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Mercury and Cadmium Thiosteroid Complexes*

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The following complexes R–Hg–X and R–Cd–OAc·2H$_2$O (R = spironolactone, spiroxazone; X = Cl, Br) have been synthesized by reacting the steroid with the corresponding metal salt in absolute or aqueous ethanol. A mechanism of this reaction is presented. The synthesized complexes have been studied and identified spectroscopically (IR, NMR, MASS); these data as well as elemental analyses are given.

Introduction

In the last five years the mercury problem has been seriously considered by scientists and has attained epidemic proportions, *e.g.* "Minamata" disease (poisoning from organic mercury compounds) [1]. The known antidotes against mercury poisoning, and especially in acute cases, have a sulfur containing group. This sulfur is believed to substitute the protein sulfur of the tissues in the reaction with mercury. Since 1970, several thiosteroids have been tried [2] as antidotes against acute mercury poisoning and extensive research has been reported with encouraging results [3].

Cadmium was recognized many years ago to be a highly toxic element. However, only recently the cadmium problem started to be under serious consideration because of its increasing utilisation and consequent increase in the general environment and because of the outbreak of the "itai–itai" disease in Japan the early 1950's [4].

We have studied the *in vitro* [5] and are presently conducting some *in vivo* [6] experiments of mercury with two thiosteroids, *i.e.* 7a-thioacetyl-17-hydroxy-3-oxo-androstene-17a-propionic acid γ-lactone (spironolactone, SNL) and 7a-thioacetyl-(17R)-spiro-[androst4-en 17,2(3H)furan] (spiroxazone, SXZ) with satisfactory results in both cases.

In this paper we report the synthesis of a series of mercury and cadmium thiosteroid complexes. The mercury salts used in this study were the chloride and bromide and that of cadmium was the acetate dihydrate. The complexes were studied and characterized using spectroscopic (IR, NMR and MASS) and analytical data.

Experimental

Methods of Preparation

Spironolactone (Searle & Co.) and spiroxazone (Merck) were used after recrystallisation from ethanol. Mercury chloride, bromide and cadmium acetate dihydrate were used without further purification. The following complexes have been synthesized and characterized: SNL–Hg–X, SXZ–Hg–X: X = Cl and Br; SNL–Cd–OAc·2H$_2$O, SXZ–Cd–OAc·2H$_2$O.

SNL–Hg–Cl. SNL (208.2 mg) was dissolved in aqueous ethanol (less than 45% in water) and the HgCl$_2$ in equimolar amount (135.8 mg) dissolved in the same solvent and was added to the above solution. After 3 hours' reflux, the solution became cloudy. A white precipitate started to be formed after one hour's heating at 50 °C, it was left overnight, collected and washed with water and ethanol. After filtration the color of the precipitate started to change to yellow. Using ethanol for recrystallization the white precipitate gave a turbid solution from which a yellow precipitate was obtained. The same yellow precipitate gave the above reaction when methanol, acetone, propanol were used as solvents. The white precipitate became yellow even at low temperatures and in the absence of light. The compound was extremely unstable, and was purified using TLC (system ethyl acetate: chloroform 1:1; R$_f$ 0.30). Yield: 68%. M.p. 180 °C (with decomp.). *Anal.* For

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*Taken in part from the M.Sc. Thesis of G.P.

SNL–Hg–Cl, Calcd C, 43.34; H, 4.76 and Hg, 32.93%. Found C, 44.02; H, 4.80 and Hg, 33.25%.

When the reaction was carried out in non aqueous solutions the complex could not be isolated because of its decomposition.

SNL–Hg–Br. SNL (208.3 mg) and $HgBr_2$ (108.2 mg) were dissolved in aqueous ethanol (30%) and refluxed for about 4 hours. The cloudy solution after one night gave a grayish precipitate which was collected and washed with ethanol and water. Further attempts to recrystallize the complex were unsuccessful, because the compound decomposed to give a yellow–red precipitate, a salt of the formula $(SHgBr)_n$, and canrenone. Yield: 60%. M.p. 125 °C with decomp. *Anal.* For SNL–Hg–Br: Calcd C, 40.73; H, 4.43 and Hg 30.68%. Found C, 41.00; H, 4.50 and Hg 30.42%.

