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Synthesis and Structures of Steroidal Oxathiolanes

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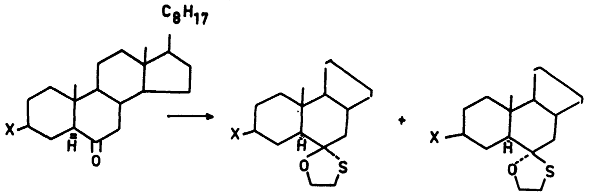
Synthesis of isomeric oxathiolanes from 6-oxosteroids is described. Configurations at spirocyclic carbon in these compounds have been established on the basis of CD and NMR spectra with the use of shift reagent [Eu(dpm)$_3$].

As an extension of a previous study,[1] the synthesis and spectrochemical studies of steroidal oxathiolanes have been carried out.



1. X=H
2. X=OAc
3. X=Cl

4. X=H
5. X=OAc
6. X=Cl

7. X=H
8. X=OAc
9. X=Cl

Results and Discussion

Reaction of ketone **1** with 2-mercaptoethanol in acetic acid ($BF_3 \cdot Et_2O$ as catalyst, room temperature) afforded a compound melting at 56 °C and a noncrystallizable oil. These compounds gave molecular ion peaks at *m/e* 446 ($C_{29}H_{50}OS$). The compound, mp 56 °C, showed characteristic bands at 1225 ($-S-CH_2$)[2] and 1065 cm^{-1} (monothioacetal group),[3] and the oil bands at 1220 ($-S-CH_2$) and 1070 cm^{-1} (monothioacetal group) in IR spectra. The NMR spectrum of the compound, mp 56°C, gave two distorted triplets at δ 4.32 and 3.92 ($-O-CH_2$) each integrating for 1 proton, and a double doublets at δ 2.78 ($-S-CH_2$; J=3.7 Hz) for 2 protons. The oil gave a distorted triplet for 2 protons at δ 4.03 ($-O-CH_2$) and a clean triplets for 2 protons at δ 2.93 ($-S-CH_2$).

The configuration of the $-O-CH_2$ and $-S-CH_2$ in the products could not be assigned with these spectral data, and [tris(dipivalomethanato) europium III] was employed as a shift reagent. Addition of the reagent to the compound, mp 56 °C, caused no significant change in the chemical shift of the signals in its NMR spectrum (Table 1), while its addition to the oily isomer showed a remarkable difference in the chemical shift of the NMR signals (Table 2). This confirmed that the $-O-CH_2$ group of monothioacetal ring attached to C(6) has an equatorial orientation in the oil, and an axial one in the compound, mp 56 °C.[4] Thus the compound is considered to be (6*S*)-6,6-oxyethylenethio-5α-cholestane **4** and the oil (6*R*)-6,6-oxyethylenethio-5α-cholestane **7**. CD data for compounds **4** (negative Cotton effect) and **7** (positive Cotton effect) (Fig. 1) further support configurational asignments for the monothioacetal ring in these compounds.[5]

By a similar treatment ketones **2** and **3** afforded oxathiolanes **5**, **8**, and **6**, **9** respectively. In NMR spectra, the splitting pattern of $-O-CH_2$ and $-S-CH_2$ protons of **5** and **6** was found identical with **4**, and oxathiolanes **8** and **9** provided similar NMR peaks for $-O-CH_2$ and $-S-CH_2$ protons as in **7**. On the basis of the NMR peak pattern the configurations at spirocyclic carbon in compounds **5**, **6**, and **8**, **9** were assigned similarly to **4** and **7**, respectively. This is supported by the negative Cotton effect (Figs. 2 and 3) for compounds **5** and **6** and positive Cotton effect (Figs. 2 and 3) for compounds **8** and **9**.

The parent ketones **1**—**3** were generated when monothioacetals **4**—**9** were treated with aqueous acetic acid.

TABLE 1. INDUCED CHEMICAL SHIFTS (δ) OF VARIOUS PROTONS OF COMPOUND **4** WITH INCREASING AMOUNT OF SHIFT REAGENT Eu(dpm)$_3$

	$-O-CH_2$	$-S-CH_2$	C(10)$-CH_3$	C(13)$-CH_3$
Sample(20.29 mg) neat	4.05	2.85	0.98	0.66
Sample(20.29 mg)+Eu(dpm)$_3$ (5.79 mg)	4.00	2.83	0.96	0.66
Sample (20.29 mg)+Eu(dpm)$_3$ (11.54 mg)	4.06	2.78	1.00	0.67
Sample (20.29 mg)+Eu(dpm)$_3$ (12.30 mg)	4.15	2.80	0.94	0.61

TABLE 2. INDUCED CHEMICAL SHIFTS (δ) OF VARIOUS PROTONS OF COMPOUND **7** WITH INCREASING AMOUNT OF SHIFT REAGENT Eu(dpm)$_3$

