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Mendeleev Commun., 2011, **21**, 186–187
Mendeleev Communications

Synthesis of 17-(1,2,3-dithiazole) androstene derivatives

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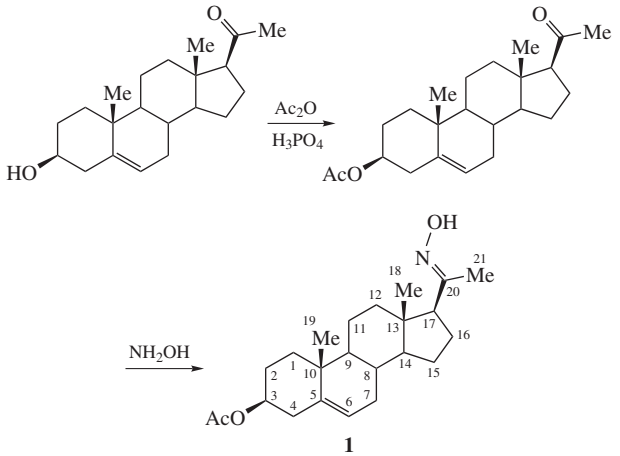
DOI: 10.1016/j.mencom.2011.07.003

17-(1,2,3-Dithiazole) androstene derivatives were synthesized from commercially available Pregnenolone acetate involving the reaction between 3β-acetoxy-20-hydroxyimino-5-pregnene with sulfur monochloride as the key step.

The enzyme 17α-hydroxylase-17,20-lyase (CYP17) is human cytochrome P-450 that catalyzes the conversion of progesterone and pregnenolone into androgens,[1] which play an important role in the development and progression of several prostatic diseases, most notably, benign prostatic hypertrophy and prostatic cancer. Inhibitors of this enzyme can block androgen synthesis in its early step, and thereby may be useful in the treatment of prostatic cancer.[2] Steroids bearing heterocycles attached to the D-ring have recently attracted much attention as inhibitors of the cytochrome P-450. A number of P-450 inhibitors containing at C-17 nitrogen heterocycles, such as imidazole, pyrazole, isoxazole,[3] triazole,[4] oxazole, thiazole,[5] indazole,[6] piperazine[7] and pyrazole,[8] has been recently described. Sulfur-containing heterocycles, for example, 1,2,3-dithiazoles are known to possess significant antiproliferative activity.[9,10] In 1994 and 1997 Rees and co-workers[11,12] reported the formation of 5-oxo- and 5-arylimino-1,2,3-dithiazoles from the reaction of acetophenone oxime (or its *p*-nitro derivative) and sulfur monochloride. Recently we have found that various ethanone oximes can be used for the synthesis of 5-oxo-, 5-thioxo- and 5-phenylimino-1,2,3-dithiazoles with various substituents at the 4-position by a one-pot reaction with sulfur monochloride, pyridine in acetonitrile followed by treatment with the corresponding nucleophiles.[10] However, steroid oximes containing different CH, CH_2 and Me groups and double C=C bond which also can be sensitive to the action of S_2Cl_2, have never been involved in the preparation of 1,2,3-dithiazoles. Here we report the study of the reaction between steroid acetoxime and S_2Cl_2 and the first preparation of steroids bearing a 1,2,3-dithiazole moiety at C-17.

3β-Acetoxy-20-hydroxyimino-5-pregnen-20-one **1**, a key precursor for the synthesis of 17-(1,2,3-dithiazolyl)androstene derivatives, was obtained from commercial Pregnenolone by two-step procedure including acetylation with acetic anhydride in the presence of phosphoric acid followed by oximation with hydroxylamine hydrochloride and pyridine in ethanol (Scheme 1).[13]



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Scheme 1

The structure of oxime **1** was confirmed by analysis of its NMR spectra. Signals in the 1D ^1H and ^{13}C NMR spectra were assigned using 2D COSY, ROESY, HSQC, and $^1H/^{13}C$ HMBC experiments (Table 1). The ^1H NMR spectrum of **1** contained the only peak for OH of the oxime at 10.32 ppm. Pre-irradiation of the protons for 0.5 s in 1D NOE experiment revealed a positive NOE for protons at C-21 (1.2%) indicating spatial proximity of OH and Me characteristic of *E*-isomer of the oxime. $^1H/^{15}N$ HMBC experiment showed correlation peaks for H-21 and H-17 with a nitrogen at –26 ppm (external nitromethane 0.0 ppm). Recently, it was found that only *E*-acetoximes formed 1,2,3-dithiazoles in the reaction with S_2Cl_2.[14]

