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. 5α-Cholestane-6-one (1), its 3β-acetoxy- (2) and 3β-chloro- (3) analogues reacted with semicarbazide and aqueous sodium acetate in refluxing ethanol to yield 5α-cholestan-6-one-semicarbazone 1a and its 3β-acetoxy and 3β-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 3β-acetoxy- and 3β-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 5α-cholestane-6-one (1) and its 3β-acetoxy- and 3β-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 3β-acetoxy and 3β-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 \(\delta 2.9\) and a double doublet at \(\delta 3.5\), assigned to C5-αH and C8-βH, respectively. Methyl protons were observed at \(\delta 1.12\) (C10-CH\(_3\)), 0.70 (C13-CH\(_3\)), 0.90 and 0.83 (C20-CH\(_3\) and C25 (-CH\(_3\))\(_2\)). 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 \( \alpha \)-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\( \alpha \)-cholest-6-eno[6,7-\( \delta \)]-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\(^{-1}\). \(^1\)H-NMR spectra were run in CDCl\(_3\) on a Bruker AC-300 (300MHz) with TMS as standard and the values are given in ppm (\( \delta \)). 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 Na\(_2\)CO\(_3\) solution, extraction with an organic solvent, washing with water to pH 7 and drying over anhydrous Na\(_2\)SO\(_4\). 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 Na$_2$SO$_4$). Evaporation of the solvent under reduced pressure gave an oil which failed to crystallize. Purification of crude product was achieved by SiO$_2$ 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 |
| α-cholestan-6-one (1) | α-cholestan-6-one- semicarbazone (1a) | 80 | 190 | 0.206 |
| 3β-acetoxy-α-cholestan- 6-one (2) | 3β-acetoxy-α-cholestan-6-one- semicarbazone (2a) | 83 | 242 | 0.428 |
| 3β-chloro-α-cholestan-6- one (3) | 3β-chloro-α-cholestan-6-one- semicarbazone (3a) | 75 | 152 | 0.603 |

$^a$ 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) |
| 5α-cholestan-6- eno[6,7- d] 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 |
| 3β-acetoxy-5α-cholestan-6-eno [6,7- d] 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 |
| 3β-chloro-5α-cholestan-6-eno [6,7- d] 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) | ¹H-NMR (δ, ppm) | MS (EI):mz (%) |
|----------|----------------|-----------------|---------------|
| 4        | 1615 (C=C)     | 2.9 (t, C₂-αH)  | 428 (M⁺),     |
|          | 1380 (C-N)     | 3.5 (dd, C₆-βH)| 400 (100)     |
|          | 1565 (N=N)     | 1.12 (C₁₀⁻CH₃)| 368 (30)      |
|          | 715 (C-S)      | 0.70 (C₁₃⁻CH₃)| 386 (10)      |
|          |                | 0.90 (C₂₀⁻CH₃) | 287 (7)       |
|          |                | 0.83 (C₂₅⁻CH₃)|              |
| 5        | 1615 (C=C)     | 4.9 (m, W₁/₂=17 Hz, C₃⁻αH A/B ring junction trans) [26] | 486 (M⁺),     |
|          | 1374 (C-N)     | 2.75 (t, C₅⁻αH), 2.95 (dd, C₈⁻βH), | 365 (100)     |
|          | 1570 (N=N)     | 2.1 (s, 3H, CH₃COO), 1.13 (C₁₀⁻CH₃), 0.67 (C₁₃⁻CH₃), 0.91 (C₂₀⁻CH₃) | 458 (20)      |
|          | 711 (C-S)      | 0.87 (C₂₅⁻CH₃). | 442 (5)       |
| 6        | 1623 (C=C)     | 2.7 (t, C₅⁻αH), 3.0 (dd, C₆-βH) | 426 (8)       |
|          | 1370 (C-N)     | 4.2 (br, m, W₁/₂=16Hz C₃⁻αH A/B ring junction trans) [26] | 398 (30)      |
|          | 1550 (N=N)     | 1.15 (C₁₀⁻CH₃), 0.68 (C₁₃⁻CH₃), 0.93 (C₂₀⁻CH₃) and 0.83 (C₂₅⁻CH₃)| 345 (7)       |
|          | 705 (C-S)      |                 | 462/464[³⁵/³⁷Cl] (M⁺)/(M⁺+2) |
|          |                |                 | (3/0.96) (0.25/0.08 peak's value), |
|          |                |                 | 394 (100) (base peak), |
|          |                |                 | 434/436 (12/3.8) (M⁺⁻N₂), |
|          |                |                 | 418/420 (10/3.5) (M⁺⁻N₂ and CH₃), |
|          |                |                 | 400/402 (30/(9.1) (M⁺⁻N₂ and S), |
|          |                |                 | 321/323 (8/2.3) (M⁺⁻N₂ and C₈H₁₇) |

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