Preparation of Platinum(II) Complexes with β-Carbolines and Tetrahydro-β-carbolines as Ligands

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Abstract

The preparation of several $PtCl_2$ complexes of synthetic analogs of β-carboline (BC) and 1,2,3,4-tetrahydro-β-carboline (THBC) is described. BC and THBC with 3-carboxamide, 3-carboxazide and 3-alkylaminomethyl side chains were used in the preparation of the complexes.

Introduction

The preparation of platinum complexes which may be able to penetrate the blood brain barrier in order to target platinum complexes to malignant brain lesions is of great importance. Select synthetic analogs of β-carboline (BC) and 1,2,3,4-tetrahydro-β-carboline (THBC) which interact specifically with central nervous system (CNS) sites (BC with benzodiazepine sites [1] and THBC with 5-HT [2] and which possess brain penetration capability may serve as vehicles for platinum transportation across the blood brain barrier. This work presents an exploratory study of the preparation of such complexes.

Results and Discussion

Ethyl β-carboline-3-carboxylate (**1**) and the tetrahydro analog (**2**) were used as starting materials. The ethyl ester was modified by three different functional groups: alkylamine, carboxylic acid hydrazide and 2-propeneamide. These modified β-carboline and tetrahydro-β-carboline derivatives were then complexed with platinum(II) chloride residues as shown in Schemes 1, 2 and 3. Although complexes **5** and **6** are formulated as chelated structures, we are not able at this time to rule out chloro-bridged dimers in which the BC and THBC ligands are unidentate. The complexes are very sparingly soluble in most solvents and are, therefore, not amenable to characterization by NMR or by molecular weight determination.

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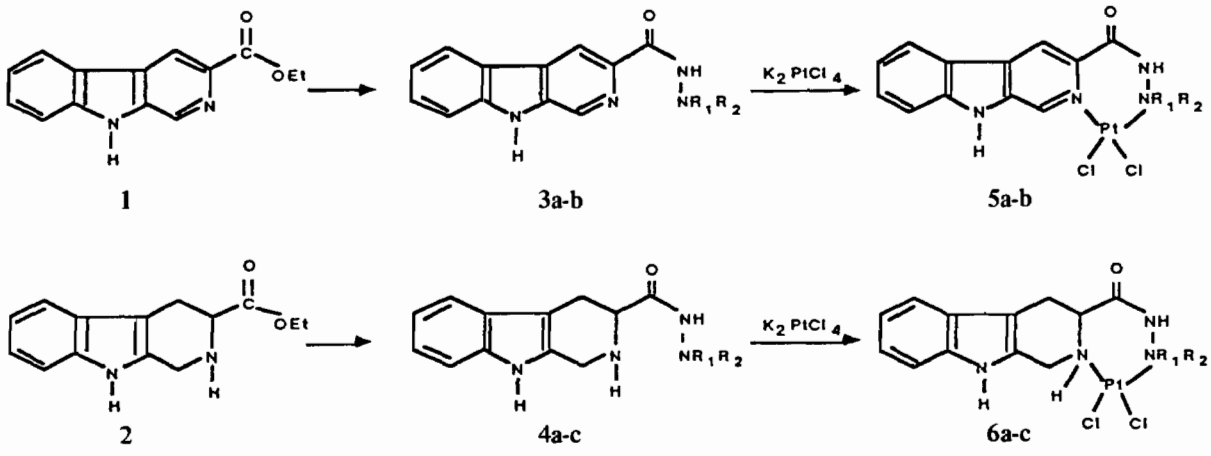

(a) $R_1 = R_2 = H$ (b) $R_1 = R_2 = Me$ (c) $R_1 = H_1$, $R_2 = -CH_2C_6H_5$

Scheme 1. Six-membered ring Pt(II) complexes of BC and THBC.

