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SHORT PAPER

The structure-activity relationships of some cyclopentadienyltitanium(IV) complexes of 1,3-dihydro-1,3-dioxo-α-(substituted)-2*H*-isoindole-2-acetates

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The newly synthesized η-cyclopentadienyltitanium complexes of 1,3-dihydro-1,3-dioxo-α-(substituted)-2*H*-isoindole-2-acetates have been screened for their toxicity against *Columba livia* (Gmelin) (the blue rock pigeon) and exhibit moderate toxicity towards this non-target bird. The bis- derivatives have been observed to be generally more active than the mono- ones, indicating the dominant contribution of ligands towards toxicity compared with cyclopentadienyl rings and chlorine atoms.

Keywords: *Columba livia*, cyclopentadienyltitanium complexes, avian toxicity

INTRODUCTION

The anticancer activity of η-cyclopentadienyltitanium derivatives has been reported.[1–5] Recently, titanocene dichloride [(η-CsHs)$_2$TiCl$_2$] itself has been found to have irritancy and anti-inflammatory activity.[6] The amino acids and their complexes have been studied for their medicinal uses.[7–9] However, organotitanium complexes have so far been proven to be effective against some insects of economic relevance,[10] yet they have not been investigated with regard to non-target groups of animals, birds or other mammals. Therefore, it has been considered worthwhile to study the effect of organotitanium complexes of *N*-substituted amino acids on birds, e.g. *Columba livia* (Gmelin), an opportunistic visitor to crop fields.

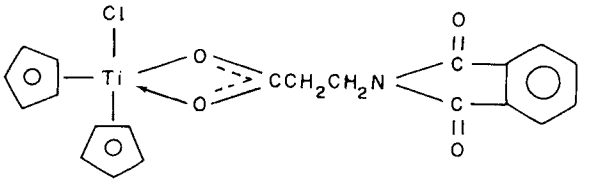

Figure 1 (η-Dicyclopentadienyl)monochloro (1,3-dihydro-1,3-dioxo-2*H*-isoindole-2-propionato)titanium (**I**).

MATERIALS AND METHODS

The ligands 1,3-dihydro-1,3-dioxo-α-(substituted)-2*H*-isoinodole-2-propionate (L_1H) and 1,3-dihydro-1,3-dioxo-α-(substituted)-2H-isoindole-2-acetate [where substituted isopropyl (L_2H) and benzyl (L_3H)] have been synthesized by a reported procedure.[11] The η-cyclopentadienyltitanium(IV) complexes of types $Cp_2TiCl(L_1)$ (Fig. 1), $CpTiCl(L_1)_2$ (Fig. 2) and $Cp_2Ti(L)_2$ (Fig. 3 where $L = L_1$ or L_2) have been synthesized by published methods,[12] by the reactions of titanocene dichloride (η-Cp_2TiCl_2) with the ligands in presence of triethylamine at different stoichiometric ratios in refluxing tetrahydrofuran solution. The resulting complexes were crystallized from chloroform–hexane solution to yield yellow solids, the structures of which have previously been established on the basis of physicochemical and spectral (IR, ^{1}H and ^{13}C) studies.

The toxicity of the ligands themselves (L_1H, L_2H and L_3H) in the complexes was assessed on healthy individuals of *Columba livia* (Gmelin), the blue rock pigeon. They were grouped and kept five to a cage measuring 30 cm × 30 cm × 45 cm in the laboratory for 15 days at temperature 26–35°C, humidity 72–75% and photoperiod of 12 h. The pigeons were fed millet daily at fixed intervals, while water was provided *ad libitum*.

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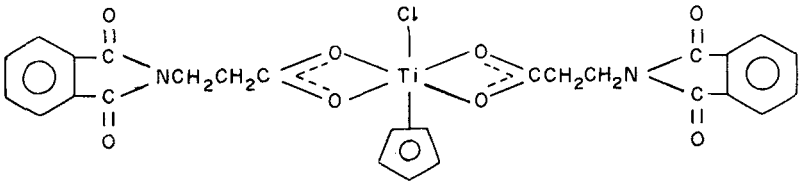


Figure 2 (η-Cyclopentadienyl)monochloro)bis(1,3-dihydro-1,3-dioxo-2*H*-isoindole-2-propionato)titanium (**II**).

For the determination of LD_{50} values, the pigeons were divided into five groups (each consisting of five individuals) and the test compounds were injected (using acetone as a vehicle) intramuscularly in the keel pectoral muscles on the ventral side of the pigeons. Different concentration doses (0.001, 0.005, 0.01, 0.02, 0.03, 0.04 and 0.05 mg kg^{-1} body weight) were prepared and administered, and mortality and the survival number of the pigeons were noted after 24 h at all doses. An equal number of pigeons were treated with acetone only and these served as controls. The LD_{50} values were determined using the log dose probit analysis method of Finney.[13]

RESULTS AND DISCUSSION

The ligands L_1H and L_2H were found to show no mortality, while at the dose levels tested preliminary tests on L_3H showed 20% increased mortality above L_1H and L_2H. The greater toxicity of L_3H may be ascribed to the presence of the phenyl ring in the molecule. Therefore, the metal complexes of L_3H were not investigated for their toxicity. In general, complexation with metals increases toxicity. The non-toxic nature of titanocene dichloride in this context[10] has already been established by us. LD_{50} values for the complexes **I–IV** have been calculated and are presented in Table 1. Summarizing, as the ligand L_3H itself is toxic, the toxicity of its metal complexes was assumed and they were therefore not considered.

