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Synthesis of Central Nervous System Stimulant Complexes of Copper(II) and Zinc(II) with Pipradrol

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Synthesis of divalent copper and zinc complexes with pipradrol (α, α-diphenyl-2-piperidinemethanol) having $[ML_2]^{2-}$ stoichiometries have been reported. Characterizations have been done on the basis of elemental analysis, conductivity, magnetic, IR and electronic spectral studies. Complexes have been found as comparatively more effective stimulants than the ligand and possess much higher toxicity as compared to the ligand.

Key Words: Synthesis, Cu(II) and Zn(II) complexes, Pipradrol.

INTRODUCTION

α,α-Diphenyl-2-piperidinemethanol[1] commonly termed as pipradrol belongs to the class of 2-benzyl piperidine and is used as central nervous system (CNS) stimulant for the psychotic and neurotic patients. A rather complete description of the central stimulant activity of piperidine appears in the report of Brown and Werner[2]. Coordination of such active compounds with suitable metals often results into the compounds of enhanced activity[3]. Therefore, synthesis, characterization and study of the drug potential of the newly synthesized coordination compounds (with copper and zinc metal) in comparison to that of the ligand were carried out with a view to get better drugs in the interest of mankind. Copper and zinc metals and their compounds have been reported to possess effective drug potential and are frequently used in Indian Ayurvedic and Homeopathic therapies for the treatment of psycho-pharmacological, cardiovascular and various otherdisorders[4, 5]. Since the coordinaton of biologically active compounds with metals often results into compounds with enhanced activity[6], therefore the coordination of the above ligand with divalent copper and zinc has been reported.

EXPERIMENTAL

All the chemicals used work were of AnalaR grade (or Merck) or were used after recrystallization. 2-Benzoyl pyridine was procured from Sigma-Aldrich Chemical Company and used as such.

Preparation of the ligand

Synthesis of α,α-diphenyl-2-pipridinemethanol (pipradrol) has been performed by Werner and Tilford[7]. Pipradrol hydrochloride was obtained from aqueous ethanol as a white solid. The yield obtained was low (35%).

Preparation of complexes

Saturated solution of pipradrol in aqueous ethanol was mixed with saturated

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solution of zinc(II) and copper(II) chlorides, acetates, nitrates and benzoates in aqueous ethanol in 2 : 1 molar ratio. The mixture was refluxed on a water bath for 4 h and concentrated, cooled to 35–40°C and was treated with 10% alcoholic KOH solution adding dropwise with constant stirring until complete precipitation. Precipitated complexes were filtered on suction, washed with absolute ethanol and finally with ether and dried at 80–85°C in a hot air oven for 3 h. The same set of experiments was repeated using 10% alcoholic NaOH instead of KOH. Elemental analysis data, molar conductance data, magnetic moment studies, percentage yield and colour of the complexes are given in Table-1.

TABLE-1
ELEMENTAL ANALYSIS DATA, PERCENTAGE YIELD, MOLAR CONDUCTANCE, COLOUR AND MAGNETIC MOMENT OF COMPLEXES OF COPPER(II) AND ZINC(ii) WITH PIPRADROL (L)

m.f. (Colour)	Molar conductance (ohm^{-1} cm^2 mol^{-1})	Yield (%)	% Analysis, Found (Calcd.)				
			C	H	N	Metal	Na/K EDTA method
$C_{18}H_{21}NO$ (Ligand)	3.82	35	86.82	7.89	5.21	—	—
(White)			(86.86)	(7.91)	(5.23)		
$K_2[Cu(C_{18}H_{19}NO)_2]$	40.60	50	64.02	5.66	4.20	8.21	11.66
(Light bluish white)			(64.30)	(5.69)	(4.17)	(8.17)	(11.63)
$K_2[Zn(C_{18}H_{19}NO)_2]$	42.12	49	63.89	5.56	4.18	8.07	11.55
(White)			(64.12)	(5.68)	(4.15)	(8.15)	(11.60)
$Na_2[Cu(C_{18}H_{19}NO)_2]$	36.44	48	67.56	5.89	4.40	8.63	7.24
(Bluish white)			(67.54)	(5.98)	(4.38)	(8.58)	(7.24)
$Na_2[Zn(C_{18}H_{19}NO)_2]$	38.32	48	67.30	5.99	4.39	8.6	7.71
(White)			(67.34)	(5.97)	(4.36)	(8.56)	(7.16)

