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Preparation and Characterization of Metal–Thiosteroid Complexes

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The complexes SNL-Hg-OAc and SXZ-Hg-OAc, where $SNLCOCH_3$ = Spironolactone or 7α-thioacetyl-17-hydroxy-3-oxo-androstene-17α-propionic acid γ-lactone, $SXZCOCH_3$ = Spiroxazone or 7α-thioacetyl-(17R)-spiro[androst-4-en17,2(3H)furan] and OAc = acetate have been prepared by the reaction between the mercuric salt $(CH_3COO)_2Hg$ and the thiosteroid by stirring at room temperature in absolute ethanol solution. Infrared, proton nuclear magnetic and analytical data are reported for the complexes and the thiosteroids.

Introduction

Recently, there has been much interest in the thiosteroid–metal interactions with respect to structure activity relationship. These thiosteroids offer considerable protection against heavy metal poisoning. In particular, mercury poisoning has been prevented by spironolactone and experiments on rats clearly show important protection against acute intoxications by arsenic[1] and effects on the distribution and excretion of $HgCl_2$ in the rat[2–4]. It has been found that pretreatment with the above thiosteroids prevents renal and kidney damage by mercury.

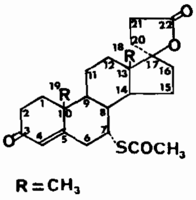
The thioacetyl group on these steroids is an effective reactive site with many metals including mercury. We have attempted to see if this group was really responsible for the mercury–thiosteroid interaction and establish, if possible, whether the Hg–S bond is responsible for this interaction.

Experimental

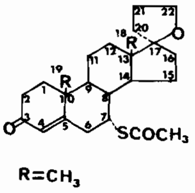
Materials and Methods

Spironolactone (Searle & Co) and Spiroxazone (Merck) were used without further purification. Hg $(CH_3COO)_2$ was obtained from Alfa Inorganics and was used directly. The chemical structures of the two steroids are the following:

$SNLCOCH_3$: Spironolactone. Aldactone A[R]
SC-9420 (Searle)



$SXZCOCH_3$: Spiroxazone (Merck)



The reaction of spironolactone was carried out at room temperature in a flask with stirring. Equimolar quantities of the ligand (208.2 mg) and the $Hg(OAc)_2$ salt (159.4 mg) were dissolved in 50 ml of absolute ethanol. A few hours later (3h), a white amorphous precipitate was formed, which was then collected on a filter and washed with absolute ethanol. Total reaction time was 12 hours. Yield: 80%. M.p. 195°C with decomp. The compound was slightly soluble in hot chloroform, methanol, acetone and soluble in dimethylsulfoxide (DMSO) and dimethylformamide (DMF). *Anal.:* Calcd. for SNL-Hg-OAc, C 45.48, H 5.05, S 5.05 and Hg 31.68%. Found: C 45.16, H 4.95, S 4.98 and Hg 31.91%.

The reaction with spiroxazone was carried out in a similar manner to spironolactone and in this case also a white precipitate was obtained. It was recrystallized from absolute ethanol. Yield: 81%. However, it was not very stable in this solvent at a temperature higher than 50°C. M.p. 178–80°C with decomp. *Anal.:* Calcd. for SXZ-Hg-OAc, C 46.75, H 5.49 and Hg 32.39%. Found: C 46.28, H 5.48 and Hg 32.19%.

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Spectra

Infrared spectra were recorded with a Perkin Elmer 621 grating spectrophotometer. The spectra of the solids were obtained in Nujol mulls or KBr pellets. ^1H NMR spectra were obtained in $CDCl_3$ solutions using a Varian T60 spectrometer. TMS was used as an internal standard. UV spectra were recorded on a Cary 14 spectrophotometer. The complexes were practically too insoluble in most solvents to allow molecular weight determinations and conductivity measurements.

Results and Discussion

The infrared spectrum for a sample of 2–3 mg of SNL-Hg-OAc in 200 mg KBr is shown in Figure 1. In the IR spectrum of the complex the band of the thiosteroid at 1685 cm^{-1}, due to the $-COCH_3$ carbonyl stretching frequency was missing. This was also shown in the NMR spectrum of the complex, where the sharp peak at 2.30 ppm due to the methyl protons of the $-COCH_3$ group was missing from the spectrum of the complex (Figure 2). In addition, both IR and NMR spectra clearly show the presence of the mercury acetate group $Hg–OCOCH_3$. The IR broad bands at 1550 cm^{-1} and 1420 cm^{-1} and the appearance of the sharp NMR peak at 2.00 ppm of the methyl protons of $Hg–OCOCH_3$ helped us to identify this group. The spironolactone IR and NMR data were compared with those published previously[5,6] with excellent agreement.

