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Synthesis of substituted 1,3-oxathianes and 1,3-oxathiolanes

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The synthesis of regioisomeric substituted 1,3-oxathianes **4**, **5**, **8**, **9**, **12** and **13** and 1,3-oxathiolanes **6**, **7**, **10**, **11**, **14** and **15** from the corresponding steroidal ketones **1-3**, is described.

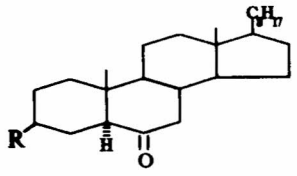
Recently synthesis of substituted 1,3-oxathiolanes[1-6] and 1,3-oxathianes[7,8] have been reported and some of them were found to possess much higher anti-HIV and anti-HBV activities[5]. 1,3-Oxathiolane derivatives are novel precursors of 2',3'-dideoxy-3'-oxa-4'-thioribonucleosides which also show anti-viral (anti-HIV) activity[6].

These facts prompted us to undertake the synthesis of steroidal 1,3-oxathiolanes and 1,3-oxathianes by the reaction of some steroidal ketones **1-3** with 1-thioglycerol in the presence of BF_3-etherate as catalyst.

The reaction of 3β-chloro- 5α-cholestan-6-one **1** with 1-thioglycerol in the presence of BF_3 -etherate as catalyst afforded 3β-chloro-(6*S*)-6,6-oxy-5'-acetoxypropylenethio-5α-cholestane **4**, 3β-chloro-(6*R*)-6, 6-oxy-5'-acetoxypropylenethio-5α-cholestane **5**, 3β-chloro-(6*S*)-6,6-oxy-5'-acetoxymethylethylenethio-5α-cholestane **6** and 3β-chloro-(6*R*)-6, 6-oxy-5'-acetoxymethylethylene-5α-cholestane **7**. Under similar conditions 3β-acetoxy-5α-cholestane-6-one **2** provided 3β-acetoxy-(6*S*)-6,6-oxy-5'-acetoxypropylenethio-5α-cholestane **8**, 3β-acetoxy-(6*R*)-6,6-oxy-5'-acetoxypropylenethio-5α-cholestane **9**, 3β-acetoxy-(6*S*)-6,6-oxy-5'-acetoxymethylethylenethio-5α-cholestane **10** and 3β-acetoxy-(6*R*)-6, 6-oxy-5'-acetoxymethylethylenethio-5α-cholestane **11**, and 5α-cholestan-6-one **3** gave (6*S*)-6, 6-oxy-5'-acetoxypropylenethio-5α-cholestane **12**, (6*R*)-6,6-oxy-5'-acetoxypropylenethio-5α-cholestane **13**, (6*S*)-6,6-oxy-5'-acetoxymethylethylenethio-5α-cholestane **14** and (6*R*)-6,6-oxy-5'-acetoxymethylethylenethio-5α-cholestane **15**.

The regioisomeric 1,3-oxathianes **4**, **5**, **8**, **9**, **12**, **13** and 1,3-oxathiolanes **6**, **7**, **10**, **11**, **14**, and **15** were characterized on the basis of their elemental analyses and spectral data (Tables I and II). In the IR spectra, absorption bands at 1425-1420, 1240-1235 cm^{-1} (S-CH_2) and 1045-1040 cm^{-1} were attributed to the hemithioketal ring[9]. The IR spectra also showed the bands for the acetoxyl group (1735-1740 cm^{-1}) as free hydroxyl groups are acetylated during the course of reaction. The ^{1}H-NMR spectra of (6*S*)-oxathianes **4**, **8**, **12** showed characteristic signals at δ 5.1-4.9 (1H, m, C5' -*H*), two distorted doublets for one proton each at δ 4.25-4.22 (C6'-*H*) and 4.0-3.95 (C6'-second *H*) and a two-proton doublet at δ 2.95-2.85 (*J*=4.9-4.8 Hz, C4'-H_2). The NMR spectra of their (6*R*)-isomers **5**, **9**, **13** had a one-proton multiplet at δ 5.1-5.0 (C5'-*H*), a two-proton doublet at δ 4.25-4.2 (*J*=4.9-4.8 Hz, C6'-H_2) and a two-proton distorted doublets at δ 2.9-2.82 (C4'-H_2). The NMR spectra of (6*S*)-oxathiolanes **6**, **10**, **14** gave a two-proton doublet at δ 4.9 (*J*=5.6-5.4 Hz, CH_2-OAc), a one-proton multiplet at δ 4.25-4.2 (C5'-*H*) and a doublet for two protons at δ 2.85-2.8 (*J*= 4.9-4.8 Hz, C4'-H_2). Their (6*R*)- isomers **7**, **11**, **15** had a two-proton doublet at δ 4.95 (*J*=5.6-5.2 Hz, CH_2-OAc), a one-proton multiplet at δ 4.22-4.2 (C5'-*H*) and distorted doublet for two protons at δ 2.85-2.8 (C4'-H_2). (In case of **10** and **11**, CH_2OAc protons merged with C3α-proton and appeared as a multiplet at 5.05-5.0).