RESULTS AND DISCUSSION

Reported complexes have been found stable at room temperature, partially soluble in water and DMSO, less soluble in ethanol and insoluble in THF, ether and acetone. Qualitative tests for anions in the complexes were not pisitive. Elemental analysis data also confirmed the absence of anions in the complexes. Sodium and potassium ions in the complexes have been estimated by EDTA method. Molar conductance data indicate ionic nature of the complexes. Elemental analysis and molar conductance data confirm the formation of 1 : 2 anionic complexes.

The decomposition temperatures of the complexes containing sodium as cation were found higher than the potassium cation containing complexes. However, the solubility of potassium containing complexes were found slightly higher than the corresponding sodium containing complexes.

In the IR spectra, a number of absorption bands have been observed in the region 3400–600 cm^{-1}, but the functional group frequencies and the stretching vibrations which have not been found to be affected by coordination to a measurable extent are omitted from the discussion.

(1) The strong ν(OH) absorption band at 3350 cm^{-1} in the ligand corresponding to O—H stretching vibration of the tertiary alcoholic group was invariably absent in the IR spectrum of all the complexes. This shows the deprotonation of the tertiary alcoholic group of the ligand during the coordination[8, 9].

(2) The disappearance of δ_{OH} band (at 1340 cm^{-1} in the ligand) also confirmed the deprotonation during complex formation[10].

(3) The ν(C—O) band of 1210 cm^{-1} in the ligand was found to be shifted 50–30 cm^{-1} on negative side in all the complexes confirming the coordination of the ligand with the metal through the oxygen of the tertiary alcoholic group after subsequent deprotonation[11].

(4) Metal to ligand coordination through the oxygen is further confirmed by the new band observed between 580–530 cm^{-1} in the far IR region in all the complexes[12, 13].

(5) The medium intensity ν(NH) band at 3190 cm^{-1} corresponding to N—H vibration in the heteroalicyclic ring of the ligand was also found to be absent in the IR spectrum of all the complexes[14]. This confirms the deprotonation of N—H hydrogen during the co-ordination.

(6) The medium intensity ν(CN) absorption band of the ligand at 1050 cm^{-1} corresponding to the C—N stretching vibration of the heteroalicyclic ring was found to suffer 30–15 cm^{-1} negative shift[15]. This confirms the involvement of nitrogen of NH moiety after subsequent deprotonation.

(7) Metal to ligand coordination through the nitrogen of the heteroalicyclic ring is confirmed by the presence of a new band between 460–430 cm^{-1} in all the complexes[16–17].

The absence of O—H, N—H stretching and deprotonation bands in the complexes, appreciable negative shifts in the C—O and C—N stretching vibrations and existence of new bands in far IR region corresponding to the M—O and M—N vibrations confirms the formation of coordination compound of the metals in which the ligand molecules are added to the metal ions in a bidentate manner after (1) deprotonation of tertiary alcoholic group (OH) present in the α-carbon atom and (2) deprotonation of NH moiety present as a part of heteroalicyclic ring attached to α-carbon atom of the ligand.

A comparatively lesser negative shift in the C—N stretching vibrations than that in the case of C—O stretching vibration as a result of coordination of ligand with the metal is an indirect indication of comparatively weaker M—N bond than M—O bond in the complexes. It may be attributed to the fact that after deprotonation of both the OH and NH groups present in the ligand, the higher electronegativity of the oxygen of the tertiary alcoholic group might have produced a little inductive effect on the heteroalicyclic ring nitrogen thus developing a little electrophilic character on it. Hence the liability of the electron pair of nitrogen (after deprotonation) might have been decreased slightly in comparison to what it would have been in the absence of the oxygen (of the tertiary alcoholic group) on the α-carbon atom.