	$-O-CH_2$	$-S-CH_2$	C(10)$-CH_3$	C(13)$-CH_3$
Sample(22.00 mg) neat	4.03	2.93	0.98	0.67
Sample (22.00 mg)+Eu(dpm)$_3$ (6.0 mg)	4.20	3.00	0.98	0.67
Sample (22.00 mg)+Eu(dpm)$_3$ (11.16 mg)	4.63	3.03	1.03	0.70
Sample (22.00 mg)+Eu(dpm)$_3$ (15.81 mg)	4.91	3.34	1.14	0.72

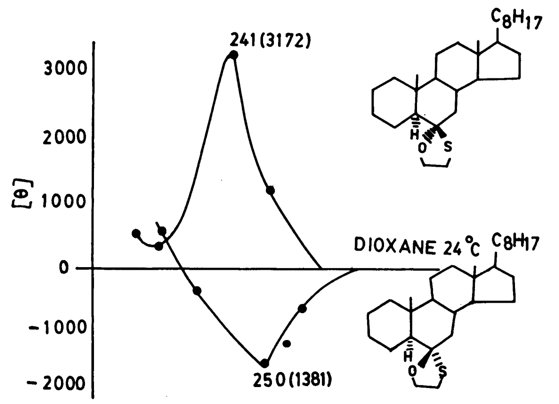


Fig. 1. CD curves of compounds **4** and **7** in dioxane at 24 °C.

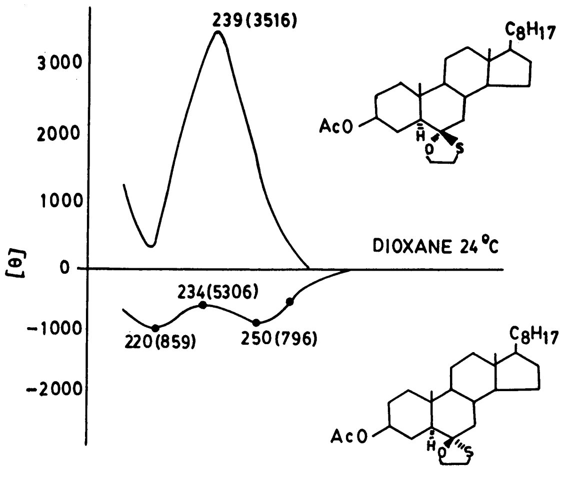


Fig. 2. CD curves of compounds **5** and **8** in dioxane at 24 °C.

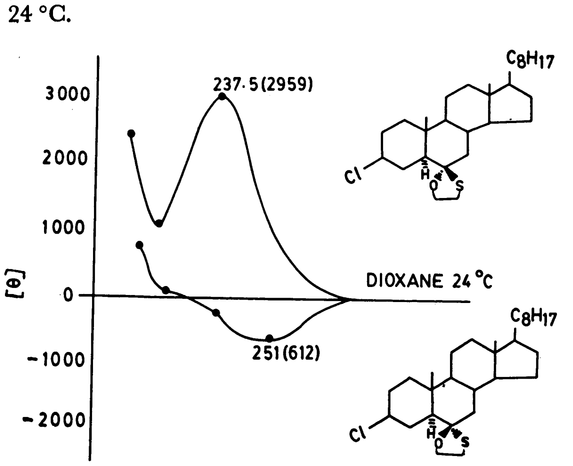


Fig. 3. CD curves of compounds **6** and **9** in dioxane at 24 °C.

Experimental

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 237 spectrophotometer, and ^{1}H-NMR spectra in $CDCl_3$ on a Varian A60 instrument (δ scale. TMS=0 ppm). CD curves were measured with a JASCO J-20 spectropolarimeter in dioxane. Mass spectra were measured on a Varian AJMS D100 mass spectrometer. TLC were performed with silica gel (BDH) and column chromatography with silica gel (BDH-60-120 mesh). NMR values in ppm (s=singlet; dd=double doublets; t=triplet; mc=multiplet centred at).

(6S)-6,6-Oxyethylenethio-5α-cholestane **4** *and (6R)-6,6-Oxyethylenethio-5α-cholestane* **7**. A solution of ketone **1**[6] (5.0 g) in AcOH (200 cm^3) was treated with 2-mercaptoethanol (10 cm^3) and $BF_3 \cdot Et_2O$ (2 cm^3) and left to stand at room temperature for 1 h. The solution was diluted with MeOH (25 cm^3), poured into water and extracted with ether. The ethereal layer was washed successively with water, $NaHCO_3$ solution (5%), water and dried (anhydrous Na_2SO_4). The oil (5.0 g) obtained after removal of ether under reduced pressure was chromatographed over silica gel (100 g). Elution with light petroleum ether afforded **4**; solidified on being left at room temperature (2.0 g); mp 56 °C; MS (70 eV) *m/e* 446 (30%) (M$^+$); Found: C, 78.03; H, 11.01%. Calcd for $C_{29}H_{50}OS$: C, 78.02; H, 11.20%; CD (dioxane) $[\theta]^{20}$(nm): −1380 (250). NMR ($CDCl_3$): δ 0.68, 0.82, 0.92, and 0.98 (C(10)–; C(13)– and side chain methyl protons).