For the synthesis of steroid-tethered 1,2,3-dithiazole-5-thione **2** (Scheme 2)† we decided to employ our method elaborated for various acetoximes.[10] However, the treatment of oxime **1** (1 equiv.) with S_2Cl_2 (2 equiv.) and pyridine (3 equiv.) in acetonitrile at 0 °C followed by addition of thioacetamide (1.1 equiv.) gave no reaction; the starting compound was recovered. We proposed that this could be attributed to poor solubility of oxime **1** in acetonitrile. On moving to THF, the target product **2** was really formed, however, it was contaminated with some impurities which com-

† New compounds **2** and **3** were characterised by ^1H and ^{13}C NMR (Table 1), mass, IR spectra and elemental analysis.

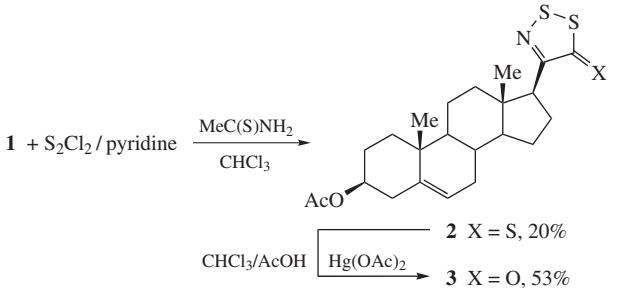
For **2**: pyridine (0.5 ml, 7 mmol) was added dropwise to a stirred solution of oxime **1** (170 mg, 0.45 mmol) and sulfur monochloride (0.4 ml, 5 mmol) in chloroform (15 ml) under argon at –5–0 °C. The mixture was stirred at 0 °C for 15 min. Then thioacetamide (100 mg, 1.3 mmol) was added, the mixture was stirred at room temperature for 2 h, filtered and solvents were evaporated. The residue was separated by column chromatography (Silica gel Merck 60, light petroleum and then light petroleum–CH_2Cl_2 mixtures) to yield 41 mg (20%) of **2** as a dark red crystalline solid, mp 236–237 °C, R_f 0.48 (CH_2Cl_2). IR (KBr, ν/cm^{-1}): 2932, 2904, 2852, 2828 (C–H), 1732 (C=O). MS (EI, 70 eV), *m*/*z* (%): 449 (M^+, 4), 389 (62), 356 (12), 325 (13), 281 (31), 253 (52), 210 (54). Found (%): C, 61.28; H, 7.19; N, 2.90. Calc. for $C_{23}H_{31}NO_2S_3$ (%): C, 61.43; H, 6.95; N, 3.11.

For **3**: mercury acetate (40 mg, 0.125 mmol) was added to the solution of thione **2** (40 mg, 0.09 mmol) in a chloroform–acetic acid (10:2 ml) mixture. The reaction mixture was stirred at room temperature for 15 min, filtered and concentrated. The residue was separated by column chromatography (Silica gel Merck 60, CH_2Cl_2) to yield 21 mg (53%) of **3** as a white solid, mp 179–180 °C, R_f 0.36 (CH_2Cl_2). IR (KBr, ν/cm^{-1}): 2960, 2940, 2852, 2828 (C–H), 1732 (C=O). MS (EI, 70 eV), *m*/*z* (%): 373 [M–SC(O), 100], 358 (24), 340 (15), 312 (16), 281 (42), 266 (68), 213 (35). Found (%): C, 63.56; H, 7.07; N, 3.45. Calc. for $C_{23}H_{31}NO_3S_2$ (%): C, 63.71; H, 7.21; N, 3.23.

Table 1 NMR data for oxime **1**, thione **2** and ketone **3**.