The infrared spectrum of a sample of 2–3 mg of SXZ-Hg-OAc in 200 mg KBr is shown in Figure 1. The complex was characterized and identified from

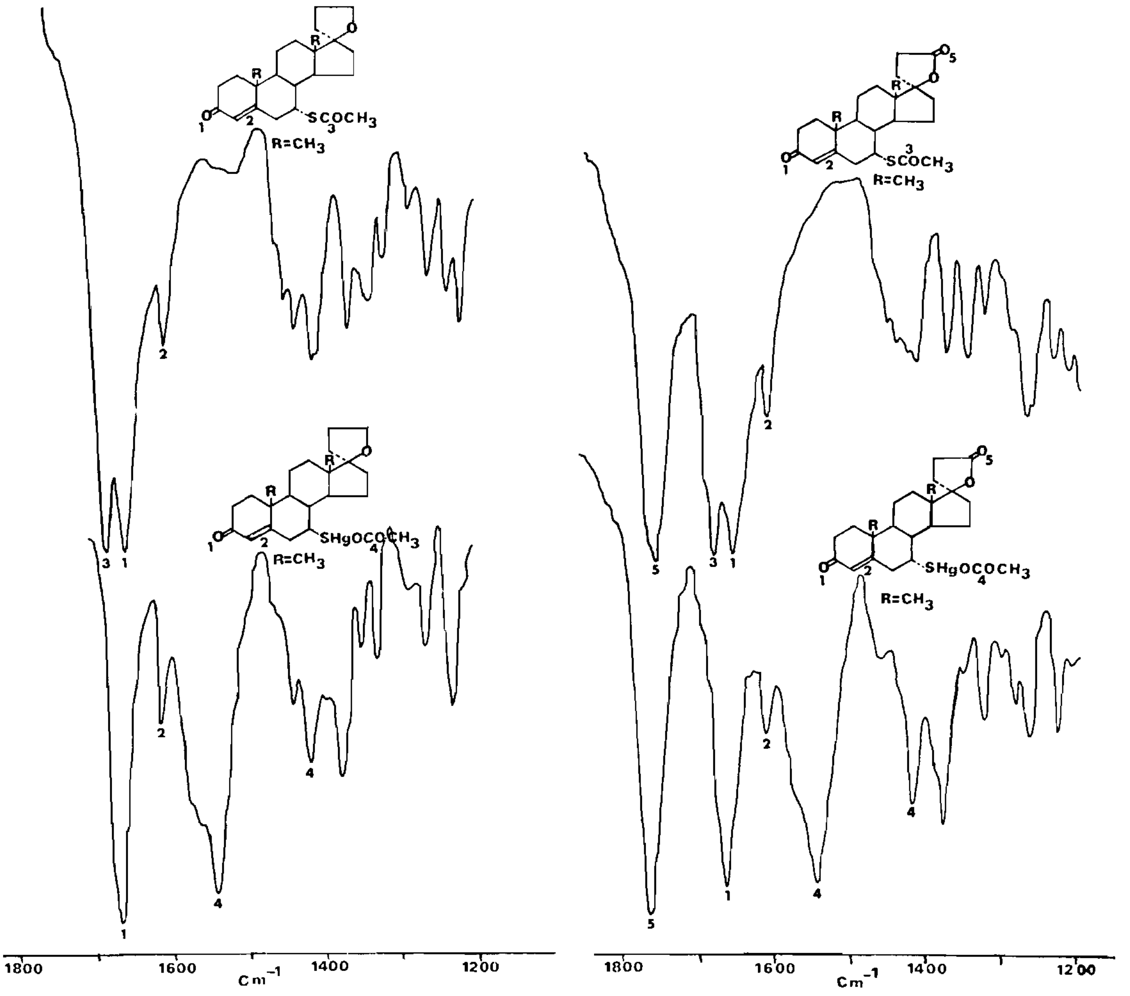


Figure 1. IR spectra of spironolactone and spiroxazone and their mercury complexes. The numbers indicate characteristic group vibrations of the steroids.

