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SIMPLE SYNTHESES OF STEROIDAL 17β-(2'-THIAZOLYL) DERIVATIVES*

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Abstract: *The utilisability of two general methods of thiazole synthesis (Hantzsch and Gabriel reactions) was proved in the preparation of 4'- and 5'-substituted 17β-(2'-thiazolyl)androstenes.*

Among semisynthetic steroidal heterocycles 2'-substituted 17β-(4'-thiazolyl)-androstanes have received more attention due to their antiarrhythmic[2], cardiotonic[3-5], and cytostatic[6] activities. Therefore it seemed interesting to prepare and test other types of steroids bearing the thiazole moiety. We report a procedure for the preparation of steroidal alcohols linked in the 17β-position to the 2'-carbon atom of the thiazole ring (**6a-e** and **10a-e**).

The key compound in the synthesis of 4'-substituted 3β-acetoxy-17β--(2'-thiazolyl)androst-5-enes (**5a-e**) was the thioamide **3** which was obtained by thionation of 3β-acetoxyandrost-5-ene-17β-carboxamide (**2**)[7] with phosphorus pentasulfide. The conversion is, however, accompanied with considerable dehydration yielding the nitrile **4** even under very mild conditions. Best results were achieved

*This communication has been presented in part[1].
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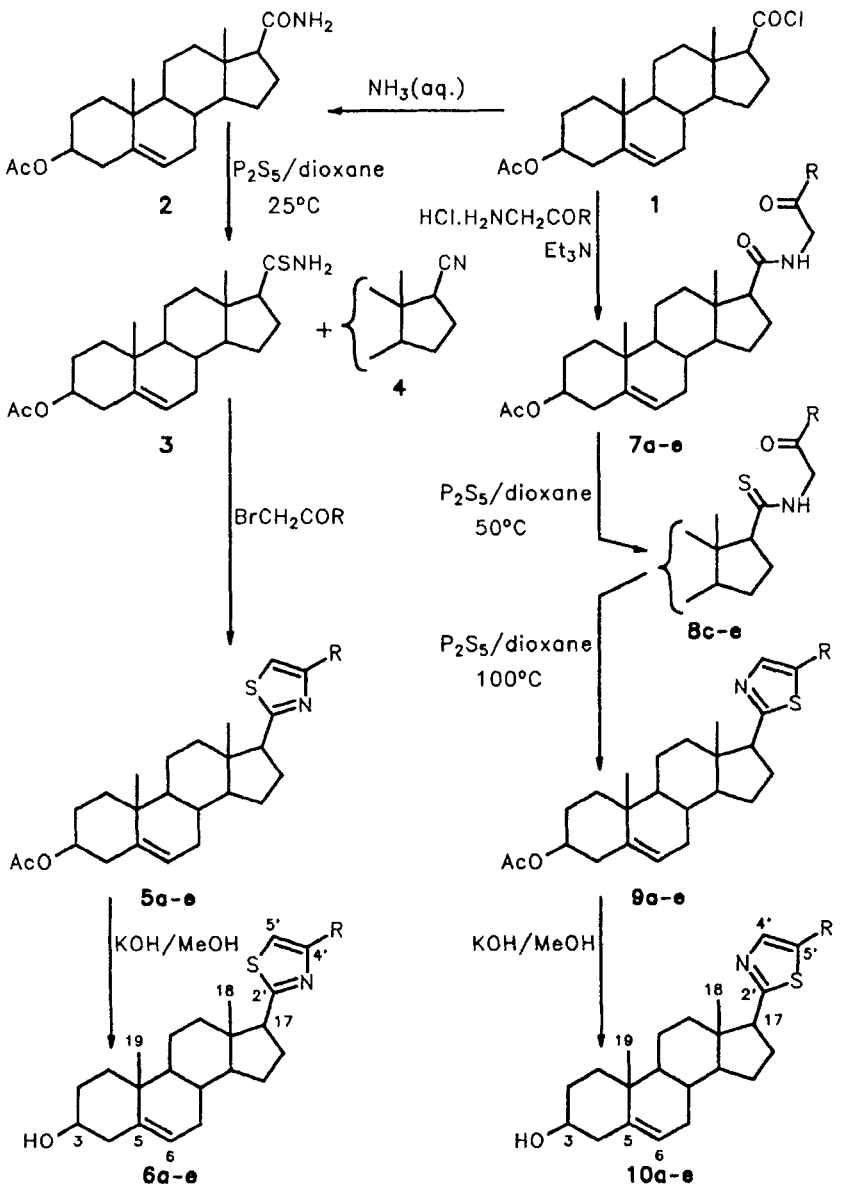

a: R = Ph, b: R = Me, c: R = OMe, d: R = OEt, e: R = OPr

when one equivalent of phosphorus pentasulfide was stirred with one equivalent of **2** in dioxane at room temperature for 5 hours. The chromatographic separation afforded 62% of the thioamide **3** and 30% of the nitrile **4**. Hantzsch reaction[8] of **3** with 2-bromoacetophenone as well as with bromoacetone in benzene solution proceeded smoothly giving 4'-phenylthiazole **5a** and 4'-methylthiazole **5b**. Condensation of **3** with less reactive methyl, ethyl, and propyl bromoacetates was successfully performed in alcohols (methanol, ethanol, and 1-propanol), in agreement with the fact that ethanol has been recently found to be the solvent of choice for synthesis of 17β-(4'-thiazolyl)androstanes by Hantzsch reaction[6]. In this case the liberated hydrogen bromide catalysed the removal of the acetate protecting group at C-3. Thus, besides 3β-acetoxy-17β-(4'-alkoxy-2'-thiazolyl)androst-5-enes (**5c-e**), considerable amounts of deprotected alcohols **6c-e** were isolated.

