

Synthesis of Steroidal Thiadiazoles from Steroidal Ketones

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Abstract: Syntheses of steroidal heterocycles containing a five-membered N,S-heterocycle attached at the 6,7 positions of the B ring are reported. 5 α -Cholestane-6-one (**1**), its 3 β -acetoxy- (**2**) and 3 β -chloro- (**3**) analogues reacted with semicarbazide and aqueous sodium acetate in refluxing ethanol to yield 5 α -cholestan-6-one-semicarbazone **1a** and its 3- β -acetoxy and 3 β -chloro derivatives **2a** and **3a**, respectively. The reactions of **1a**, **2a** and **3a** with thionyl chloride in dichloromethane at low temperature afforded the cyclized thiadiazole **4** and its 3 β -acetoxy- and 3 β -chloro analogues **5** and **6** in good yields.

Keywords: Thiadiazoles, steroidal thiadiazoles, steroidal heterocycles, cyclization, thionyl chloride, semicarbazide, dichloromethane.

Introduction

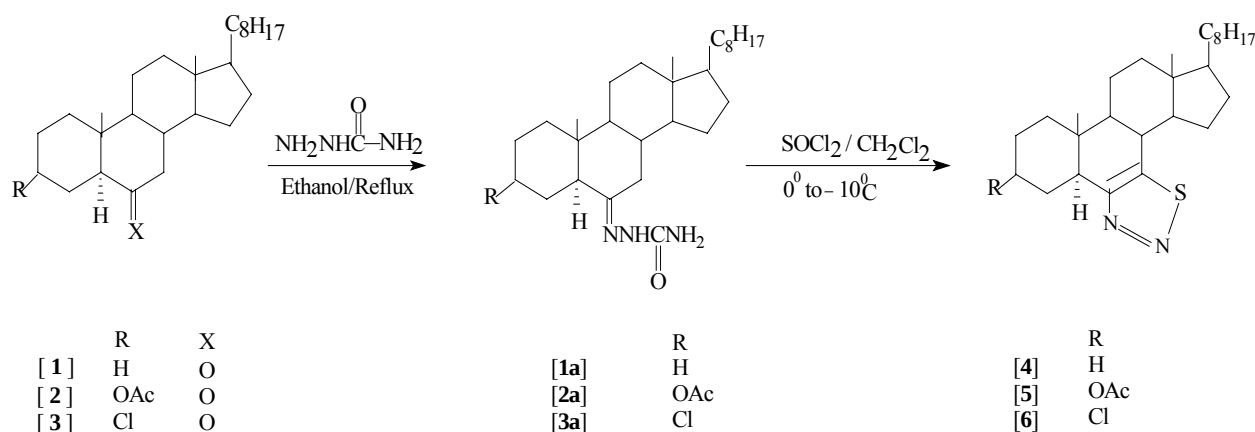
Important biological activities like antibacterial, antiviral, anticonvulsant, analgesic, antithrombotic and antitumour properties [1-8] associated with molecules incorporating nitrogen and sulfur atoms individually or in combinations thereof have been the focus for the ongoing synthesis of a number of thiadiazole derivatives [9-14]. A literature survey reveals that little attention has been paid however to the synthesis of systems containing 1,2,3-and other thiadiazoles at various steroidal positions [15], which are good candidates for possessing the aforementioned biological properties. Another notable feature of the thiadiazole moiety was also observed recently when it was found to possess male contraceptive properties [16]. Synthetically, heterocyclic steroidal compounds have generated a great deal of interest in exploiting more than one proximal functional group in designing novel structures for performing a variety of synthetic functions in transformations and synthesis. One such functionality is

the α -ketomethylene group which has been used as a building block for thiadiazole systems [17-18]. We now report the preparation of the desired steroidal thiadiazoles. The reaction of 5 α -cholestane-6-one (**1**) and its 3 β -acetoxy- and 3 β -chloro- analogues **2** and **3** [19-21] with semicarbazide and sodium acetate gave semicarbazones **1a**, **2a** and **3a**, respectively [22]. Further reaction of **1a**, **2a** and **3a** with thionyl chloride in dichloromethane at -10 °C yielded the desired products **4**, **5** and **6**, with a fused heterocycle attached at the C-6 and C-7 positions of the cholestane skeleton B ring.