SNL–Cd–OAc·2H₂O and SXZ–Cd–OAc·2H₂O

Equimolar quantities of SNL (208.3 mg) or SXZ (201.2 mg) and $Cd(OAc)_2 \cdot 2H_2O$ (133.2 mg) were refluxed overnight in absolute ethanol. A white amorphous precipitate was collected and washed with absolute ethanol. It was insoluble in most solvents except in DMSO. Yield: 78%; M.p. 245 °C with decomp. *Anal.* For SNL–Cd–OAc·$2H_2O$: Calcd C, 49.65; H, 6.19; S, 5.50 and Cd, 19.34%. Found C, 50.13; H, 6.20; S, 5.60 and Cd, 19.19%.

Yield 84% M.p. 236 °C with decomp. *Anal.* For SXZ–Cd–OAc·$2H_2O$: Calcd C, 50.79; H, 6.70; S, 5.64 and Cd 19.82%. Found C, 51.03; H, 6.80; S, 5.66 and Cd 19.98%.

SXZ–Hg–Cl. SXZ (201.2 mg) was dissolved in aqueous–ethanol solution (45% water) in which a solution of $HgCl_2$ (135.8 mg) in the same solvent was

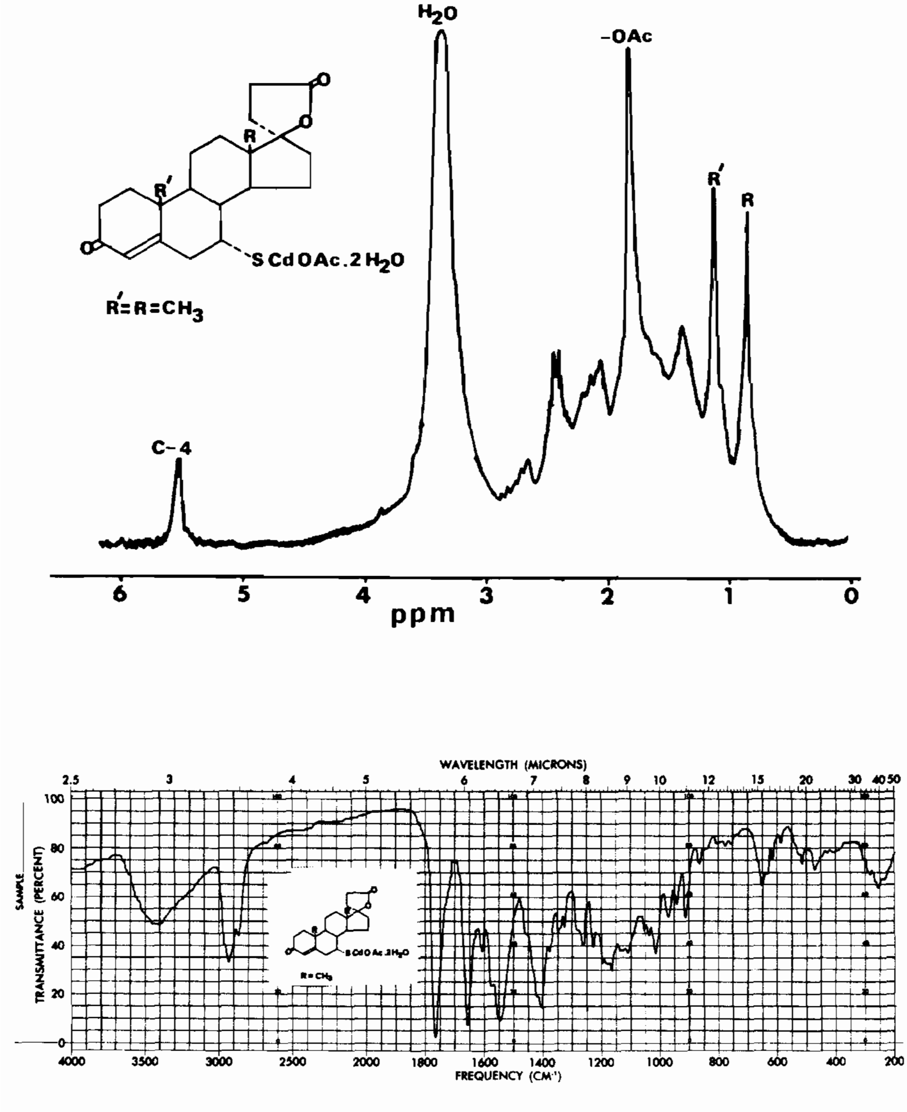


Figure 1.

added and it was stirred at 80 °C for about 4 hours until it started to become cloudy. It was then left overnight and a light gray precipitate was formed. As in the case of SNL–Hg–Cl, recrystallization was abandoned due to decomposition. However, nice crystals were obtained when the mother liquid was left for long after filtration. Yield: 75% M.p. 170 °C with decomp. *Anal.* For SXZ–Hg–Cl: Calcd C, 44.37; H, 5.21; S, 5.37 and Hg, 33.68%. Found C, 44.65; H, 5.23; S, 5.19 and Hg 33.73%.