It is evident from the LD_{50} values that the toxicity of complexes **I–III**, i.e. metal complexes of L_1H, increases in the order **I**<**II**<**III**. Complex **I** contains two η-cyclopentadienyl rings together with one chlorine atom and one ligand moiety and has been found to be less toxic than **III**, in which the chlorine atom has been replaced with another ligand moiety. It is suggested, therefore, that the ligand moiety induces more toxicity than the chlorine atom. Although the presence of chlorine atoms often increases biological activity,

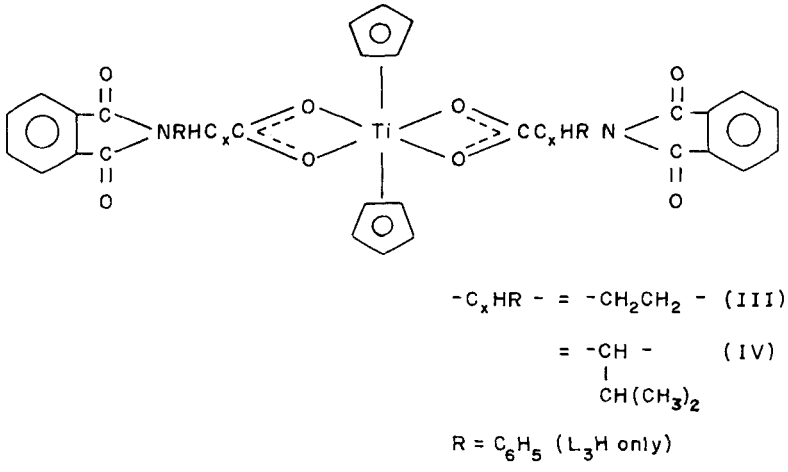
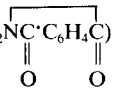
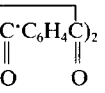
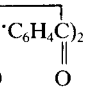
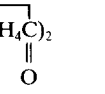


Figure 3 (η-Dicyclopentadienyl)bis[1,3-dihydro-1,3-dioxo-α-(substituted)-2*H*-isoindole-2-acetato] titanium (**III** and **IV**).

Table 1 LD_{50} values of cyclopentadienyltitanium(IV) complexes against *Columba livia*

No.	Compound	LD_{50} (mg kg^{-1} body weight)
I	$(\eta\text{-}C_5H_5)_2TiCl(O_2CCH_2CH_2NC{\cdot}C_6H_4C)$ 	0.018
II	$(\eta\text{-}C_5H_5)TiCl(O_2CCH_2CH_2NC{\cdot}C_6H_4C)_2$ 	0.015
III	$(\eta\text{-}C_5H_5)_2Ti(O_2CCH_2CH_2NC{\cdot}C_6H_4C)_2$ 	0.002
IV	$(\eta\text{-}C_5H_5)_2Ti(O_2C{\cdot}CH{\cdot}NC{\cdot}C_6H_4C)_2$ 	0.005

in these complexes this does not appear to be the case. The presence of two carboxylate groups in **III** (bidentate bonding) increases the electron density around the titanium atom and this may be considered as the most plausible reason for its greater toxicity than **I**, where the extent of electron delocalization is somewhat reduced.

A comparison of complexes **II** and **III** indicates that the replacement of the η-cyclopentadienyl ring with a chlorine atom decreases the toxicity of **II**, i.e. the effect of the η-cyclopentadienyl ring is greater than that of the chlorine atom towards toxicity. Similarly, the replacement of the η-cyclopentadienyl ring with a ligand moiety slightly increases the toxicity of **II** in comparison with **I**. It is therefore suggested that the ligand moiety induces greater toxicity than the η-cyclopentadienyl ring, which in turn is more active than the chlorine atom.

The complex **IV**, i.e., the metal derivative of L_2H, was found to be less toxic than **III**. The lesser toxicity of **IV** may be due to the presence of substituent isopropyl $[-CH(CH_3)_2]$ groups in the ligand moiety, which renders the complex more bulky and possibly less able to render toxicity, as compared to **III** with no side chain. It has already been reported that the bulkier the group, the lesser will be the toxicity, as bulk hinders the transport of the complex across membranes to the site of action[14] because of the reduction of the rate of penetration.[15] This might suggest that the total complex may be responsible for the observed toxicity.

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