PREPARATION OF HIGHLY HINDERED STEROID ESTERS; APPLICATION OF SOME NEWER METHODS OF ESTERIFICATION

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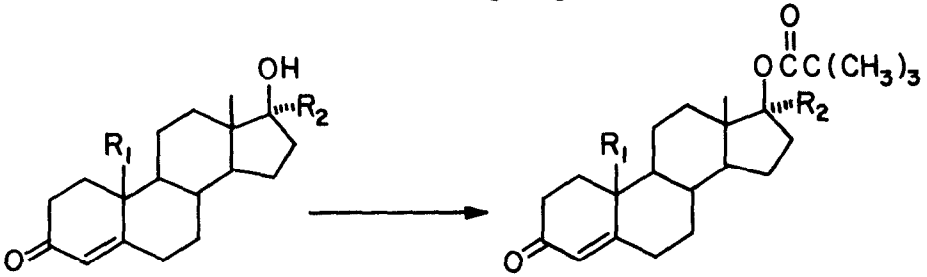
ABSTRACT

The scope and limitation of some recent acylation methods were investigated as applied to the preparation of steroidal esters of highly hindered acids. As representative steroids, 19-nor-17α-ethinyl testosterone (19-NET) and testosterone, and as representative acid, pivalic (trimethylacetic) acid were used.

INTRODUCTION

The esters of highly hindered acids and 19-nor-17α-ethinyltestosterone (19-NET) are potentially useful as long-acting anti-conceptive agents in the female (1). Similar esters of testosterone may have applications as long-acting male anti-fertility agents and therapeutic androgens. Large doses of testosterone given over a prolonged period of time produce suppression of spermatogenesis, while in combination with a gestagen the two classes of compounds act synergistically to decrease sperm production, enabeling the dosage of each to be markedly reduced. The addition of the androgen to the gestagen also overcomes a decrease in libido which would be seen if the gestagen were used alone (2).



I $R' = CH_3$, $R^2 = H$ Testosterone

II $R' = H$, $R^2 = -C \equiv CH$ 19-NET

Conventional esterification methods, such as the reaction of an acid chloride with the steroidal alcohol in presence of pyridine fail to give such esters of 19-NET. Recently, three methods for the preparation of highly hindered esters of 19-NET have been published:(a) the reaction of 19-NET with an acid chloride in the presence of thallous ethoxide (3),(b) the reaction of the lithium salt of 19-NET ethylene ketal with the acid chloride (4) and(c) esterification of 19-NET with a carboxylic acid using benzenesulfonyl chloride as coupling agent (5). Novel esterification methods utilizing the following coupling agents have also been recently described:(d) silver cyanide (6),(e) 4-dimethylaminopyridine (7),(f) 2-bromo-1-methylpyridinium iodide (8),(g) 2-bromo-1-ethylpyridinium tetrafluoroborate (8) and(h) trifluoroacetic anhydride (9). Methods(d) to(h) had not been previously used to esterify steroidal alcohols with hindered acids. In this publication we describe the results of applying methods(c) to(h) to the preparation of 19-NET pivalate and testosterone pivalate, and compare them with those of methods(a) and(b).

RESULTS AND DISCUSSION

The Table 1 compares the yields of testosterone pivalate and 19-NET pivalate obtained with the different methods. The reactions were carried out under the general conditions described in the literature. If necessary, reaction times and temperature were modified to give higher yields. The yields of the esters were determined by quantitative TLC comparison with authentic samples or isolation by chromatography on a silica gel column.

CONCLUSION

For the preparation of 19-NET pivalate, method (a)(thallous ethoxide as coupling agent)(2) gives the highest yield, followed by method (b). None of the other methods gave acceptable yields. Comparable results can be expected with similar highly hindered acids. As could be foreseen, the yields are much higher when testosterone is used as the steroidal alcohol. In this case methods (f) and (h) may be more advantageous than (a) since they utilize the free acid instead of the acid chloride.

T a b l e 1: Esterification of Testosterone (I), 19-Norethisterone (II) with Pivalic Acid or Chloride.

	Coupling Agent	Acid Component	Steroid	Reaction time and temperature	Yield of testosterone and 19-NET ester (%)
(a)	Thallous Ethoxide	Chloride	Testosterone	2 h, 80°	90 Isolated
			19-NET	2 h, 80°	80 Isolated
(b)	n-Butyl Lithium	Chloride	19-NET		
			3-KETAL	5 h, 55°	60 Isolated
(c)	Benzenesulfonyl Chloride	Free Acid	Testosterone	3 d, 20°	20 Isolated
			19-NET	10 d, 20°	5 TLC
(d)	Silver Cyanide	Chloride	Testosterone	4 d, 80°	70 Isolated
			19-NET	4 d, 80°	8 Isolated
(e)	4-Dimethylamino pyridine	Chloride	Testosterone	1 d, 20°	53 Isolated
			19-NET	1 d, 20°	5 TLC
(f)	2-Bromo-1-methyl pyridinium Iodide	Free Acid	Testosterone	1 d,100°	80 Isolated
			19-NET	5 d,100°	10-15 TLC
(g)	2-Bromo-1-ethyl pyridinium Tetrafluoro borate	Free Acid	Testosterone	7 d, 20°	5 TLC
(h)	Trifluoroacetic Anhydride	Free Acid	Testosterone	5 min, 20°	83+Isolated
			19-NET	5 min, 20°	10-15+TLC

+ With longer reaction times the formed ester decomposed.