Magnetic moments and electronic spectral studies

The complexes of copper were found to be paramagnetic and μ_{eff} values were

found between 1.71–1.86 B.M. The values suggest the existence of square-planar geometry around copper(II) ions[18].

A broad electronic absorption band observed in the high energy region 16100 cm^{-1} in the K^+ containing copper(II) complexes which may be attributed to $^2B_{1g} \rightarrow {}^2B_{2g}$ transition of square-planar geometry[19, 20], while the Na^+ containing copper(II) complexes show 3 absorption bands at 14700, 20000 and 26300 cm^{-1} corresponding to $^2B_{1g} \rightarrow {}^2A_{1g}$, $^2B_{1g} \rightarrow {}^2E_g$ and charge transfer transitions respectively which indicates the square-planar symmetry around copper(II) ion in these complexes[21].

All the zinc complexes were found to be diamagnetic. A band around 30,000 cm^{-1} in all complexes is attributed as M → L or L → M charge transfer band. On the basis of analogy with the other complexes, a tetrahedral geometry is suggested for all the zinc complexes.

Effect of coordination on the drug potential of the ligand

The CNS stimulant activity of complexes was studied in comparison with that of pipradrol on mice by the method of Rinaldi and Himwich[22].

Lightly phenobarbital-anesthetized mice (dose 0.05 mg/kg body weight) were treated (subcutaneous administration) with the aqueous solution of pipradrol and complexes respectively. Increase in the coordinated motor activity was noted over a wide dose range of the complexes and the results of the study have been reported in Table-2.

TABLE-2
DRUG POTENTIAL STUDIES
CNS STIMULANT EFFECT OF THE TREATMENT OF LIGAND AND COMPLEX ON THE COORDINATED MOTOR ACTIVITY OF THE MICE ON SUBCUTANEOUS ADMINISTRATION

Compound	LED_{100}* (Dose mg/kg body wt.)	HED_{200}* (Dose mg/kg body wt.)	MED_{400}* (Dose mg/kg body wt.)	LD_{50}*
Pipradrol (Ligand)	2.50†	8.00	12.00	18.00
Pot-Cu-Complex	1.00	3.25	5.00	8.25
Pot-Zn-Complex	1.00	3.50	5.25	8.75
Sod-Cu-Complex	1.25	3.50	5.25	8.25
Sod-Zn-Complex	1.25	4.00	5.50	9.00

LED_{100} = Lower effective dose which produced an increase of approximately 100 spontaneous movements in the first half an hour after subcutaneous administration.
HED_{200} = Highest effective dose which produced 200 spontaneous movements after half an hour.
MED_{400} = Maximum effective dose which produced 400 spontaneous movements after half an hour.
LD_{50} = Lethal dose which increased the mobility to an extent of noxious stimuli in addition to elict postural activity in 50% of the mice treated.
* = LED, HED and MED studies were done on two mice only for each compound. However, LD studies were done on four mice per compound.
† = Dose variation was done in multiples of 0.25 mg/kg body weight only.

(1) In lower dose, 1 to 2.5 mg/kg body weight (LED_{50}) depression was not observed. Duration of sleep was shortened. The response of the mice to EEG sensory stimuli (direct stimulation of the reticular formation) was observed. The mice behaved in righting the refluxes in a coordinated way.

(2) Higher dose (2.75–4 mg per kg body weight) caused altering pattern characteristic of increased activity of the reticular formation. No evidence of convulsive EEG patterns have been reported. Righting the refluxes was quite coordinated and more swift, mobility was found increased (HED_{200}).

(3) With MED_{400} (4.5 to 5.5 mg/kg body wt.) highest mobility was observed. Beyond the range (6 to 9 mg/kg body wt., LD_{50}) the incoordinated motor activity, exaggeration of refluxes to an extent of noxious stimuli in addition to postural activity were observed. Mortality in any case was not observed and the mice became almost normal after passing urine and faeces within 4 to 5 h time of drug administration. Further, anionic complexes containing sodium as cation seem to be milder in effect as compared to the potassium complexes.

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