SXZ–Hg–Br. Equimolar quantities of SXZ (201.2 mg) and $HgBr_2$ (180.2 mg) were refluxed in an aqueous ethanol solution. After 4 hours, the solution became cloudy. The complex was separated by TLC (system ethyl acetate: chloroform 16:1; R_f 0.80). Yield 72%. M.p. 121–2 °C with decomp. The product was recrystallized twice from ethanol and gave nice single crystals. *Anal.* For SXZ–Hg–Br: Calcd C, 41.25; H, 4.84; S, 5.00 and Hg, 31.34%. Found C, 41.37; H, 4.90; S, 5.05 and Hg, 31.60%.

Using same procedures as before attempts were made to complex the 7a-Ethylthio-17-hydroxy-3-oxo-4-androstene-17a-propionic acid, γ lactone (SNL-Et) ligand with HgX_2 (X = Cl, Br) but did not give any complex formation.

Attempts were also made to complex SNL with $CdCl_2$ but no complex could be isolated. Canrenone and CdS were the final results.

Spectra

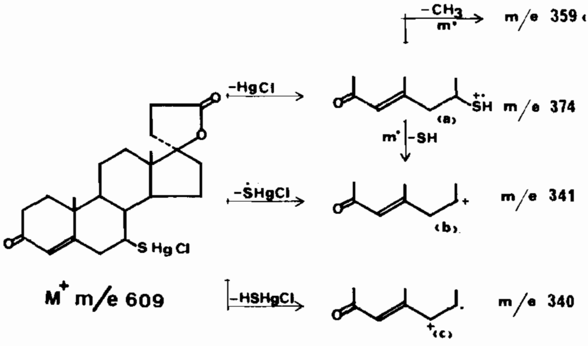
Infrared spectra were recorded with a Perkin–Elmer 621 grating spectrophotometer. The spectra of the complexes were obtained in nujol mulls or KBr pellets. ^1H NMR spectra were obtained in $CDCl_3$ as well as DMSO solutions using a Varian T60 spectrometer. TMS was used as internal standard. Mass spectra were recorded in a Hitachi–Perkin Elmer R.M.U. 60 spectrometer. Metal analyses were performed by Atomic Absorption using a Perkin–Elmer 403 spectrophotometer.

Results and Discussion

The formation of the complexes from metals and ligands used is shown from their IR and NMR spectra. The IR spectrum of SNL [5] shows the three carbonyl stretching frequencies at 1760 cm^{-1} (C_{22}=O), 1685 cm^{-1} (C_{24}=O) and 1660 cm^{-1} (C_3=O). The C_3=C_4 double bond absorption is located at 1615 cm^{-1}. Comparing the IR spectrum of SNL with that of the complex SNL–M–X (M = Hg, Cd; X = Cl, Br, OAc·$2H_2O$) shows that the band at 1685 cm^{-1} (C_{24}=O) of the SNL is missing from the spectra of the complexes. The formation of the complexes is further confirmed by their NMR spectra. The NMR spectrum of SNL [5] showed a sharp peak at 2.30 ppm due to the methyl protons (–CO–CH_3). This caracteristic peak was missing from the spectra of the complexes. In addition, both IR and NMR spectra clearly show the presence of the cadmium acetate group (–Cd–OAc·$2H_2O$). The two strong bands at 1545 cm^{-1} and 1410 cm^{-1} (Fig. 1) and the appearance of the sharp NMR peak at 1.78 ppm (Fig. 1) of the methyl protons of the –$CdOCOCH_3$·$2H_2O$ helped in the identification of this group. The presence of the water was indicated by the IR band at 3420 cm^{-1} as well as by the large and brood NMR peak at about 3.20 ppm.