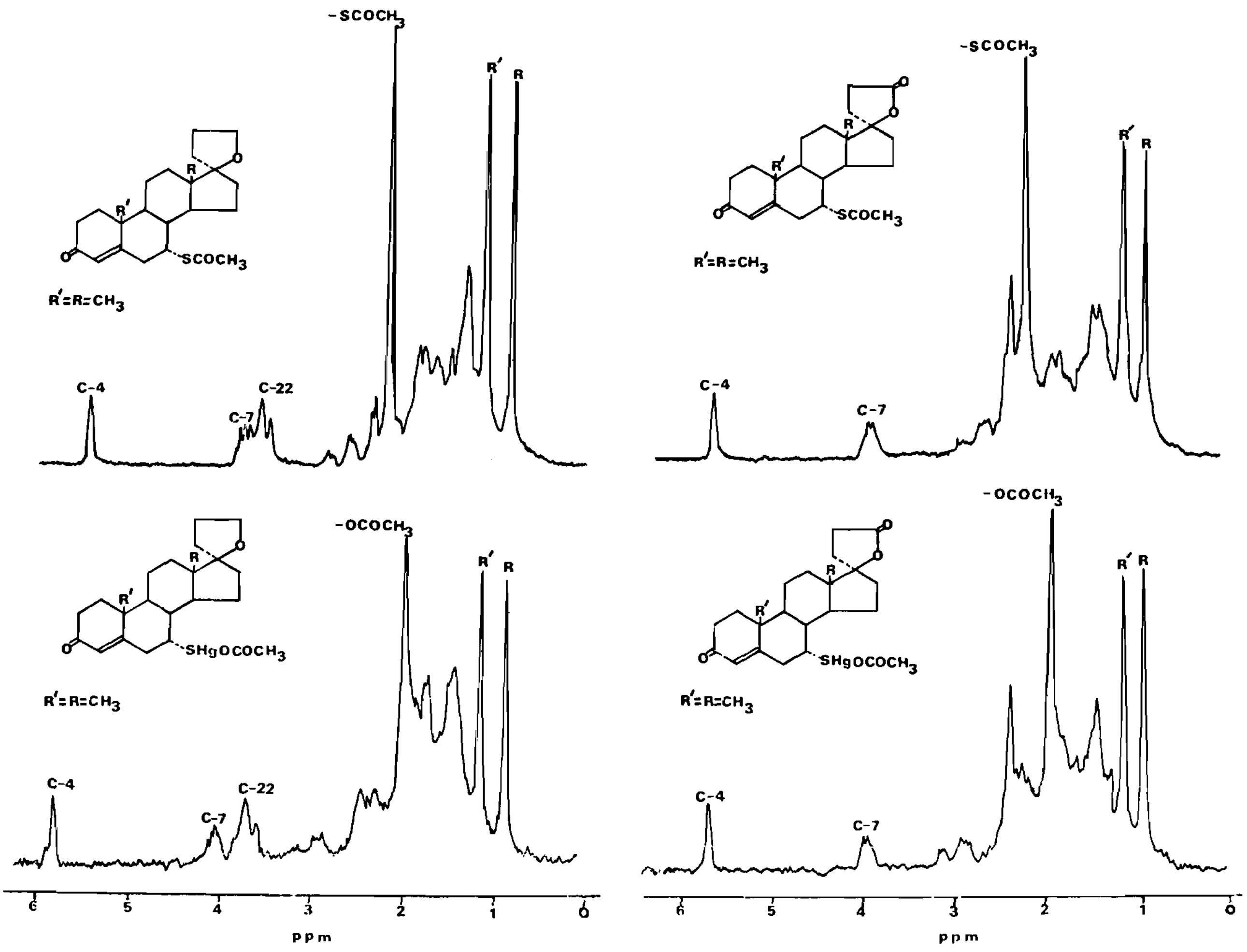
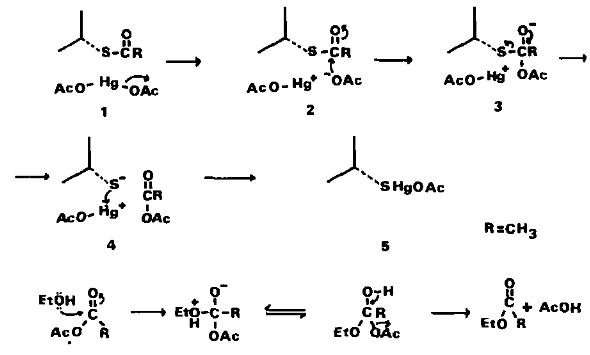


Figure 2. ${}^1H$ NMR spectra of spironolactone and spiroxazone and their mercury complexes.

analytical, IR and NMR data. In this case, we have also observed in the IR spectrum of the complex the two bands at 1420 and 1550 cm^{-1} due to the presence of $Hg–OCOCH_3$ group, while we did not observe the 1685 cm^{-1} band due to the acetyl group, $–COCH_3$. The two bands at 1660 and 1610 cm^{-1} were shown in the spectrum of the complex as well as in that of the ligand (Figure 1). This result was corroborated with NMR data which showed that the peak at 2.32 of the methyl protons of the acetyl group ($–COCH_3$) was missing from the spectrum of the complex SXZ-Hg-OAc (Figure 2).

The mercury–sulfur bond formation is the most logical attack by a metal such as mercury, since this is the most reactive site. Furthermore, the elimination of the acetyl group facilitates this attack by leaving a charge on the sulfur atom. The overall reaction is given below:



The role of the thioacetyl group is indicated in the above reaction which is corroborated by experiments *in vivo*.[3] In addition, attempts to react under the same conditions thiosteroids without the $–COCH_3$ group, *i.e.* $SNLC_2H_5$, failed to produce similar complexes.

Based on the present results, it seems that the protection against mercury intoxication by the thiosteroids is due to their ability to complex with the metal *via* the thio- moiety.

Acknowledgement

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