Deprotection of the 3β-hydroxy group of compounds **5a-e** with potassium hydroxide in methanol afforded the desired alcohols **6a-e**.

For the preparation of isomeric 5'-substituted 3β-acetoxy-17β-(2'-thiazolyl)-androst-5-enes **9a-e** Gabriel thiazole synthesis[9,10] appears to be particularly valuable. Hydrochlorides of aminoacetone, 2-aminoacetophenone, methyl, ethyl, and propyl glycinate were acylated by chloride **1**[7] in the presence of triethylamine affording the α-acylamino carbonyl compounds **7a-e**. Reaction of the amide **7a** with phosphorus pentasulfide in refluxing dioxane furnished the thiazole **9a**. Phenyl derivative **9b** was achieved from **7b** in the same way. The N-methoxycarbonylmethylcarboxamide **7c** under these conditions underwent partial decomposition and only small amounts of the 5'-methoxythiazole **9c** and the acyclic intermediate **8c** were isolated. We found that the acyclic thioamides **8c-e** were formed as main products when phosphorus pentasulfide was stirred with N-alkoxycarbonylmethylcarboxamide in dioxane at 50°C for 4 hours. Subsequent short heating of the reaction mixture to 100°C resulted in the cyclization to thiazoles **9c-e**.

Finally, the acetates **9a-e** were treated with methanolic potassium hydroxide affording alcohols **10a-e**.

Table 1: ^{1}H-NMR Spectral Parameters of Thiazoles **9**, **10**

No.	H-3 (1H)	H-6 (1H)	H-17 (1H)	H-18 (3H)	H-19 (3H)	H-4' (1H)	H-5' (1H)	thiazole substituent
6a	3.53m W=32	5.38bd J=4.5	3.07t J=10	0.60s	1.02s	-	7.34s	7.92m (2H) W=11 7.38m (3H) W=29
6b	3.54m W=31	5.36bd J=4.5	3.01t J=10	0.56s	1.01s	-	6.72s	2.43s (3H)
6c	3.54m W=31	5.37bd J=4.5	2.92t J=10	0.57s	1.01s	-	5.89s	3.86s (3H)
6d	3.53m W=32	5.36bd J=4.5	2.91t J=10	0.57s	1.01s	-	5.87s	4.09q (2H) J=7.0 1.44t (3H) J=7.0
6e	3.53m W=31	5.37bd J=4.5	2.92t J=10	0.57s	1.01s	-	5.87s	3.97t (2H) J=6.6 1.05t (3H) J=7.2
10a	3.53m W=32	5.36bd J=4.5	3.03t J=10	0.62s	1.02s	7.87s	-	7.55m (2H) W=10 7.36m (3H) W=15
10b	3.54m W=32	5.36bd J=4.5	2.96t J=10	0.57s	1.01s	7.34s	-	2.43s (3H)
10c	3.53m W=32	5.36bd J=4.5	2.83t J=10	0.59s	1.01s	6.94s	-	3.88s (3H)
10d	3.53m W=32	5.35bd J=4.5	2.83t J=10	0.59s	1.01s	6.95s	-	4.08q (2H) J=7.0 1.41t (3H) J=7.0
10e	3.53m W=32	5.36bd J=4.5	2.84t J=10	0.59s	1.01s	6.95s	-	3.97t (3H) J=6.5 1.01t (3H) J=7.4

Physical properties and spectral data of the products **6a-e** and **10a-e** are given in Tables 1, 3, and 4. Table 1 lists the ^{1}H-NMR data for 10 steroidal thiazoles prepared in which the chemical shift of the 5'-thiazole proton (in **6a-e**) ranges from δ = 5.87 to δ = 7.34 and the 4'-thiazole proton (in **10a-e**) exhibits signals from δ = 6.95 to δ = 7.87 depending on the substituent on the thiazole ring. The chemical shift of the H-17 proton signal (δ = 2.83 - 3.07) and its multiplicity (t, J=10) indicate that in all the compounds the thiazole moiety is bonded to the steroid system in the same stereochemical way. IR spectral data (Table 4) generally contain bands at 1521 - 1540, 1602 - 1605 cm^{-1} (thiazole ring) and 1042 - 1044, 3604 - - 3610 cm^{-1} (hydroxy group). The structure of thiazoles is confirmed also by their mass spectra (Table 4) which exhibit loss of methyl (m/z M-15) of the steroid part of the molecule and the fragments containing the thiazole grouping together with fragments of D-ring.

Biological data of the compounds prepared will be reported elsewhere.

Experimental:

Melting points were determined on a Boëtius melting point microscope and are uncorrected. Optical rotations were measured in chloroform at 23-25°C on an Opton polarimeter with an error of ±3°, IR spectra on a Perkin-Elmer PE 580 spectrometer (wavenumbers in cm^{-1}). ^{1}H-NMR spectra were taken on a Tesla BS-497 (FT mode, 100 MHz) and on a Varian XL-200 (FT mode, 200 MHz) instruments at 23°C in deuteriochloroform with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (J) and widths of multiplets (W) in Hz. All parameters were obtained by first order analysis. Electron impact mass spectral measurements were made on a VG Analytical ZAB-EQ (70 eV) instrument.