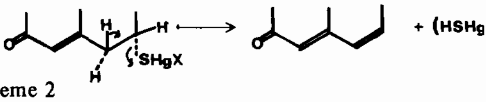
For the complexes SNL–Hg–X (X = Cl, Br) the NMR spectra (Fig. 2) did not show the presence of the –$COCH_3$ group of the ligand. The metal–halide vibrations were too weak in the IR spectra (Fig. 2). However, analytical results do show the halide presence in the complexes.

The mass spectrum of the SNL–Hg–Cl (Fig. 3) gave a base peak at m/e 340 which is due to the loss of the HSHgCl moiety. The presence of mercury was shown by the peaks at m/e 198, 199, 200, 201, 202 and 204 with 100% according to their natural abundances (10, 12, 23, 13, 30 and 7% respectively). The half atomic weight peaks at m/e 99, 99.5, 100, 100.5, 101 and 102 were also observed. The molecular ion peak could not be seen in the spectrum. Other important peaks were at m/e 374 (a), m/e 341 (b), m/e 340 (c) and m/e 359 (d) which have been interpreted (see scheme 1):



Scheme 1

The complexes were not stable in ethanol, methanol and chloroform solutions. In the solid state they decompose slowly turning yellow–orange. The decomposition products from both the solution and the solid state reactions were the same. The following mechanism is proposed for this decomposition (see scheme 2):



Scheme 2

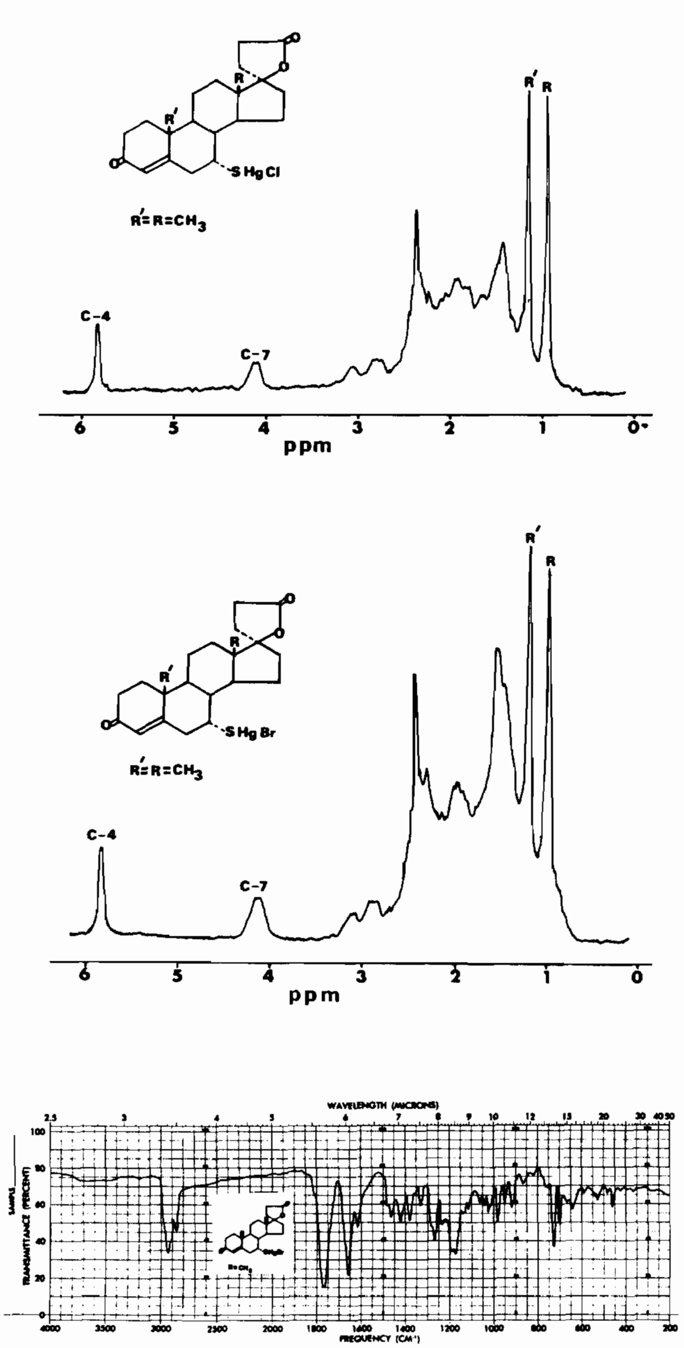
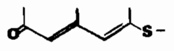


Figure 2.