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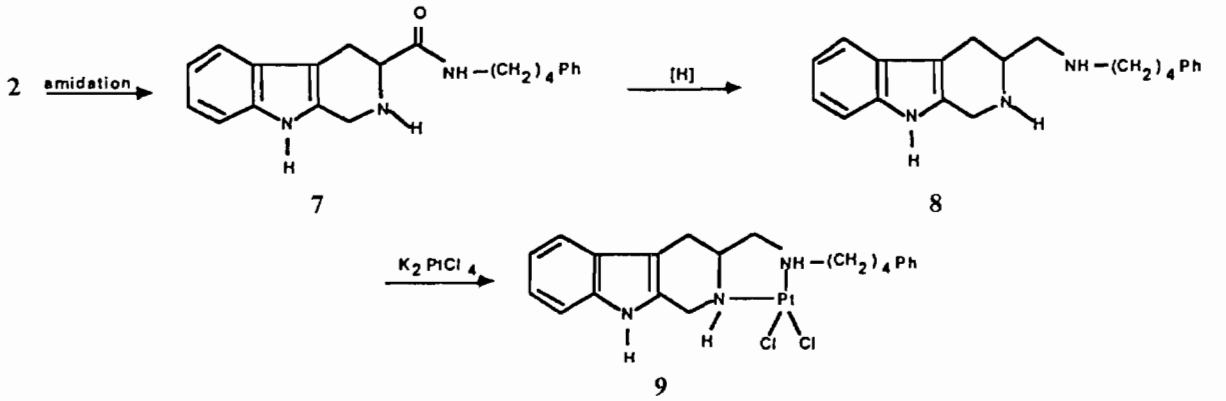
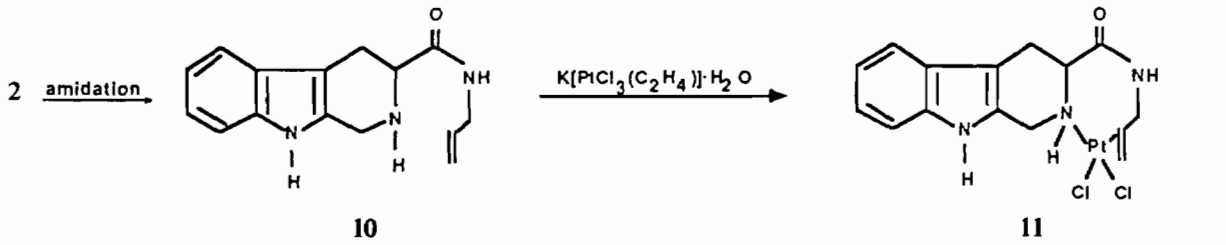
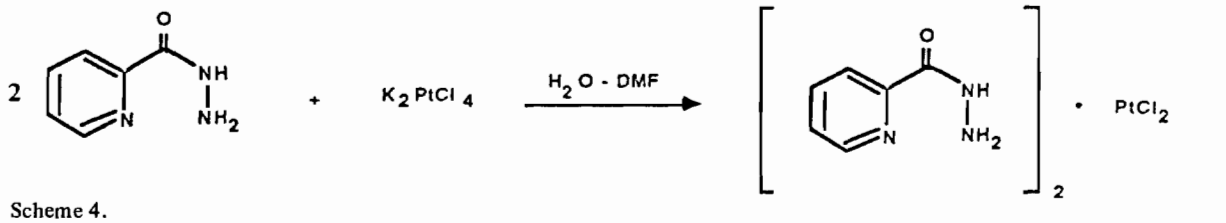


Scheme 2. Five-membered ring Pt(II) complex of THBC.



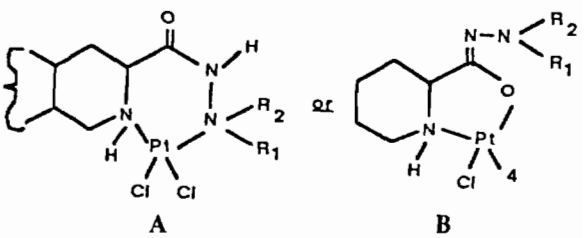
Scheme 3. Eight-membered ring Pt(II) complex of THBC.



Scheme 4.

Compound **5a** is unsual in that it contains two molecules of β-carboline-3-carboxazide, as shown by the analytical results. Similar results were obtained with a simpler model, the nicotinic acid hydrazide, and again the analytical data show a 2:1 ligand-to-metal stoichiometry. All other complexes prepared from BC (**5b**, **5c**) or THBC (**6a**, **6b**, **6c**, **9**, **11**) showed a 1:1 ligand-to-metal stoichiometry (Scheme 4).

The IR spectra of THCB complexes containing 3-carboxylic acid hydrazide side chains (Table I) indicate the presence of a coordinated amino group (ν(N–H) of the ligands is at 3400 and 3300 cm^{-1} and of the complexes at 3360 to 3340 and 3160 to 3150 cm^{-1}). There is a significant shift in the position of the amide I band (the carbonyl absorption) in the complexes of THBC with respect to the free ligand (Table I), which is not observed in the BC analogs. This may be due to enolization of the carbonyl functional group of the platinum complexes or even coordination in the enolized form [3]. Diacylhydrazines of several platinum complexes are known to coordinate in the enolized form shown in structure **B** [3]. Consequently, based on the IR data alone, we cannot rule out structures **A** or **B** as possible representations of complexes **6a-c.**



The IR spectrum of complex **11** shows no shift in the amide I band with respect to the free ligand **10** (1660 cm^{-1}); however, the olefin band at 1640 cm^{-1} in compound **10** is shifted to 1610 cm^{-1}, and the position of the ν(N–H) mode at 3260 cm^{-1} in the free ligand is shifted to 3360 cm^{-1} in the complex.