The reaction course was followed, and purity of the samples checked, by thin-layer chromatography on silica gel (ICN Biochemicals), spots were detected with sulfuric acid and heating. Flash column chromatography was performed on silica gel Silpearl (Kavalier, Votice) or on neutral alumina (Reanal, activity II).

Phosphorus pentasulfide dest. was purchased from Fluka AG. Benzene and dioxane were dried by distillation from sodium, dichloromethane was distilled from phosphorus pentoxide. All other reagents were purchased commercially and used without further purification.

3β-Acetoxyandrost-5-ene-17β-thiocarboxamide (3)

Phosphorus pentasulfide (1.85 g, 8.3 mmol) was added to a solution of the amide **2**[7] (3.00 g, 8.3 mmol) in anhydrous dioxane. The mixture was stirred under argon at room temperature for 5 hours. The slurry was then filtered through a column of alumina (30 g) and washed with ether (600 mL). Solvents were removed in vacuo and the residue was chromatographed on a column of silica gel (100 g) in chloroform-ethyl acetate (9:1). The first fraction afforded 860 mg (30%) of the nitrile **4** whose properties were identical to those published[7]. The more polar fraction gave 1.94 g (62%) of the thioamide **3**; m.p. 252-253°C (acetone); $[\alpha]_D^{25}$-64°(c 1.4, chloroform). IR: 3494, 3377, 1599 (NH_2); 1333 (C=S); 1725, 1255, 1033 (AcO). ^{1}H-NMR (200 MHz): 7.52 and 6.68 (bs, each 1H, NH_2), 5.38 (bd, 1H, H-6, J=4.5), 4.60 (m, 1H, H-3, W=31), 2.04 (s, 3H, CH_3COO), 1.03 (s, 3H, 19-CH_3), 0.76 (s, 3H, 18-CH_3). MS, m/z(%): 375(3), 315(87), 300(18), 281(100), 266(31). For $C_{22}H_{33}NO_2S$ (375.6) calculated 70.36%C, 8.86%H, 3.73%N, 8.54%S; found 70.05%C, 8.78%H, 3.73%N, 8.58%S.

3β-Acetoxy-17β-(4'-phenyl-2'-thiazolyl)androst-5-ene (5a)

A suspension of the thioamide **3** (1.0 g, 2.7 mmol) and 2-bromoacetophenone (636 mg, 3.2 mmol) in 100 mL of dry benzene was stirred at room temperature for 2 hours. The mixture was then heated for 2 min to the boiling point with 8 g of alumina. The solvent was evaporated and the solid residue applied on a column of silica gel (60 g). Chromatography with light petroleum-ethyl acetate (9:1) afforded 960 mg (76%) of the thiazole **5a**; m.p. 146-148°C (methanol); $[\alpha]_D^{24}$-64°(c 1.6, chloroform). IR: 1603, 1520, 1490, 1445 (aromatic rings); 1725, 1255, 1033 (AcO).

^{1}H-NMR (200 MHz): 7.93 (m, 2H, aromatic H, W=10), 7.38 (m, 3H, aromatic H, W=29), 7.34 (s, 1H, thiazole H-5'), 5.40 (bd, 1H, H-6, J=4.5), 4.62 (m, 1H, H-3, W=31), 3.08 (t, 1H, H-17, J=10), 2.04 (s, 3H, CH_3COO), 1.04 (s, 3H, 19-CH_3), 0.61 (s, 3H, 18-CH_3). MS, m/z(%): 475(3), 460(3), 415(85), 400(73), 188(100), 175(96). For $C_{30}H_{37}NO_2S$ (475.7) calculated 75.75%C, 7.84%H, 2.94%N, 6.74%S; found 75.86%C, 7.74%H, 2.89%N, 6.94%S.

3β-Acetoxy-17β-(4'-methyl-2'-thiazolyl)androst-5-ene (5b)

The same procedure described above using bromoacetone (438 mg, 3.2 mmol) afforded 705 mg (64%) of the thiazole **5b**; m.p. 154-157°C (methanol); $[\alpha]_D^{24}$-74° (c 1.5, chloroform). IR: 1725, 1255, 1033 (AcO); 1531 (thiazole). ^{1}H-NMR (200 MHz): 6.72 (s, 1H, thiazole H-5'), 5.39 (bd, 1H, H-6, J=4.5), 4.60 (m, 1H, H-3, W=32), 3.01 (t, 1H, H-17, J=10), 2.43 (s, 3H, CH_3), 2.04 (s, 3H, CH_3COO), 1.02 (s, 3H, 19-CH_3), 0.56 (s, 3H, 18-CH_3). MS, m/z(%): 413(2), 398(6), 353(95), 338(94), 126(100), 113(92). For $C_{25}H_{35}NO_2S$ (413.6) calculated 72.60%C, 8.53%H, 3.39%N, 7.75%S; found 72.62%C, 8.41%H, 3.20%N, 7.84%S.

General procedure for the preparation of 5c-e

A solution of the thioamide **3** (1.0 g, 2.7 mmol) and the corresponding bromoacetate (2.9 mmol) in 50 mL of the appropriate alcohol was refluxed under argon for 1h. The mixture was then concentrated to about one-third of the volume and poured into water (70 mL). The volatile substances were removed by steam distillation and the residue treated with ether (200 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and the solvent evaporated. Chromatography on silica gel (50 g) with light petroleum-ethyl acetate (95:5 to 8:2) afforded acetates **5c-e** and the free 3β-alcohols **6c-e** in more polar fractions.