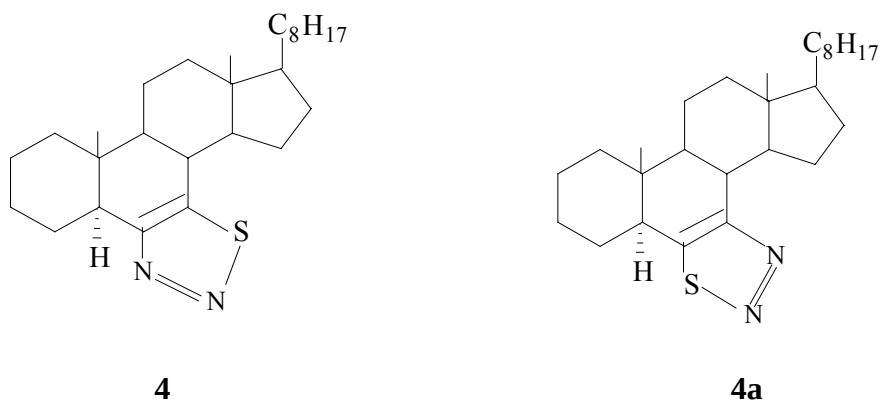
Results and Discussion

Steroidal semicarbazones **1a**, **2a** and **3a** were prepared starting from α -cholestane-6-one (**1**) and its 3 β -acetoxy and 3 β -chloro analogues **2** and **3** following the Hurd-Mori procedure [23] to furnish steroidal thiadiazoles **4**, **5** and **6**, respectively (Scheme 1).

Scheme 1



The structure of compound **4** was established by IR, ^1H -NMR spectra and elemental analyses (Tables II and III). The IR spectrum displayed bands at 1615 cm^{-1} (C=C), 1565 cm^{-1} (N=N), 1380 cm^{-1} (C-N) and 715 cm^{-1} (C-S), indicating the presence of a thiadiazole ring. The ^1H -NMR spectrum of **4** showed a triplet at δ 2.9 and a double doublet at δ 3.5, assigned to C₅- α H and C₈- β H, respectively. Methyl protons were observed at δ 1.12 (C₁₀-CH₃), 0.70 (C₁₃-CH₃), 0.90 and 0.83 (C₂₀-CH₃ and C₂₅ (-CH₃)₂). The elemental analyses and remaining IR absorption bands are in complete agreement with the proposed possible structures **4** and **4a**.



The reaction mechanism [23-25] clearly shows that the C₆-N bond in the imino intermediate **1a** remains intact and further two α -hydrogens are required. These facts favour structure **4** rather than **4a**. The ring is planar and must be stable due to aromatization. Therefore, the product is characterized as 5 α -cholest-6-eno[6,7-*d*]-thiadiazole (**4**), satisfying all observed spectral properties. The products **5** and **6** were also characterized on the basis of similar spectroscopic analyses and mechanistic accounts.

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Experimental

General

Melting points were determined on a Kofler apparatus and are uncorrected. IR spectra were recorded on KBr pellets with a Pye Unicam SP3-100-spectrophotometer and values are given in cm⁻¹. ¹H-NMR spectra were run in CDCl₃ on a Bruker AC-300 (300MHz) with TMS as standard and the values are given in ppm (δ). Mass spectra were measured on VG Micromass model ZAB-IF apparatus at 70ev ionization voltage. Silica gel coated Thin Layer Chromatographic plates (TLC) were used to check product purity and were developed in an iodine chamber. Silica gel (mesh size 60-120, BDH) was used for product purification (20 gram/gram of material) using gravity column chromatography. Usual work up involved the decomposition of unreacted reagents with aqueous Na₂CO₃ solution, extraction with an organic solvent, washing with water to pH 7 and drying over anhydrous Na₂SO₄. Reactions of **4**, **5** and **6** were performed under anhydrous conditions at room temperature.

General procedure for preparation of semicarbazones: [26]

To a solution of ketone (**1**, **2** or **3**, 0.005 moles) in ethanol (50mL) was added a solution of semicarbazide hydrochloride (0.008 moles) and 15% aqueous solution of sodium acetate (20 mL). The resulting mixture was refluxed for one hour and cooled to furnish a solid which was filtered under suction and washed with water. The residue was air dried and recrystallised from methanol to afford the corresponding semicarbazones **1a**, **2a** or **3a**, as per Table I [22].

General procedure for preparation of steroidal thiadiazoles

Caution! Care must be taken while using thionyl chloride as it is irritant and corrosive to skin.

Freshly distilled thionyl chloride (5-8 mL, 0.069-0.110 moles), was charged into a round bottomed flask (50 mL) placed in a salt-ice bath at about -10 °C and to this was added, under continuous stirring, steroidal semicarbazone **1a**, **2a** or **3a** (0.005 mol) in 3 portions, maintaining the temperature between 0 and -10 °C. After complete addition, the temperature was allowed to rise to room temperature and dichloromethane (25 mL) was added. The mixture was stirred for another two hours.

Excess thionyl chloride was decomposed by slowly adding a saturated cold aqueous solution of sodium carbonate (approximately 15-20 mL to maintain pH 7) and the desired product was isolated using solvent extraction (the organic layer was separated, washed thoroughly with water followed by 5 % aqueous sodium bicarbonate solution and water again and dried over anhydrous Na₂SO₄). Evaporation of the solvent under reduced pressure gave an oil which failed to crystallize. Purification of crude product was achieved by SiO₂ gel column chromatography eluting with light petroleum ether (b.p. 60-80°C fraction) and ether mixtures (9:1, 7:3 or 8:2 petroleum ether-ether for compounds **4**, **5** and **6**, respectively). The products were further purified by repeated crystallization from methanol to afford glossy light yellow semi-solids. These were characterized by physical and spectral data (Tables II and III).