The configuration of oxathiane rings **4**, **5**, **8**, **9**, **12** and **13** at C-6 was established on the basis of splitting pattern of their OCH_2 and SCH_2 protons in the NMR spectra. In case of (6*S*)-isomers **4**, **8** and **12** the appearance of two distorted doublets of one proton each at δ 4.25-4.22 and 4.0-3.95 for OCH_2 protons clearly indicated that C6-O bonds in **4**, **8** and **12** was axial or oxygen of oxathiane ring was axially β-oriented, while in case of their (6*R*)-isomers **5**, **9** and **13**, OCH_2 protons appeared as doublet at δ 4.25-4.2. It could be explained by assuming that the methylene protons bonded with



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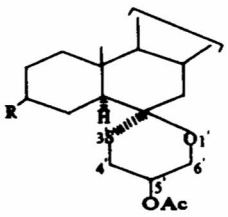

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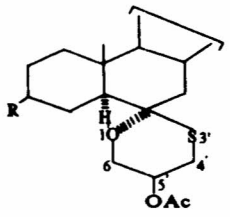
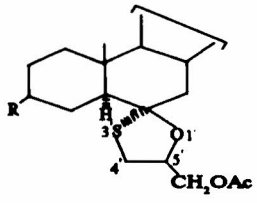
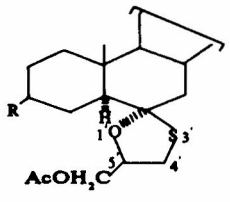


5, 9, 13



6, 10, 14



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1, 4-7 : R, Cl

2, 8-11 : R, OAc

3, 12-15 : R, H

Table I—Physical and analytical data for compounds 4-15

Compd	m.p. (°C)	Yield (%)	Mol. formula	Found (Calc.) % C	H
4	Semi-solid	32.47	$C_{32}H_{53}O_3SCl$	69.41 (69.47	9.68 9.65)
5	Oil	23.51	$C_{32}H_{53}O_3SCl$	69.42 (69.47	9.63 9.65)
6	Semi-solid	16.8	$C_{32}H_{53}O_3SCl$	69.51 (69.47	9.62 9.65)
7	Oil	12.8	$C_{32}H_{53}O_3SCl$	69.54 (69.47	9.59 9.65)
8	88	30.25	$C_{34}H_{56}O_5S$	70.73 (70.79	9.85 9.78)
9	79	21.62	$C_{34}H_{56}O_5S$	70.71 (70.79	9.81 9.78)
10	128	18.75	$C_{34}H_{56}O_5S$	70.75 (70.79	9.83 9.78)
11	119	14.53	$C_{34}H_{56}O_5S$	70.83 (70.79	9.85 9.78)
12	98	27.85	$C_{32}H_{54}O_3S$	74.02 (74.08	10.56 10.49)
13	83	20.92	$C_{32}H_{54}O_3S$	74.12 (74.08	10.53 10.49)
14	68	15.27	$C_{32}H_{54}O_3S$	74.05 (74.08	10.51 10.49)
15	61-62	11.82	$C_{32}H_{54}O_3S$	74.11 (74.08	10.45 10.49)