3β-Acetoxy-17β-(4'-methoxy-2'-thiazolyl)androst-5-ene (5c)

From thioamide **3** (1.0 g, 2.7 mmol) and methyl bromoacetate (448 mg, 2.9 mmol) in methanol 314 mg (27%) of **5c** and 360 mg (35%) of **6c** were obtained.

Compound **5c**: m.p. 196-198°C (methanol); $[\alpha]_D^{23}$-70°(c 1.5, chloroform). IR: 1725, 1255, 1033 (AcO); 1537 (thiazole). ^{1}H-NMR (200 MHz): 5.89 (s, 1H, thiazole H-5'), 5.38 (bd, 1H, H-6, J=4.5), 4.61 (m, 1H, H-3, W=31), 3.86 (s, 3H, CH_3O), 2.91 (t, 1H, H-17, J=10), 2.03 (s, 3H, CH_3COO), 1.01 (s, 3H, 19-CH_3), 0.56 (s, 3H, 18-CH_3). MS, m/z(%): 429(9), 414(14), 369(50), 354(100), 142(95), 129(60). For $C_{25}H_{35}NO_3S$ (429.6) calculated 69.89%C, 8.21%H, 3.26%N, 7.46%S; found 69.84%C, 8.22%H, 3.15%N, 7.22%S.

3β-Acetoxy-17β-(4'-ethoxy-2'-thiazolyl)androst-5-ene (5d)

From thioamide **3** (910 mg, 2.4 mmol) and ethyl bromoacetate (434 mg, 2.6 mmol) in ethanol 505 mg (47%) of **5d** and 214 mg (22%) of **6d** were obtained. Compound **5d**: m.p. 173-175°C (methanol); $[\alpha]_D^{24}$-66°(c 1.7, chloroform). IR: 1725, 1255, 1034 (AcO); 1533 (thiazole). ^{1}H-NMR (200 MHz): 5.84 (s, 1H, thiazole H-5'), 5.39 (bd, 1H, H-6, J=4.5), 4.61 (m, 1H, H-3, W=32), 4.09 (q, 2H, $CH_3\underline{CH_2}O$, J=7), 2.91 (t, 1H, H-17, J=10), 2.03 (s, 3H, CH_3COO), 1.44 (t, 3H, $\underline{CH_3}CH_2O$, J=7), 1.02 (s, 3H, 19-CH_3), 0.57 (s, 3H, 18-CH_3). MS, m/z(%): 443(10), 428(6), 385(52), 368(100), 156(98), 143(79). For $C_{26}H_{37}NO_3S$ (443.7) calculated 70.39%C, 8.41%H, 3.16%N, 7.23%S; found 70.39%C, 8.44%H, 3.04%N, 7.41%S.

3β-Acetoxy-17β-(4'-propoxy-2'-thiazolyl)androst-5-ene (5e)

From thioamide **3** (1.0 g, 2.7 mmol) and propyl bromoacetate (525 mg, 2.9 mmol) in 1-propanol 379 mg (32%) of **5e** and 483 mg (44%) of **6e** were obtained. Compound **5e**: m.p. 103-104°C (methanol); $[\alpha]_D^{24}$-64°(c 1.5, chloroform). IR: 1725, 1255, 1032 (AcO); 1531 (thiazole). ^{1}H-NMR (200 MHz): 5.86 (s, 1H, thiazole H-5'), 5.39 (bd, 1H, H-6, J=4.5), 4.60 (m, 1H, H-3, W=32), 3.97 (t, 2H, $CH_3CH_2\underline{CH_2}O$, J=6.6), 2.92 (t, 1H, H-17, J=10), 2.03 (s, 3H, CH_3COO), 1.04 (t, 3H, $\underline{CH_3}CH_2CH_2O$, J=7.6), 1.02 (s, 3H, 19-CH_3), 0.57 (s, 3H, 18-CH_3). MS, m/z(%): 457(10), 442(7), 397(52), 382(100), 170(98), 157(81). For $C_{27}H_{39}NO_3S$ (457.7) calculated 70.86%C, 8.59%H, 3.06%N, 7.01%S; found 71.05%C, 8.53%H, 2.91%N, 6.92%S.

General procedure for the preparation 6a-e

An aqueous solution of potassium hydroxide (200 mg in 1 mL H_2O) was added to a solution of the acetate **5a-e**, (200 mg) in methanol (50 mL). The mixture was allowed to stand at room temperature for 24 h. Solvents were evaporated, the residue was diluted with water (100 mL) and extracted with ethyl acetate. The extract was washed successively with 5% hydrochloric acid (50 mL), 5% aqueous sodium hydrogen carbonate (50 mL), water, dried over sodium sulfate, and the solvent was evaporated affording **6a-e**. Analytical samples were obtained by crystallization of the solid residues in methanol. Yields of **6a-e** and **10a-e** prepared from **9a-e** by the same procedure are given in Table 2.