Table I. Physical properties of the semicarbazones **1a-3a**

Starting Ketone	Products	Yield (%)	M.p. (°C)	Rf	TLC ^a (mL)
α -cholestan-6-one (1)	α -cholestan-6-one-semicarbazone (1a)	80	190	0.206	2: 1.00 :0.10
3 β -acetoxy- α -cholestan-6-one (2)	3 β -acetoxy- α -cholestan-6-one-semicarbazone (2a)	83	242	0.428	2 : 0.6: 0.10
3 β -chloro- α -cholestan-6-one (3)	3 β -chloro- α -cholestan-6-one-semicarbazone (3a)	75	152	0.603	2 : 0.6: 0.10

^a Solvents: Petroleum ether -AcOEt -AcOH

Table II. Physical properties and analytical data of compounds **4 - 6**.

Compound	Physical state	Molecular formula (Mol. Wt.)	Yield (%)	% found (calcd.)				Rf value	TLC ^a (mL)
				C	H	N	S		
5 α -cholest-6-eno[6,7- <i>d</i>]thiadiazole (4)	Glossy semi-solid	C ₂₇ H ₄₄ N ₂ S (428)	58	75.66 (75.70)	10.24 (10.28)	6.54 (6.50)	7.42 (7.48)	0.155	2:1.00:0.10
3 β -acetoxy-5 α -cholest-6-eno[6,7- <i>d</i>]thiadiazole (5)	Glossy semi-solid	C ₂₉ H ₄₆ N ₂ OS (486)	62	71.56 (71.60)	9.41 (9.46)	5.72 (5.76)	6.51 (6.58)	0.301	2 : 0.6: 0.10
3 β -chloro-5 α -cholest-6-eno[6,7- <i>d</i>]thiadiazole (6)	Glossy semi-solid	C ₂₇ H ₄₃ N ₂ ClS (462/464)	58	69.78 (70.08)	9.48 (9.50)	6.02 (6.05)	6.78 (6.91)	0.492	

^a Solvents: Petroleum ether -AcOEt -AcOH

Table III Spectral data for compounds 4-6

Compound	IR (KBr, cm ⁻¹)	¹ H-NMR (δ , ppm)	MS (EI):mz (%)
4	1615 (C=C) 1380 (C-N) 1565 (N=N) 715 (C-S)	2.9 (t, C ₅ - α H) 3.5 (dd, C ₈ - β H) 1.12 (C ₁₀ -CH ₃) 0.70 (C ₁₃ -CH ₃) 0.90 (C ₂₀ -CH ₃) and 0.83 (C ₂₅ -CH ₃).	428 (M ⁺), 400 (100) (base peak), 368 (30) (M ⁺ -N ₂ and S), 386 (10) (M ⁺ -N ₂ and CH ₃), 287 (7) (M ⁺ -N ₂ and C ₈ H ₁₇),
5	1615 (C=C) 1374 (C-N) 1570 (N=N) 711 (C-S)	4.9 (m, W _{1/2} =17 Hz, C ₃ - α H A/B ring junction trans) [26] 2.75 (t, C ₅ - α H), 2.95 (dd, C ₈ - β H), 2.1 (s, 3H, CH ₃ COO), 1.13 (C ₁₀ - CH ₃), 0.67 (C ₁₃ -CH ₃), 0.91 (C ₂₀ - CH ₃) and 0.87 (C ₂₅ -CH ₃).	486 (M ⁺), 365 (100) (base peak), 458 (20) (M ⁺ -N ₂), 442 (5) (M ⁺ -N ₂ and CH ₃), 426 (8) (M ⁺ -AcOH), 398 (30) (M ⁺ -N ₂ and AcOH), 345 (7) (M ⁺ -N ₂ and C ₈ H ₁₇)
6	1623 (C=C) 1370 (C-N) 1550 (N=N) 705 (C-S)	2.7 (t, C ₅ - α H), 3.0 (dd, C ₈ - β H) 4.2 (br, m, W _{1/2} =16Hz C ₃ - α H A/B ring junction trans) [26] 1.15 (C ₁₀ -CH ₃), 0.68 (C ₁₃ -CH ₃), 0.93 (C ₂₀ -CH ₃) and 0.83 (C ₂₅ - CH ₃)	462/464 [^{35/37} Cl] (M ⁺)/(M ⁺ +2) (3/0.96) (0.25/0.08 peak's value), 394 (100) (base peak), 434/436 (12/3.8) (M ⁺ -N ₂), 418/420 (10/3.5) (M ⁺ -N ₂ and CH ₃), 400/402 (30/9.1) (M ⁺ -N ₂ and S), 321/323 (8/2.3) (M ⁺ -N ₂ and C ₈ H ₁₇)

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