TABLE I. Some frequencies in the IR Spectra of the Pt(II) Complexes and the Free Ligands

Compound	ν(N–H)	ν(C=O)		ν(Pt–Cl) (KBr)	ν(Pt–Cl) (CsI)
4a	3400(b), 3330	1650			
6a	3360(b), 3160(b)	1620(s)			340, 320
4b	3400(w), 3250(s)	1680			
6b	3350(b), 3150(w,b)	1630(m)		330(b)	
4c	3400, 3250	1650(s)			
6c	3340(w,b), 3160(w,b)	1620(w)			320
3a	3220(s)	1650	725		
5a	3500(b), 3200(b)	1650	750, 735	325(b)	340, 330
3b	3100(s,b)	1655	740		
5b	3300(b), 2950(s,b)	1650	750, 725	330(b)	multiplicities 330 340 350
3c	3220(s)	1650	730		

We conclude, therefore, that the coordination in **11** takes place between the tetrahydropyridine nitrogen and the olefin functional group.

A five-membered ring Pt(II) complex of THBC was prepared from the diamine **8** (Scheme 2). The PtCl stretching absorption appears in the CsI spectrum as a doublet at 330 and 345 cm^{-1}, indicating *cis* geometry in complex **9**. Simpler analogs of **9**, for example, dichloro(2-piperidylmethylamine)platinum(II) or dichloro(2-pyridylmethylamine)platinum(II), are of the *cis* configuration [4].

Experimental

Infrared spectra were recorded using a Perkin-Elmer 421 grating spectrophotometer. Melting points, uncorrected, were determined on a melt-temp apparatus. The ^1H NMR spectra were determined with a Nicole NT-200 NMR spectrometer. Chemical shifts are expressed as δ values with Me_4Si as internal standard. Mass spectra were obtained on CEC/Bell and Howell 21-491 and 21-110c spectrometers. Ethyl 1,2,3,4-tetrahydro-β-carboline-3-carboxylate and ethyl β-carboline-3-carboxylate were prepared by reported procedures [5, 6]. Compounds **3a** and **4a** were prepared by the method of Dodd *et al.* [7], while **3b**, **3c**, **4b** and **4c** were prepared by a modification of the method of Weinreb *et al.* [8, 9].

Preparation of the Carboxazides 3a and 4a

A solution of **1** or **2** (8.3 mmol) in ethanol (20 ml) containing 85% hydrazine hydrate (10 ml) was refluxed under Ar atmosphere for 6 h. The resulting precipitate was collected by filtration, washed with ethanol and dried, yielding 80% of **3a** or **4a**. Compound **3a** (crystallized from ethanol): melting point (m.p.) 290–291 °C; IR (KBr) 3225, 1650, 1620, 1600 cm^{-1}; mass spectrum 226.08494 (calc. for $C_{12}H_{14}N_4O$: 226.08546). Compound **4a** (crystallized from MeOH): m.p. 242–244 °C; IR (KBr) 3310, 3295, 1650, 1610 cm^{-1}; mass spectrum 230.11625 (calc. for $C_{12}H_{14}NO$: 230.1675).

Preparation of Carboxazides 3b, 4b and 4c

A solution of trimethylaluminum in toluene (7.95 ml, Aldrich, 2 M; 15.9 mmol) was added dropwise (15 min) under argon to a solution of alkylhydrazine (16 mmol in 25 ml dry $CHCl_3$). The mixture was then stirred at room temperature for 1 h. Subsequently, ethyl β-carboline-3-carboxylate or ethyl 1,2,3,4-tetrahydro-β-carboline 3-carboxylate (6 mmol) was added and the mixture was kept at 50 °C for 10 h. The reaction mixture was then poured carefully into 100 ml of 1 N HCl (exothermic reaction) and was stirred at 40 °C for 30 min. The precipitate formed was washed with 1 N aqNa_2CO_3, then with water, and was dried over P_2O_5 (80 °C, *in vacuo*).