The C_7–S bond is activated because of the coordination of the metal and the S atom becomes more positive and as a result this bond is cleaved. The halide attracts electrons from S *via* Hg and thus reduces further the density of the S. Furthermore, the system:



with two double bonds renders C_7 electropositive, and the C_7–S bond cleaves to give canrenone [6] and $(HS–Hg–X)_n$.

The S–M bond is the most logical site of attack in the present complexes. Furthermore, the presence of the acetyl group ($-COCH_3$) on the sulfur atom makes the S–M bond more labile and the elimination of this

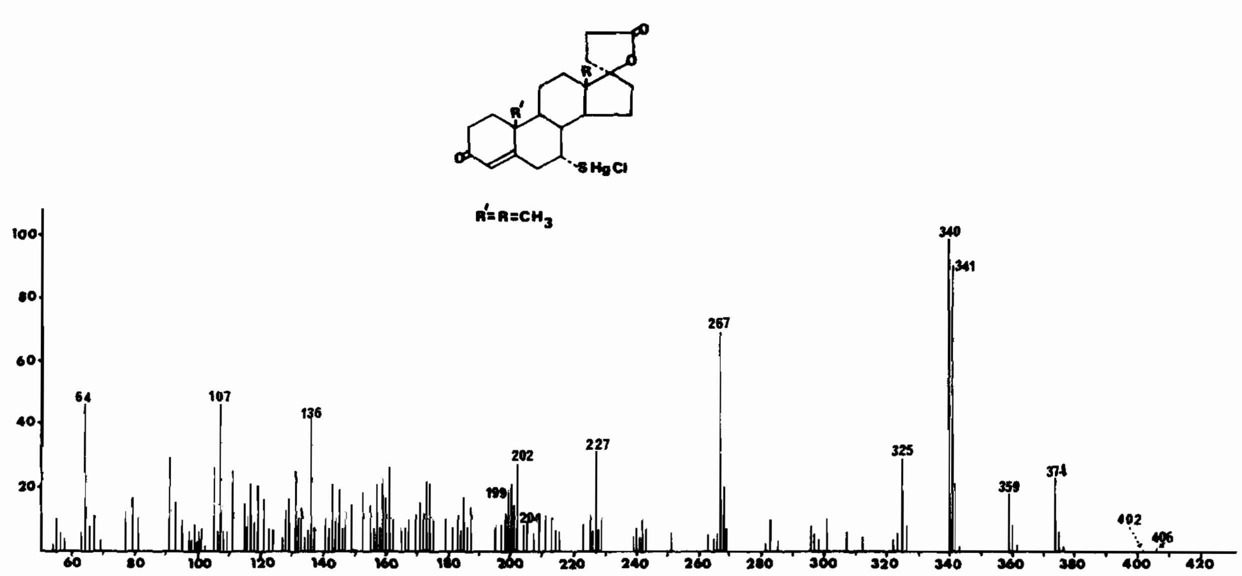
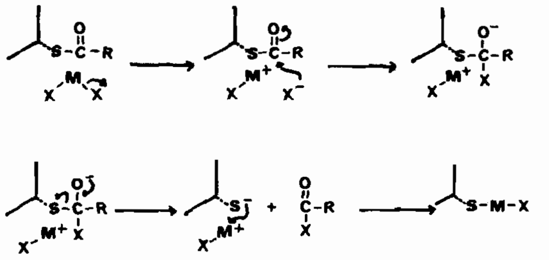


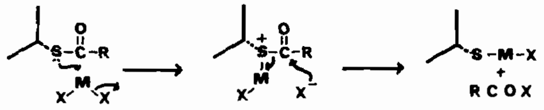
Figure 3.

group could facilitate the attack by leaving a charge on the sulfur atom. The overall proposed mechanism of reaction is given in scheme 3:



Scheme 3

The carbonyl group attached to the S plays an important role in the whole mechanism by making the S–C bond more labile. This is further supported by the fact that the above reaction did not take place if in the SNL the –Ac group is substituted by the –Et group. The above proposed S_N1 mechanism is not the only possible explanation for the reaction because a S_N2 mechanism is also possible (see scheme 4):



Scheme 4

A kinetic study of this reaction should be performed in order to differentiate between these two possibilities.

