterone enantiomers have all been demonstrated to have neuroprotective activities as antioxidants or by GABA receptors [3–8]. Heterocycles fused to the steroid nucleus such as pyrazole, pyrimidine, pyridine, isoxazoline and oxazoline systems have been found to possess antimicrobial, hypotensive, anabolic, anti-estrogenic and anti-proliferative agents against LNCaP, PC-3 and DU-145 Cells [9–12]. Steroidal glycoside is found to exhibit anti-viral activity on herpes virus type [13].

Substitution of the 17α-H on the testosterone nucleus with a methyl group to make 17α-methyltestosterone (**1**) can definitely confer oral activity. On first-pass metabolism of methyltestosterone, 17α-methyl group prevents deactivation of it by sterically hindering oxidation of the 17β-hydroxyl group. Although some products derived from the testosterone scaffold are utilized as anabolic steroids in numerous countries worldwide, they last to be accessible as pharmaceutical preparations in others, for example methyltestosterone (**1**), methandienone (**2**), oxandrolone (**3**) and stanozolol (**4**) (Table 1). Currently, testosterone, nandrolone (**5**) and oxymetholone (**6**) are available as licensed products for human use in the United Kingdom (Table 1). Body builders and sports competitors can administer boldenone (**7**) and trenbolone (**8**) in