Table II—Spectral data for compounds **4-15**

Compd	I R (KBr)/ Nujol/Neat (ν_{max} in cm^{-1})	^{1}H-NMR($CDCl_3$) δ_H (ppm; 200 MHz)[a]	Mass (m/z)
4	1740($OCOCH_3$), 1420,1235(SCH_2) 1045(hemithio-ketal)[9]	5.1 (1H,m,5'-*H*), 4.25 (1H, distorted d, 6'-*H*), 4.0 (1H,distorted d, 6'-second *H*), 3.82 (1H, m, w½ 17 Hz, 3- α*H*)[14], 2.95 (2H, d, *J*=4.9 Hz, 4'- H_2), 2.05 (3H, s, $OCOCH_3$)	M^+ 552/554, 493/495 (M-OAc), 420/422 (M-$SCH_2CHOAcCH_2$), 516 (M-HCl), 384 (516-$SCH_2CHOAcCH_2$), 356 (384-CO).
5	1735($OCOCH_3$), 1420, 1235(SCH_2) 1045(hemithio-ketal)[9]	5.0 (1H, m, 5'-*H*), 4.2 (2H, d, *J*=4.8 Hz, 6'- H_2), 3.88 (1H, m, w½ 18 Hz, 3-αH)[14], 2.83 (2H, distorted d, 4'-H_2), 2.08 (3H, s, $OCOCH_3$)	M^+ 552/554, 493/495 (M-OAc), 420/422 (M-$SCH_2CHOAcCH_2$), 516 (M-HCl), 384 (516-$SCH_2CHOAcCH_2$), 356 (384-CO).
6	1735($OCOCH_3$), 1425,1240(SCH_2) 1040(hemithio-ketal)[9]	4.9 (2H, d, *J*=5.6 Hz, CH_2OAc), 4.25 (1H, m, 5'-*H*), 3.95 (1H, m, w½ 16 Hz, 3α-*H*)[14], 2.9 (2H, d, *J*=4.8 Hz, 4'-H_2), 2.06 (3H, s, $OCOCH_3$	M^+ 552/554, 493/495 (M-OAc), 479/481 (M-CH_2OAc), 420/422 (M-SCH_2CHCH_2OAc), 516(M-HCl), 384 (516-SCH_2CHCH_2OAc), 356(384-CO).
7	1740($OCOCH_3$), 1420,1235(SCH_2) 1045(hemithio-ketal)[9]	4.95 (2H, d, *J*=5.5 Hz, CH_2OAc), 4.22 (1H, m, 5'-*H*), 3.9 (1H, m, w½ 15 Hz, 3-α*H*)[14], 2.8 (2H, distorted d, 4'-H_2), 2.08 (3H, s, $OCOCH_3$)	M^+ 552/554, 493/495 (M-OAc), 479/481 (M-CH_2OAc), 420/422 (M-SCH_2CHCH_2OAc), 516(M-HCl), 384 (516-SCH_2CHCH_2OAc), 356(384-CO).
8	1740($OCOCH_3$), 1420,1235(SCH_2) 1045(hemithio-ketal)[9]	5.0 (2H, m, 3-α*H* & 5'-*H*), 4.25 (1H, distorted d, 6'-*H*), 3.95(1H,distorted d,6'-second *H*), 2.9 (2H, d, *J*=4.8 Hz 4'-H_2), 2.08, 2.01 (2 x $OCOCH_3$).	M^+ 576, 516 (M-AcOH), 444 (M-SCH_2-CHOAc CH_2), 416 (444-CO), 384 (516-SCH_2 CHOAc CH_2), 356 (384 -CO).
9	1740 ($OCOCH_3$), 1425, 1240 (SCH_2) 1045 (hemithio-ketal)[9]	5.1 (2H, m, 3-α*H* & 5'-*H*), 4.2 (2H, d, *J*=4.9 Hz 6'-H_2), 2.82 (2H, distorted d, 4'-H_2), 2.06, 2.01 (2 x $OCOCH_3$)	M^+ 576, 516 (M-AcOH), 444 (M-SCH_2-CHOAc CH_2), 416 (444-CO), 384 (516-SCH_2CHOAc CH_2), 356 (384 -CO).
10	1735 ($OCOCH_3$), 1420, 1235 (SCH_2) 1040 (hemithio-ketal)[9]	5.0 (3H, m, 3-α*H* & CH_2OAc) 4.25 (1H, m, 5'-*H*), 2.85 (2H, d, *J*=4.9 Hz, 4'-H_2), 2.08, 2.01 (2 x $OCOCH_3$)	M^+ 576, 516 (M-AcOH), 503 (M-CH_2OAc), 444 (M-SCH_2CHCH_2OAc), 416 444-CO), 384 (516-SCH_2-$CHCH_2OAc$), 356 (384 -CO).
11	1740 ($OCOCH_3$), 1420, 1235 (SCH_2) 1045 (hemithio-ketal)[9]	5.05 (3H, m, 3-α*H* & CH_2OAc) 4.2 (1H, m, 5'-*H*), 2.82 (2H, distorted d, 4'-H_2), 2.08, 2.01 (2 x $OCOCH_3$)	M^+ 576, 516 (M-AcOH), 503 (M-CH_2OAc), 444 (M-SCH_2CHCH_2OAc), 416 444-CO), 384 (516-SCH_2-$CHCH_2OAc$), 356 (384 -CO).
12	1740 ($OCOCH_3$), 1425, 1235 (SCH_2) 1045 (hemithio-ketal)[9]	4.9 (1H, m, 5'-*H*), 4.22 (1H, distorted d, 6'-*H*), 3.95 (1H, distorted d, 6'-second *H*), 2.85 (2H, d, *J*=4.8 Hz, 4'-H_2), 2.06 (3H, s,$OCOCH_3$)	M^+ 518, 459 (M-OAc), 386 (M-$SCH_2CHOAcCH_2$), 358 (386-CO).
13	1740 ($OCOCH_3$),	5.0 (1H, m, 5'-*H*), 4.25 (2H,	M^+ 518, 459 (M-OAc),