The ligand SXZ, the second steroid studied, showed the following characteristic NMR peaks [5]:

C_{18}	C_{19}	C_4	C_7	C_{22}	C_{24}
1.24(s)	0.94(s)	5.72(s.br.)	3.97(db)	3.77(w)	2.32(s)

Its IR spectrum showed the two characteristic carbonyl stretching frequencies at 1685 cm^{-1} (C_{24}=O) and 1660 cm^{-1} (C_3=O). The double bond (C_4=C_5) was located at 1610 cm^{-1} (Fig. 4).

The complexes were characterized and identified by their analytical, IR and NMR data. There were also observed in the IR spectrum of the complex SXZ–Cd–OAc·$2H_2O$ the two strong bands of the Cd–OAc group at 1555 and 1410 cm^{-1}. A weak band at 248 cm^{-1} could be attributed to the Cd–S while the weak band at 340 cm^{-1} to the Hg–S vibration. The band at 1685 cm^{-1} (SXZ) was not observed in the IR spectra of the complexes (Fig. 4). This result was corroborated with NMR data which showed that the peak of the methyl protons of the acetyl group (SXZ) at 2.32 ppm was missing from the spectra of the complexes (Fig. 5). The methyl protons of the –$CdOCOCH_3 \cdot 2H_2O$ moiety appeared at 1.17 ppm (DMSO). The water peak was located at about 3.35 ppm as a broad band. The absence of the peak at 2.32 ppm in the NMR spectra of the halide complexes is evidence for the elimination of the –$COCH_3$ group. The two halide complexes were not very stable but they were more stable than those of SNL. A similar mechanism for the formation of those complexes could be proposed as in the case of SNL complexes.