General procedure for the preparation of 7a-e

A solution of 3β-acetoxyandrost-5-ene-17β-carboxylic acid chloride (**1**)[7] (3.8 g, 10.0 mmol) in dry dichloromethane (40 mL) was cooled to 0°C, and 12.0 mmol of α-aminoketone (or alkyl glycinate) hydrochloride was added. Triethylamine (2.8 mL, 20.0 mmol) was added under argon and the reaction mixture was stirred at room temperature for 1h. It was then concentrated to one-fifth of the volume, diluted with ethyl acetate (200 mL), washed successively with 5% hydrochloric acid, 5% sodium hydrogen carbonate, water, and dried over anhydrous sodium sulfate. The solvents were evaporated and the residue was chromatographed on a column of silica gel (140 g).

N-Benzoylmethyl-3β-acetoxyandrost-5-ene-17β-carboxamide (7a)

Acylation of 2-aminoacetophenone hydrochloride by **1** followed by chromatography with benzene-ether (95:5) afforded 3.46 g (69%) of **7a**; m.p. 87-90°C (ether-light petroleum); $[\alpha]_D^{24}$-32°(c 1.6, chloroform). IR: 3420, 1664, 1506 (NH); 1725, 1253, 1032 (AcO); 1581 (aromatic ring). ^{1}H-NMR (100 MHz): 7.99 (m, 2H, aromatic H, W=10), 7.55 (m, 3H, aromatic H, W=32), 6.39 (bt, 1H, NH, J=4.5), 5.37 (bd, 1H, H-6, J=4.5), 4.76 (ddd, 2H, $NH_X\underline{CH}_A\underline{H}_BCO$, $J_{AX}=J_{BX}=4.5$, $J_{AB}=20$), 4.60 (m, 1H, H-3, W=32), 2.02 (s, 3H, CH_3COO), 1.02 (s, 3H, 19-CH_3), 0.71 (s, 3H,

Table 2: Yields of Products of Alkaline Hydrolysis

Starting compound	**5a**	**5b**	**5c**	**5d**	**5e**	**9a**	**9b**	**9c**	**9d**	**9e**
Yield [%]	98	98	96	97	98	99	99	97	98	97
Product	**6a**	**6b**	**6c**	**6d**	**6e**	**10a**	**10b**	**10c**	**10d**	**10e**

Table 3: Physical and Analytical Data of Thiazoles **6**, **10**

No.	M.p. [°C]	$[\alpha]_D^{25}(c)^*$	Formula (M.W.)	Calcd. (Found) %C	%H	%N	%S
6a	166-167	-71°(1.6)	$C_{28}H_{35}NOS$ (433.7)	77.55 (77.21	8.14 8.21	3.23 2.89	7.39 7.18)
6b	168-170	-79°(1.6)	$C_{23}H_{33}NOS$ (371.6)	74.34 (74.29	8.95 8.96	3.77 3.41	8.63 8.42)
6c	181-182	-70°(1.5)	$C_{23}H_{33}NO_2S$ (387.6)	71.28 (71.43	8.58 8.32	3.61 3.51	8.27 8.09)
6d	147-148	-71°(1.4)	$C_{24}H_{35}NO_2S$ (401.6)	71.78 (71.94	8.78 8.45	3.49 3.24	7.98 7.75)
6e	127-128	-69°(1.4)	$C_{25}H_{37}NO_2S$ (415.6)	72.24 (72.33	8.97 8.79	3.37 3.29	7.71 7.83)
10a	215-217	-45°(1.6)	$C_{28}H_{35}NOS$ (433.7)	77.55 (77.88	8.14 7.95	3.23 3.13	7.39 7.24)
10b	196-198	-73°(1.9)	$C_{23}H_{33}NOS$ (371.6)	74.34 (74.57	8.95 8.92	3.77 3.59	8.63 8.45)
10c	175-176	-67°(1.7)	$C_{23}H_{33}NO_2S$ (387.6)	71.28 (71.21	8.58 8.56	3.61 3.67	8.27 8.01)
10d	161-164	-67°(1.5)	$C_{24}H_{35}NO_2S$ (401.6)	71.78 (71.64	8.78 8.80	3.49 3.35	7.98 7.94)
10e	148-149	-68°(1.4)	$C_{25}H_{37}NO_2S$ (415.6)	72.24 (72.45	8.97 8.93	3.37 3.23	7.71 7.64)

*Optical rotations of all samples were measured in chloroform.

Table 4: Characteristic IR Bands and Mass Spectrometric Data of Thiazoles **6**, **10**

No.	IR [cm^{-1}]	MS: m/z (%)
6a	3610,1603,1521,1490,1445,1042	433(32),418(32),188(84),175(100)
6b	3608,1603,1531,1043	371(19),356(48),126(85),113(100)
6c	3609,1602,1537,1042	387(39),372(65),142(100),129(75)
6d	3604,1602,1532,1043	401(34),386(50),156(100),143(94)
6e	3609,1602,1531,1044	415(51),400(63),170(98),157(100)
10a	3608,1602,1574,1530,1489,1042	433(44),418(48),188(77),175(100)
10b	3609,1602,1540,1042	371(24),356(53),126(97),113(100)
10c	3608,1602,1537,1042	387(65),372(100),142(94),129(98)
10d	3608,1533,1043	401(52),386(54),156(81),143(100)
10e	3608,1042,1605,1533	415(54),400(59),170(69),157(100)

18-CH_3). MS, m/z(%): 417(100), 402(9), 283(16), 255(26). For $C_{30}H_{39}NO_4$ (477.6) calculated 75.44%C, 8.23%H, 2.93%N; found 75.65%C, 8.21%H, 2.92%N.