Contd.

Table II—Spectral data for compounds **4-15**

Compd	I R (KBr)/ Nujol/Neat (ν_{max} in cm^{-1})	^{1}H-NMR($CDCl_3$) δ_H (ppm; 200 MHz)[a]	Mass (m/z)
	1420, 1240 (SCH_2) 1040 (hemithio-ketal)[9]	d, J=4.6 Hz, 6'-H_2), 2.8 (2H, distorted d, 4'-H_2), 2.08 (3H, s, $OCOCH_3$)	386 (M-$SCH_2CHOAcCH_2$), 358 (386-CO).
14	1740 ($OCOCH_3$), 1420, 1240 (SCH_2) 1045 (hemithio-ketal)[9]	4.9 (2H, d, J=5.4 Hz, CH_2OAc), 4.2 (1H, m, 5'-H), 2.83 (2H, d, J=4.9 Hz, 4'-H_2), 2.05 (3H, s, $OCOCH_3$)	M^+ 518, 459 (M-OAc), 445 (M-CH_2OAc), 386 (M-SCH_2CHCH_2OAc), 358 (386-CO).
15	1740 ($OCOCH_3$), 1420, 1240 (SCH_2) 1045 (hemithio-ketal)[9]	4.95 (2H, d, J=5.6 Hz, CH_2OAc), 4.2 (1H, m, 5'-H), 2.80 (2H, distorted d, 4'-H_2), 2.08 (3H, s, $OCOCH_3$)	M^+ 518, 459 (M-OAc), 445 (M-CH_2OAc), 386 (M-SCH_2CHCH_2OAc), 358 (386-CO).

[a]Angular and side-chain methyl protons appeared at δ 1.2-0.67

the axially oriented oxygen atom were magnetically non-equivalent, thus they behave differently towards the applied field and appeared at different chemical shifts and when oxygen is equatorially oriented the methylene protons were almost magnetically equivalent[10] and thus had the same chemical shifts. The distortion in doublets might be considered due to the long-range coupling[10].

Experimental Section

IR spectra were recorded in KBr/nujol mull/neat on a Perkin Elmer infrared 782 spectrophotometer, ^{1}H-NMR spectra in $CDCl_3$ on a Bruker BZH-52 instrument using TMS as internal standard.

Reactions of Steroidal ketones with 1-thioglycerol in the presence of BF_3-etherate: General procedure. To a solution of ketone **1**[11] (1.7 g, 4.037 mmol) in acetic acid was added 1-thioglycerol (0.487 g, 4.5 mmol) and freshly distilled BF_3- etherate (1.5 mL) and left at room temperature for 30 min. After completion of reaction, methanol (10 mL) was added, reaction mixture was poured into water and extracted with ether. The ethereal layer was washed successively with water, aq. $NaHCO_3$ solution (5%) and water, and dried over anhyd. Na_2SO_4. Removal of the solvents gave an oily residue which was chromatographed over a silica gel column (light pet.ether-diethyl ether as eluant, 9:1) to afford the oxathianes **4** as semi-solid and **5** as non-crystallizable oil, and oxathiolanes **6** as semi-solid and **7** as a non-crystallizable oil.

Similar treatment of ketone **2**[12] afforded the isomeric oxathianes **8**, m.p. 88 °C and **9**, m.p. 79 °C (recrystallized from methanol) and isomeric oxathiolanes **10**, m.p. 128 °C and **11**, m.p. 119 °C, recrystallized from methanol. Under similar reaction conditions ketone **3**[13] provided oxathianes **12**, m.p. 98 °C and **13**, m.p. 83 °C, and oxathiolanes **14**, m.p. 68 °C and **15**, m.p. 61-62 °C (recrystallized from methanol). Yields, m.ps, spectral and elemental analytical data of the products **4-15** are given in the Tables I and II.

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