Further elution with light petroleum ether afforded **7** (2.10 g) as an oil; MS (70 eV) *m/e* 446 (28.3%) (M$^+$); Found: C, 78.03; H, 11.01%. Calcd for $C_{29}H_{50}OS$: C, 78.02, H,11.20; CD (dioxane) $[\theta]^{20)}$ (nm): +3170 (241). NMR ($CDCl_3$): δ 0.67, 0.70, 0.75, and 0.98 (C(10)–; C(13)– and side chain methyl protons).

3β-Acetoxy-(6S)-6,6-oxyethylenethio-5α-cholestane **5** *and 3β-Acetoxy(6R)-6,6-oxyethylenethio-5α-cholestane* **8**. The ketone **2**[7] (5.0 g) was treated with 2-mercaptoethanol (10 cm^3) and $BF_3 \cdot Et_2O$ (2 cm^3) in AcOH (200 cm^3) in the same way as for **1**. The oil obtained after removal of the solvent was chromatographed over silica gel (100 g). Elution with light petroleum ether–ether (22 : 1) afforded **5**, recrystallized from light petroleum ether (2.20 g); mp 142 °C, MS (70 eV) *m/e* 504 (12.5%) (M$^+$); Found: C, 73.81; H, 10.49%. Calcd for $C_{31}H_{52}O_3S$: C, 73.8; H, 10.51%; CD (dioxane) $[\theta]^{20)}$ (nm): −860 (220) and −800 (250). IR (KBr): 1740 (CH_3–CO–O–), 1240 (C–O), and 1030 cm^{-1} (monothioacetal group); NMR ($CDCl_3$): δ 4.7 (mc, $W_{1/2}$=16 Hz, C(3)α-$\underline{H}$), 4.28, 3.9 (distorted tripletes, –O–C$\underline{H}_2$–), 2.86 (dd, J=3.6 Hz, –S–C$\underline{H}_2$–), 2.03 (s, C(3)–O–CO–C$\underline{H}_3$), 0.70, 0.83, 0.93, and 1.0 (C(10)–, C(13)–, and side chain methyl protons).

Further elution with light petroleum ether-ether (20 : 1) yielded **8** recrystallized from light petroleum ether (2.0 g), mp 106°C; MS (70 eV) *m/e* 504 (11.4%) (M$^+$); Found: C, 73.80; H, 10.49%. Calcd for $C_{31}H_{52}O_3S$: C, 73.8; H, 10.51%; CD (dioxane) $[\theta]^{20)}$ (nm): +3520 (239). IR (KBr): 1740 (CH_3–CO–O–), 1240 (C–O–), and 1030 cm^{-1} (monothioacetal group); NMR ($CDCl_3$): δ 4.73 (mc, $W1/2$=16 Hz, C(3)α-H), 4.03 (distorted triplet, –O–C$\underline{H}_2$–), 1.96 (t, –S–C$\underline{H}_2$–), 2.03 (s, C(3)β-O–CO–C$\underline{H}_3$), 0.70, 0.80, 0.90, and 0.98 (C(10)–(C(13)–, and side chain methyl protons).

3β-Chloro-(6S)-6,6-oxyethylenethio-5α-cholestane **6** *and 3β-Chloro-(6R)-6,6-oxyethylenethio-5α-cholestane* **9**. The ketone **3**[8] (5.0 g) was treated with 2-mercaptoethanol (10 cm^3) and $BF_3 \cdot Et_2O$ (2 cm^3) in AcOH (200 cm^3) in the same way as for **1** and **2**. Compounds **6** and **9** were separated. Compound **6** was recrystallized from light petroleum ether (1.8 g), mp 152 °C; MS (70 eV) *m/e* 480/482 (3 : 1) (26.0%) (M$^+$); Found C, 72.30; H, 10.10%. Calcd for $C_{29}H_{49}OSCl$: C, 72.5; H, 10.20%; CD (dioxane) $[\theta]^{20)}$ (nm): −610 (251). IR (KBr): 1070 (monothioacetal group), and 760 cm^{-1}; NMR ($CDCl_3$): cm^{-1}; NMR ($CDCl_3$): δ 4.0 (mc, C(3)α-H, –O–C$\underline{H}_2$), 3.86 (dd, J=3.6 Hz, –S–C$\underline{H}_2$–), 0.68, 0.80, 0.92, and 1.0 (C(10)–, C(13)–, and side chain methyl protons).

Conpound **9** was recrystallized from petroleum ether (1.75 g); mp 115 °C; MS (70 eV) *m/e* 480/482 (3 : 1) (7.0%) (M$^+$); Found: C, 72.31; H, 10.12%. Calcd for $C_{29}H_{49}OSCl$: C, 72.5; H, 10.20%; CD (dioxane) $[\theta]^{20}$ (nm): +2960 (237.5). IR (KBr): 1070 (monothioacetal group), and 760 cm^{-1} (C–Cl); NMR ($CDCl_3$): δ 4.05 (mc, C(3)α-H, $-O-C\underline{H}_2-$), 2.97 (t, $-S-C\underline{H}_2-$), 0.68, 0.78, 0.92, 0.98 (C(10)–, C(13)–, and side chain methyl protons).

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