N-Acetylmethyl-3β-acetoxyandrost-5-ene-17β-carboxamide (7b)

Acylation of aminoacetone hydrochloride by **1** followed by chromatography with chloroform-ethanol (98:2) afforded 3.58 g (86%) of **7b**; m.p. 207-209°C (acetone); $[\alpha]_D^{25}$-46°(c 1.5, chloroform). IR: 3424, 1662, 1505 (NH); 1725, 1254, 1029 (AcO). ^{1}H-NMR (100 MHz): 6.05 (bt, 1H, NH, J=4.5), 5.40 (bd, 1H, H-6, J=4.5), 4.59 (m, 1H, H-3, W=32), 4.18 (ddd, 2H, $NH_X\underline{CH}_A\underline{H}_BCO$, $J_{AX}=J_{BX}=4.5$, $J_{AB}=20$), 2.20 (s, 3H, $\underline{CH}_3COCH_2$), 2.02 (s, 3H, CH_3COO), 1.02 (s, 3H, 19-CH_3), 0.69 (s, 3H, 18-CH_3). MS, m/z(%): 355(100), 340(11), 283(12), 255(22), 74(21). For $C_{25}H_{37}NO_4$ (415.6) calculated 72.26%C, 8.97%H, 3.37%N; found 72.19%C, 8.96%H, 3.16%N.

N-Methoxycarbonylmethyl-3β-acetoxyandrost-5-ene-17β-carboxamide (7c)

Acylation of methyl glycinate hydrochloride by **1** followed by chromatography with chloroform-ethylacetate (9:1) afforded 3.9 g (91%) of **7c**; m.p. 148-149°C (light

petroleum-benzene); $[\alpha]_D^{25}$-36°(c 2.0, chloroform). IR: 3457, 3437, 1669, 1511 (NH); 1745, 1254, 1029 (AcO); 1726 (CO ester). ^{1}H-NMR (100 MHz): 5.85 (bt, 1H, NH, J=5.0), 5.38 (bd, 1H, H-6, J=4.5), 4.55 (m, 1H, H-3, W=32), 4.07(ddd, 2H, $NH_X\underline{CH}_A\underline{H}_BCO$, $J_{AX}=J_{BX}=5$, $J_{AB}=19$), 3.76 (s, 3H, $COOCH_3$), 2.03 (s, 3H, CH_3COO), 1.02 (s, 3H, 19-CH_3), 0.71 (s, 3H, 18-CH_3). MS, m/z(%): 400(6), 371(100), 356(13), 254(19). For $C_{25}H_{37}NO_5$ (431.6) calculated 69.58%C, 8.64%H, 3.25%N; found 69.26%C, 8.44%H, 2.96%N.

N-Ethoxycarbonylmethyl-3β-acetoxyandrost-5-ene-17β-carboxamide (7d)

Acylation of ethyl glycinate hydrochloride by **1** followed by chromatography with chloroform-ethyl acetate (95:5) afforded 3.56 g (96%) of **7d**; m.p. 164-166°C (acetone); $[\alpha]_D^{23}$-36°(c 1.5, chloroform). IR: 3457, 3435, 1661, 1511 (NH); 1728, 1255, 1029 (AcO). ^{1}H-NMR (200 MHz): 5.80 (bt, 1H, NH, J=5), 5.38 (bd, 1H, H-6, J=4.5), 4.60 (m, 1H, H-3, W=32), 4.21 (q, 2H, $CH_3\underline{CH}_2O$, J=7.1), 4.06 (ddd, 2H $NH_X\underline{CH}_A\underline{H}_BCO$, $J_{AX}=J_{BX}=5$, $J_{AB}=19$), 2.03 (s, 3H, CH_3COO), 1.29 (t, 3H, $CH_3\underline{CH}_2O$, J=7.1), 1.02 (s, 3H, 19-CH_3), 0.71 (s, 3H, 18-CH_3). MS, m/z(%): 400(10), 385(100), 370(15), 254(27). For $C_{26}H_{39}NO_5$ (445.6) calculated 70.08%C, 8.82%H, 3.14%N; found 70.21%C, 8.82%H, 3.04%N.

N-Propoxycarbonylmethyl-3β-acetoxyandrost-5-ene-17β-carboxamide (7e)

Acylation of propyl glycinate hydrochloride by **1** followed by chromatography with chloroform-ethyl acetate (98:2) afforded 3.48 g (91%) of **7e**; m.p. 150-151°C (acetone); $[\alpha]_D^{25}$-35°(c 1.8, chloroform). IR: 3435, 1510 (NH); 1727, 1254, 1033 (AcO). ^{1}H-NMR (200 MHz) 5.81 (bt, 1H, NH, J=5), 5.37 (bd, 1H, H-6, J=4.5), 4.62 (m, 1H, H-3, W=32), 4.12 (t, 2H, $CH_3CH_2\underline{CH}_2O$, J=6.7), 4.07 (ddd, 2H, $NH_X\underline{CH}_A\underline{H}_BCO$, $J_{AX}=J_{BX}=5$, $J_{AB}=19$), 2.04 (s, 3H, CH_3COO), 1.02 (s, 3H, 19-CH_3), 0.95 (t, 3H, $\underline{CH}_3CH_2CH_2O$, J=7.4), 0.71 (s, 3H, 18-CH_3). MS, m/z(%): 400(37), 399(100), 384(10), 254(15). For $C_{27}H_{41}NO_5$ (459.6) calculated 70.56%C, 8.99%H, 3.05%N; found 70.32%C, 8.84%H, 3.04%N.