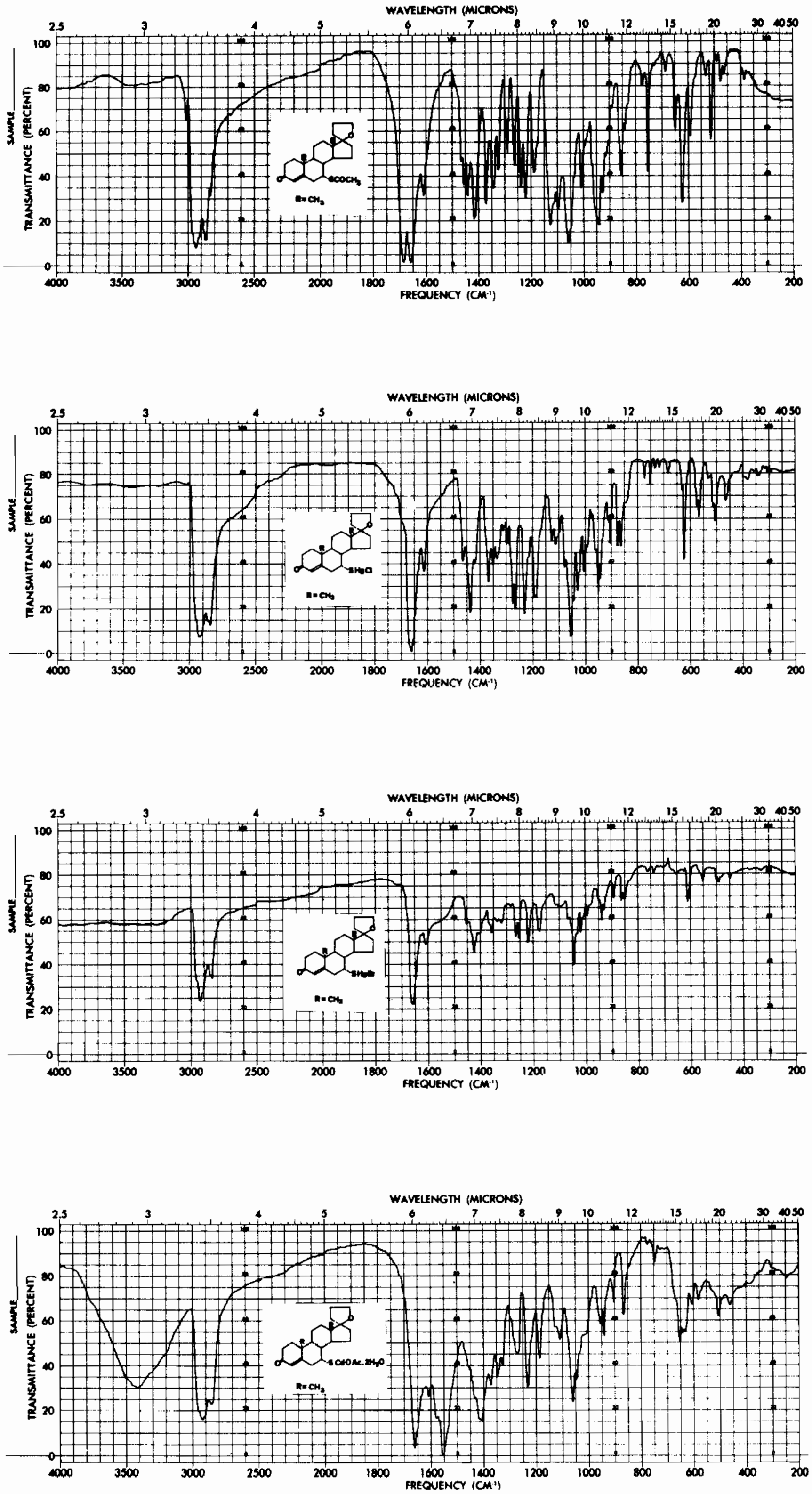

WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
30
40 50
100
80
60
40
20
0
SAMPLE
TRANSMITTANCE (PERCENT)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
200
FREQUENCY (CM⁻¹)
SCOCH₃
R = CH₃
SHgCl
R = CH₃
SHgBr
R = CH₃
S CdOAc.2H₂O
R = CH₃

Figure 4.

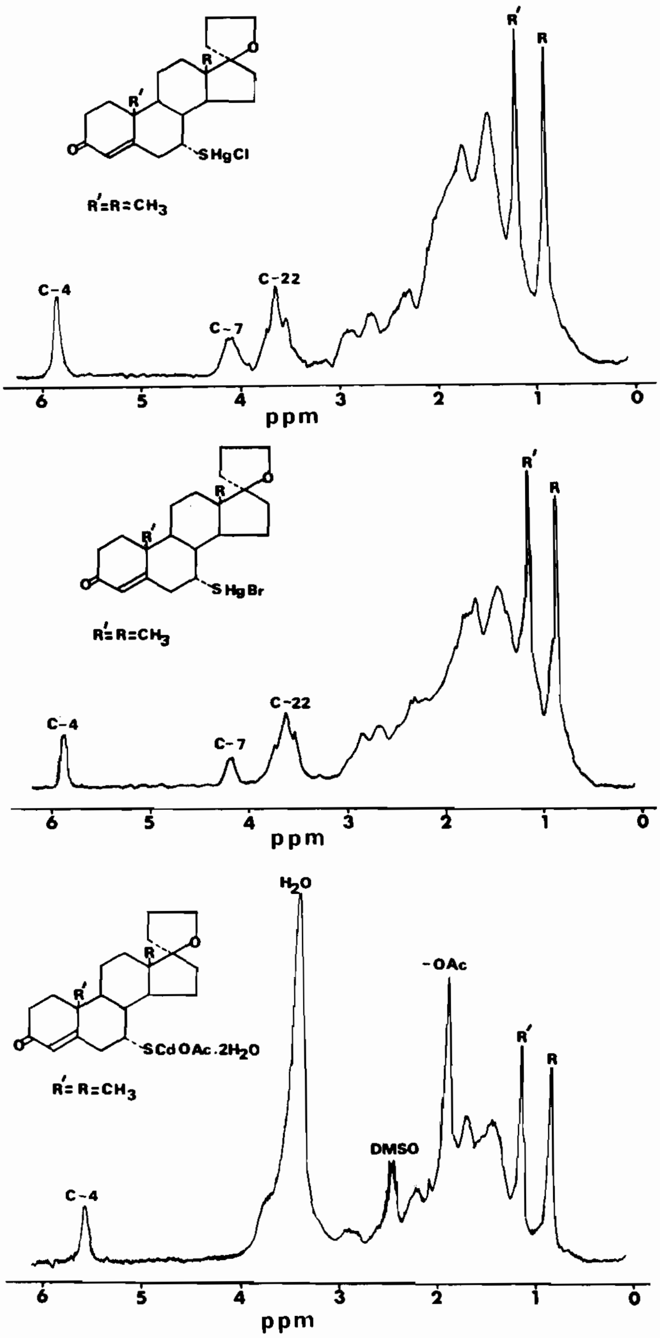


Figure 5.

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