EXPERIMENTAL PART

Thallous ethoxide:

Method (a): The reaction was carried out under the same conditions as described in Herz et al (3). Testosterone (2 g), 2.1 g thallium(I) ethoxide and 1.26 g of pivalyl chloride were allowed to react in 150 ml of benzene. After work-up the product was crystallized from ether to give testosterone pivalate mp. 159-60°C $|\alpha_D|$ + 90°(Chf) λ_{max}^{EtOH} 245 nm (log ε = 4.48).

In a similar fashion 19-nor-17α-ethinyltestosterone pivalate mp. 221-2°C, $|\alpha|_D$ - 40°(Chf) λ_{max}^{EtOH} 241 nm, log ε = 3.78 was obtained. The product was purified by column chromatography on silicagel.

Benzenesulfonyl chloride (5)

Method (c): A solution of 408 mg (4 mmoles) of pivalic acid and 354 mg (2 mmoles) of benzenesulfonyl chloride in 1.5 ml of pyridine was left 2 hours at room temperature. A solution of 288 mg (1 mmole) of testosterone in 1.5 ml of pyridine was added. After standing 3 days at room temperature the product was worked up in the usual way and the product isolated by SiO_2 column chromatography. Yield: 20% under the literature conditions. After 10 days of reaction, less than 5% of 19-NET pivalate (TLC) was obtained.

Silver cyanide (6)

Method (d): A mixture of 1 mmole of testosterone, 1 mmole of pivalyl chloride, 300 mg (2.24 mmoles) of silver(I)cyanide and 2 ml of benzene was heated under reflux with agitation for 4 days. After the usual work up, and column chromatography on SiO_2 a 70% yield of the product was obtained. Under the same conditions, 19-NET gave an 8% yield by isolation.

4-Dimethylaminopyridine (7)

Method (e): A solution of 1 mmole of testosterone, 1 mmole of (125 mg) 4-dimethylaminopyridine, 1 ml of pyridine and 1.5 mmoles (180 mg) of pivalyl chloride in 4 ml of chloroform was left 24 hours at room temperature. After work up and column chromatography the ester was obtained in 53% yield.

Under the same conditions 19-NET was transformed into its pivalyl ester in less than 5% yield (TLC).

2-Bromo-1-methylpyridinium iodide (8)

Method (f): A suspension of 1 mmole of pivalic acid, 1 mmole of testosterone, 1.2 mmoles (360 mg) of 2-bromo-1-methylpyridinium iodide and 2.4 mmoles (0.6 ml) of tri-n-butylamine in 1 ml of toluene was heated 24 hours under an argon atmosphere at 100°C. After the usual work-up the testosterone ester was obtained in 80% yield by column chromatography.

19-NET under identical conditions yielded 10-15% ester (TLC).

2-Bromo-1-ethylpyridinium tetrafluoroborate (8)

Method (g): A mixture of 1 mmole of testosterone, 1 mmole of pivalic acid, 1.2 mmoles (330 mg) of 2-bromo-1-ethyl pyridinium tetrafluoroborate, 2.4 mmoles (0.6 ml) of tri-n-butylamine and 2 ml of methylene chloride was stirred 7 days at room temperature under an argon atmosphere. The yield of ester was less than 5% (TLC).

Trifluoracetic anhydride (9)

Method (h): A solution of 1.1 mmoles of pivalic acid and 3.6 mmoles (0.5ml) of trifluoracetic anhydride in 5 ml of benzene was stirred 20 min at 40°C. Then 1 mmole of testosterone was added and the mixture was stirred 5 min at room temperature. After the usual work up, testosterone pivalate was obtained in 83% yield.

When 19-NET was used as the steroidal alcohol, under identical conditions, a yield of 15% (TLC) of 19-NET pivalate was obtained.

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REFERENCES

1. Sixth Annual Report, Special Programme of Research, Development and Research Training in Human Reproduction, WHO, 1977, p. 29.
2. Seventh Annual Report, Special Programme of Research, Development and Research Training in Human Reproduction, WHO, 1978, p. 91.
3. Herz, J.E., Cruz, S., Torres, J.V., Murillo, A., Synth. Commun., 7 (6), 383 (1977).
4. Herz, J.E., Cruz, S., Murillo, A., Steroids, 30 (1), 111 (1977).
5. Leslie Gunatilaka, A.A., Sotheeswaran, S., J.C.S. Chem. Commun., 22, 980 (1978).
6. Takimoto, S., Inanaga, J., Katsuki, T., Yamaguchi, M., Bull. Chem. Soc. Japan, 49, 2335 (1976).
7. Hoefle, G., Steglich, W., Vorbruggen, H., Angew. Chem. Int. Ed. English, 569 (1978).
8. Saigo, K., Usui, M., Kikuchi, K., Shimada, E., Mukaiyama, T., Bull. Chem. Soc. Japan, 50, 1863 (1977).
9. Parish, R.C., Stock, L.M., J. Org. Chem., 20, 927 (1965).