General procedure for the preparation of 8c-e

N-Alkoxycarbonylmethyl-3β-acetoxyandrost-5-ene-17β-carboxamide (**7c-e**) (1.1 mmol) and phosphorus pentasulfide (244 mg, 1.1 mmol) in dioxane (10 mL) were stirred at 50°C for 4 h. The mixture was then filtered through a column of alumina (5 g) and the column eluted with ether (100 mL). The solvents were evaporated and the residue chromatographed on silica gel (25g) in light petroleum--ethylacetate (8:2).

N-Methoxycarbonylmethyl-3β-acetoxyandrost-5-ene-17β-thiocarboxamide (8c)

Yield 79%; m.p. 192-194°C (methanol); $[\alpha]_D^{25}$-48°(c 1.6, chloroform). IR: 3381, 1507 (NH); 1727, 1254, 1034 (AcO). ^{1}H-NMR (100 MHz): 7.52 (bt, 1H, NH, J=4.5), 5.38 (bd, 1H, H-6, J=4.5), 4.61 (m, 1H, H-3, W=32), 4.45 (ddd, 2H, $NH_X\underline{CH_A}\underline{H_B}CO$, $J_{AX}=J_{BX}=4.5$, $J_{AB}=19$), 3.81 (s, 3H, $COOCH_3$), 2.03 (s, 3H, CH_3COO), 1.02 (s, 3H, 19-CH_3), 0.71 (s, 3H, 18-CH_3). For $C_{25}H_{37}NO_4S$ (447.6) calculated 67.08%C, 8.33%H, 3.13%N, 7.16%S; found 67.46%C, 8.43%H, 3.09%N, 6.86%S.

N-Ethoxycarbonylmethyl-3β-acetoxyandrost-5-ene-17β-thiocarboxamide (8d)

Yield 88%; m.p. 178-180°C (acetone); $[\alpha]_D^{25}$-46°(c 1.8, chloroform). IR: 3380, 1508 (NH); 1729, 1255, 1029 (AcO). ^{1}H-NMR (200 MHz): 7.54 (bt, 1H, NH, J=4.5), 5.38 (bd, 1H, H-6, J=4.5), 4.59 (m, 1H, H-3, W=32), 4.44 (ddd, 2H $NH_X\underline{CH_A}\underline{H_B}CO$, $J_{AX}=J_{BX}=4.5$, $J_{AB}=19$), 4.27 (q, 2H, $CH_3\underline{CH_2}O$, J=7.3), 2.04 (s, 3H, CH_3COO), 1.32 (t, 3H, $CH_3\underline{CH_2}O$, J=7.3), 1.02 (s, 3H, 19-CH_3), 0.71 (s, 3H, 18-CH_3). For $C_{26}H_{39}NO_4S$ (461.7) calculated 67.64%C, 8.51%H, 3.03%N, 6.95%S; found 67.45%C, 8.51%H, 3.05%N, 6.95%S.

N-Propoxycarbonylmethyl-3β-acetoxyandrost-5-ene-17β-thiocarboxamide (8e)

Yield 66%; m.p. 115-117°C (ether-light petroleum); $[\alpha]_D^{25}$-48°(c 1.4, chloroform). IR: 3379, 1507 (NH); 1729, 1255, 1034 (AcO). ^{1}H-NMR (200 MHz): 7.55 (bt, 1H, NH, J=4.5), 5.39 (bd, 1H, H-6, J=4.5), 4.61 (m, 1H, H-3, W=32), 4.45

(ddd, 2H, $NH_X\underline{CH}_A\underline{H}_BCO$, $J_{AX}=J_{BX}=4.5$, $J_{AB}=19$), 4.17 (t, 2H, $CH_3CH_2\underline{CH}_2O$, J=6.7), 2.04 (s, 3H, CH_3COO), 1.02 (s, 3H, 19-CH_3), 0.97 (t, 3H, $\underline{CH}_3CH_2CH_2O$, J=7.5), 0.71 (s, 3H, 18-CH_3). For $C_{27}H_{41}NO_4S$ (475.7) calculated 68.17%C, 8.69%H, 2.94%N, 6.74%S; found 68.27%C, 8.65%H, 2.75%N, 7.00%S.

3β-Acetoxy-17β-(5'-phenyl-2'-thiazolyl)androst-5-ene (9a)

Phosphorus pentasulfide (1.9 g, 8.6 mmol) was added to a solution of amide **7a** (3.15 g, 6.6 mmol) in 120 mL of dry dioxane. The mixture was vigorously stirred under reflux for 30 min. Then it was poured into water (300 mL) and extracted with ether (3x100 ml). The combined organic extracts were dried over anhydrous sodium sulfate, solvent was removed and the residues were chromatographed on a column of silica gel (90 g) in benzene. The main fraction gave 2.04 g (65%) of **8a**; m.p. 184-186°C (benzene-ethanol); $[\alpha]_D^{23}$-41°(c 1.6, chloroform). IR: 1725, 1254, 1033 (AcO); 1601, 1574, 1530, 1489 (aromatic rings). ^{1}H-NMR (100 MHz): 7.87 (s, 1H, thiazole H-4'), 7.54 (m, 2H, aromatic H, W=11), 7.36 (m, 3H, aromatic H, W=16), 5.39 (bd, 1H, H-6, J=4.5), 4.57 (m, 1H, H-3, W=33), 2.03 (s, 3H, CH_3COO), 1.03 (s, 3H, 19-CH_3), 0.62 (s, 18-CH_3). MS, m/z(%): 475(6), 460(13), 415(92), 400(83), 188(100), 175(97). For $C_{30}H_{37}NO_2S$ (475.7) calculated 75.75%C, 7.84%H, 2.94%N, 6.74%S; found 75.76%C, 7.89%H, 2.84%N, 6.55%S.