Number of atom	Oxime **1**[a]		Thione **2**		Ketone **3**		Important correlation peaks in $^1H/^{13}C$ and $^1H/^{15}N$ HMBC spectra
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	
1	36.4	1.85, 1.08	37.0	1.86, 1.15	37.0	1.86, 1.15	
2	27.3	1.79, 1.56	27.7	1.88, 1.59	27.7	1.87, 1.58	
3	73.1	4.46	73.9	4.62	73.9	4.60	
4	37.6	2.28, 2.28	38.1	2.34, 2.34	38.0	2.34, 2.34	
5	139.5		139.8		139.8		
6	121.9	5.35	122.3	5.40	122.3	5.39	
7	31.2	1.95, 1.56	31.8	2.04, 1.62	31.8	2.04, 1.62	
8	31.5	1.41	32.3	1.55	32.3	1.53	
9	49.5	0.98	49.9	1.03	49.9	1.01	
10	36.1		36.6		36.6		
11	20.5	1.56, 1.40	21.0	1.55, 1.38	20.9	1.57, 1.40	
12	38.1	1.85, 1.29	38.5	1.60, 1.49	38.1	1.66, 1.42	
13	42.9		46.8		46.1		
14	55.4	1.12	56.6	1.38	56.4	1.30	
15	23.8	1.61, 1.13	25.0	1.82, 1.40	24.8	1.80, 1.38	
16	22.6	2.13, 1.58	29.1	2.18, 2.06	27.2	2.34, 2.03	
17	56.1	2.19	50.1	3.72	51.6	3.01	C-12, C-13, C-16, C-18, C-20, C-21; N-20
18	12.9	0.56	13.4	0.71	13.7	0.63	C-12, C-13, C-14, C-17
19	18.9	0.99	19.3	1.02	19.3	1.02	C-1, C-5, C-9, C-10
20	154.9		173.0		162.0		
21	15.0	1.73[c]	210.7		191.9		C-17, C-20; N-20[b]
MeCO_2	21.0	1.98	21.4	2.03	21.4	2.03	
Me*C*O_2	169.6		170.5		170.5		
OH		10.32[c]					C-20[b]

[a]Spectral data for oxime **1** are given in ref. 13. [b]For oxime **1** only. [c]A spatial closeness of the protons was observed in 1D NOE spectrum.



Scheme 2

plicated its purification. In chloroform, the reaction of oxime **1** gave selectively thione **2**, though in low yield (Scheme 2). The low yield of thione **2** can be explained by side reactions of acetoxime group, as well as sensitivity of double bond in steroid part to action of S_2Cl_2. Our attempts to isolate side products from the reaction mixtures failed because of their instability in a column of Silica gel. The structure of thione **2** with retained steroid part of the molecule was confirmed by analysis of its NMR spectra (Table 1). $^1H/^{15}N$ HMBC experiment displayed correlation peak for H-17 with a nitrogen at –48 ppm.

Unfortunately, all our endeavours to directly prepare ketone **3** from oxime **1** by our recently published procedure[10] (with replacement of thioacetamide by formic acid at the last step of the reaction) were unsuccessful. Treatment of thione **2** with mercury(II) acetate in AcOH which was previously used to convert 1,2-dithiole-3-thiones into 1,2-dithiol-3-ones,[15] afforded in fact low yield of ketone **3**. This could be due to poor solubility of thione **2** in AcOH which led to prolonged reaction time and formation of several by-products. The similar situation was observed with chloroform used as a solvent: the reaction was incomplete within 10 h because $Hg(OAc)_2$ is practically insoluble in chloroform. The best yield of keto derivative **3** (53%) was achieved when the reaction was carried out in a mixture of chloroform and acetic acid at room temperature for 15 min (Scheme 2).[†] Note that direct conversion of 5*H*-1,2,3-dithiazole-3-thiones into 5*H*-1,2,3-dithiazol-3-ones has never been reported. ^1H and ^{13}C NMR data for compound **3**, which confirm 1,2,3-dithiazole ring retaining, are given in Table 1.

The biological properties of steroidal 1,2,3-dithiazoles **2** and **3** are under investigation.

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Received: 11th February 2011; Com. 11/3685