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Semicarbazones and copper complexes of semicarbazones and thiosemicarbazones derived from 1-indanones: synthesis, structure and spectroscopy

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Introduction

Thiosemicarbazones (TSCs) have received considerable attention because of their therapeutic activities against viral and bacterial infections (Shipman *et al.*, 1986; Boon, 1997), tuberculosis (Dobek *et al.*, 1983) and leprosy (Klayman *et al.*, 1979). These compounds have proved particularly interesting activities as antitumorals apparently due to the inhibition of DNA synthesis (Beraldo and Gambino, 2004).

In a significant number of cases TSCs complexes with transition metals showed higher biological activity than non-complexed ligands. This fact led to carry out detailed studies on the coordination chemistry of different families of thiosemicarbazones.

In contrast to what happens with TSCs, a less number of papers have been reported about the biological properties of the structural analogues, semicarbazones (SCs). Recently, there have been reports on SCs derived from unsaturated and aromatic ketones showing anticonvulsant properties, and the high advantage on their analogues, TSCs, is the lower neurotoxicity (Dimmock *et al.*, 2000; Sridhar *et al.*, 2002).

During last years we have been working on the synthesis and biological properties of a series of thiosemicarbazones derived from aromatic ketones, terpenones, and recently indanones. The latter have shown a very interesting property as antiviral agents. The activity of these thiosemicarbazones derived from 1-indanones has been tested against Junin virus (García *et al.*, 2003) and against bovine diarrhea virus, used as a model of hepatitis C virus (García *et al.*, 2005). At the present time, we are carrying out the synthesis of Cu complexes of some of these thiosemicarbazones, whose antiviral activity has already been checked, and we have started the synthesis of semicarbazones from the same indanones with the aim of testing *a posteriori* their antiviral activity, synthesizing their copper complexes, and comparing results of these analogues.

Methodology

The series of prepared compounds tested as antivirals are shown in Table 1.

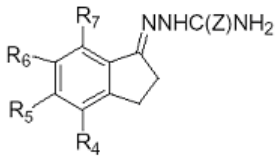

Table 1

	R_4	R_5	R_6	R_7	Ketones
1	H	CH_3	H	H	Fukuoka *et al.*, 1983.
2	CH_3	H	H	H	Commercial
3	H	CH_3	H	CH_3	Kadesch, 1944.
4	Br	CH_3	H	CH_3	Finkielsztein *et al.*, 2006.
5	H	CH_3	Cl	CH_3	Synthesized
6	CH_3	Cl	CH_3	H	Synthesized
7	H	CH_3	CH_3	H	Boykin *et al.*, 1989.
8	CH_3	CH_3	H	H	Elsner and Parker, 1957.
9	OCH_3	H	H	H	Commercial
10	H	OCH_3	OCH_3	H	Commercial
11	OCH_3	OCH_3	H	H	Commercial
12	H	Cl	H	H	Commercial
13	H	Br	H	H	Commercial
14	H	H	OCH_3	H	Commercial

Performed syntheses and used methodology are subsequently described. Ketones **2**, **9**-**14**, which are the starting material for the corresponding thiosemicarbazones, are commercially available. Ketones **1**, **3**, **4**, **7** and **8** have been previously described in the literature, and ketones **5** and **6** were synthesized according to the reaction scheme of Fig. 1.

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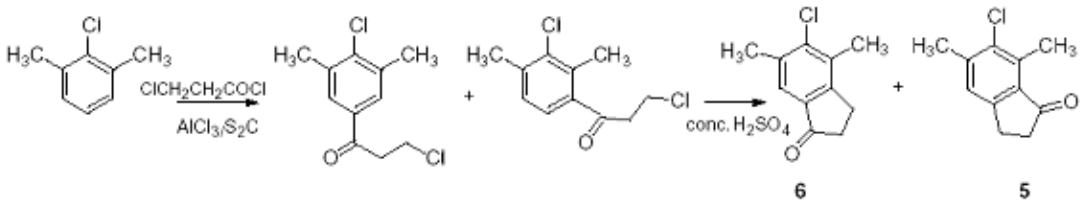
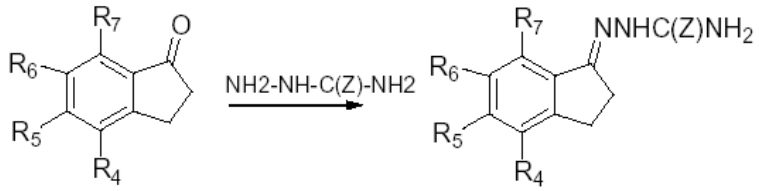


Figure 1

The general synthetic sequence used for the preparation of thio- and semicarbazones is shown in Fig. 2.



Z= S, O

Figure 2

Results

Thio- and semicarbazones were prepared by heating to reflux an ethanolic solution of indanone with thiosemicarbazide or semicarbazide. Crystalline compounds were isolated in good yields, and were stable both in solid state and in solution. The structure of all compounds was confirmed by proton and carbon nuclear magnetic resonance spectra (^{1}H-RMN, ^{13}C-NMR) and IR.

Copper complexes of thio- and semicarbazones **2**, **10**, **11** and **14** were prepared by reaction of thio- and semicarbazones with a water:ethanol solution pentahydrated copper sulfate in a ratio of 0.43 mmols of thio- or semicarbazone per 107.36 mg of Cu salt. Solids, usually yellow-coloured, are not hygroscopic, insoluble in water, methanol, ethanol, but soluble in DMF and DMSO.

IR of ligands and their complexes were compared, showing significant differences, especially in signal frequencies. Complexes were also studied by UV-visible-NIR spectra, showing significant differences in absoption λmax and absorbance, especially those related to $\pi \rightarrow \pi^*$ transitions due to a complex extended conjugation in relation to non-complexed ligand.

Conclusions

A series of semicarbazones derived from 1-indanones were synthesized, which were stable crystalline solids, and their structures were confirmed by different spectroscopies.

Furthermore, copper (II) complexes of thio- and semicarbazones were prepared, and their UV, IR and EPR spectra were analysed.

According to previous results with thiosemicarbazones derived from 1-indanones, these new structures are attractive for obtaining specific antivirals against BVDV, and probably against hepatitis C virus (HCV).

Note: This study was presented at the "XXVI Congreso Argentino de Química" , San Luis, Argentina, 2006

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