3β-Acetoxy-17β-(5'-methyl-2'-thiazolyl)androst-5-ene (9b)

The same procedure described above gave from **7b** the thiazole **9b** in 48% yield; m.p. 177-178°C (methanol); $[\alpha]_D^{23}$-71°(c 1.4, chloroform). IR: 1725, 1255, 1033 (AcO); 1538 (thiazole ring). ^{1}H-NMR (100 MHz): 7.34 (s, 1H, thiazole H-4'), 5.38 (bd, 1H, H-6, J=4.5), 4.57 (m, 1H, H-3, W=33), 2.43 (s, 3H, CH_3), 2.03 (s, 3H, CH_3COO), 1.03 (s, 3H, 19-CH_3), 0.57 (s, 18-CH_3). MS, m/z(%): 413(3), 398(9), 353(79), 338(90), 126(100), 113(84). For $C_{25}H_{35}NO_2S$ (413.6) calculated 72.60%C, 8.53%H, 3.39%N, 7.75%S; found 72.78%C, 8.55%H, 3.21%N, 7.79%S.

General procedure for the preparation of 9c-e

Amide **7c-d** (2.2 mmol) and phosphorus pentasulfide (485 mg, 2.2 mmol) in anhydrous dioxane (20 mL) were stirred under argon at 50°C. After 4h was the reaction mixture refluxed for another 30 min. It was then applied onto a column of alumina (10 g) and eluted with ether (200 mL). Solvents were evaporated and the solid residues chromatographed on alumina (60 g) in light petroleum-ethyl acetate.

3β-Acetoxy-17β-(5'-methoxy-2'-thiazolyl)androst-5-ene (9c)

Yield 71% ; m.p. 139-140°C (methanol); $[\alpha]_D^{24}$-67°(c 1.6, chloroform). IR: 1725, 1255, 1033 (AcO); 1537 (thiazole). ^{1}H-NMR (200 MHz): 6.95 (s, 1H, thiazole H-4'), 5.39 (bd, 1H, H-6, J=4.5), 4.62 (m, 1H, H-3, W=32), 3.88 (s, 3H, CH_3O), 2.86 (t, 1H, H-17, J=10), 2.03 (s, 3H, CH_3COO), 1.02 (s, 3H, 19-CH_3), 0.59 (s, 3H, 18-CH_3). MS, m/z(%): 429(5), 414(16), 369(80), 354(100), 142(93), 129(81). For $C_{25}H_{35}NO_3S$ (429.6) calculated 69.89%C, 8.21%H, 3.26%N, 7.46%S; found 69.62%C, 8.15%H, 3.12%N, 7.47%S.

3β-Acetoxy-17β-(5'-ethoxy-2'-thiazolyl)androst-5-ene (9d)

Yield 75% ; m.p. 137-138°C (methanol); $[\alpha]_D^{25}$-64°(c 1.5, chloroform). IR: 1725, 1254, 1034 (AcO); 1532 (thiazole). ^{1}H-NMR (200 MHz): 6.96 (s, 1H, thiazole H-4'), 5.39 (bd, 1H, H-6, J=4.5), 4.61 (m, 1H, H-3, W=32), 4.08 (q, 2H, $CH_3\underline{CH_2}O$, J=7.1), 2.84 (t, 1H, H-17, J=10), 2.03 (s, 3H, CH_3COO), 1.41 (t, 3H, $\underline{CH_3}CH_2O$, J=7.1), 1.02 (s, 3H, 19-CH_3), 0.59 (s, 3H, 18-CH_3). MS, m/z(%): 443(13), 428(16), 385(63), 368(72), 156(91), 143(100). For $C_{26}H_{37}NO_3S$ (443.7) calculated 70.39%C, 8.41%H, 3.16%N, 7.23%S; found 70.68%C, 8.38%H, 3.13%N, 7.08%S.

3β-Acetoxy-17β-(5'-propoxy-2'-thiazolyl)androst-5-ene (9e)

Yield 61% ; m.p. 137-138°C (methanol); $[\alpha]_D^{25}$-60°(c 1.6, chloroform). IR: 1725, 1255, 1033 (AcO); 1533 (thiazole). ^{1}H-NMR (200 MHz): 6.95 (s, 1H, thiazole H-4'), 5.39 (bd, 1H, H-6, J=4.5), 4.61 (m, 1H, H-3, W=32), 3.97 (t, 2H, $CH_3CH_2\underline{CH_2}O$, J=6.5), 2.84 (t, 1H, H-17, J=10), 2.04 (s, 3H, CH_3COO), 1.02 (t,

3H, $\underline{CH_3}CH_2CH_2O$, J=7.4), 1.02 (s, 3H, 19-CH_3), 0.59 (s, 3H, 18-CH_3). MS, m/z(%): 457(10), 442(7), 397(52), 382(100), 170(98), 157(81). For $C_{27}H_{39}NO_3S$ (457.7) calculated 70.86%C, 8.59%H, 3.06%N, 7.01%S; found 71.05%C, 8.53%H, 2.91%N, 6.92%S.

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