Compound **3b**, made from 1,1-dimethylhydrazine and ester **1** was isolated in 85% yield: m.p. (from MeOH) 260 °C dec; NMR (DMSO-d_6–acetone-d_6) δ 11.7 (1H, s, b, NH), 9.1 (1H, s, NH), 8.9 (1H, s, H-1), 8.85 (1H, s, H-4), 8.4 (1H, d, *J* 8.7 Hz), 7.65 (2H), 7.35 (1H), 2.75 (6H, s, $N(CH_3)_2$); mass spectrum (*m/e*) 254.28101 (calc. for $C_{14}H_{14}N_4O$: 254.28098) 254(50), 211, 194(25), 168(100), 140(50), 59(25).

Compound **4b**, made from 1,1-dimethylhydrazine and ester **2**, was isolated in 83% yield: m.p. (from MeOH) 250–255 °C dec; NMR (acetone-d_6) δ 7.45 to 7.35 to 6.95 (4H two multiplets, aromatic), 4.05 (2H, s, b, H-1) 3.75 (2H, s, H-4) 3.5 to 3.9 (1H, d of d, H-3), 2.65 (6H, $N(CH_3)_2$).

Compound **4c**, made from benzylhydrazine and ester **2**, was isolated in 80% yield: m.p. (MeOH) 176–178 °C dec; NMR ($CDCl_3$/DMSO-d_6) δ 9.6 (1H, s, b,

NH) 8.75 (1H, s, b, NH), 7.5 to 7 (9H, m, aromatic), 5.05 to 4.9 (1H, s, b, NH), 4.0 (2H, s, CH_2), 4.0 (2H, s, H-1), 3.6 (1H, d of t, H-3), 3.17 to 3.05 (1H, m, H_A-4), 2.85 (1H, m, H_B-4); mass spectrum (*m/e*) 370 (30), 215 (20), 199 (50), 171 (100), 144 (80), 115 (50), 106 (85), 91 (85), 77 (50).

Preparation of Complexes 5a, 5b, 6a, 6b and 6c

In each preparation potassium tetrachloroplatinate(II) (0.5 mmol in 4 ml H_2O) was added to a solution of the carboxylic acid hydrazide (0.5 mmol in 4 ml DMF). The mixture was kept at 50–55 °C for 3 h and the pH was adjusted periodically to 6–6.5 with 0.5 N NaOH. The precipitate formed was collected and washed with water, ethanol and ether.

Compound **5a** did not form a chelated complex, but a compound made of two β-carboline-3-carboxylic acid hydrazides was formed in 35% yield as a yellow powder, m.p. > 250 °C. *Anal.* Calc. for $[C_{24}H_{20}N_8O_2PtCl_2]\cdot 2H_2O$: C, 38.0; H, 2.93; N, 14.8. Found: C, 37.75; H, 3.10; N, 14.33%.

Compound **5b** was obtained from **3b** as a yellow powder (52%), m.p. > 250 °C. *Anal.* Calc. for $[C_{14}H_{14}N_4OPtCl_2]\cdot 2H_2O$: C, 30.22; H, 3.26; N, 10.07. Found: C, 30.47; H, 3.09; N, 10.15%.

Compound **6a** was obtained from **4a** as a yellow powder (40%), m.p. > 250 °C. *Anal.* Calc. for $[C_{12}H_{14}N_4OPtCl_2]\cdot H_2O$: C, 28.02; H, 3.13; N, 10.89. Found: C, 27.79; H, 3.27; N, 9.77%.

Compound **6b** was obtained from **4b** as a yellow powder (51%), m.p. > 250 °C. *Anal.* Calc. for $[C_{14}H_{18}N_4OPtCl_2]\cdot 2H_2O$: C, 30.01; H, 3.59; N, 9.9. Found: C, 29.73; H, 3.31; N, 9.78%.

Compound **6c** was obtained from **4c** as a yellow powder (78%), m.p. 270–275 °C dec. *Anal.* Calc. for $[C_{19}H_{20}ONPtCl_2]\cdot H_2O$: C, 37.75; H, 3.66; N, 9.27. Found: C, 37.38; H, 3.42; N, 9.49%.

Preparation of the Carboxamides 7 and 10

A solution of trimethylaluminum in toluene (7.5 ml, Aldrich, 2 M; 15 mmol) was added dropwise (15 min) under argon to a solution of alkylamine (15 mmol) in dry $CHCl_3$ (25 ml). The mixture was kept at 40 °C for 1.5 h, then **2** was added portionwise (10 min) and the resultant mixture was kept overnight at 40 °C with stirring. At the end of reaction (TLC), the mixture was poured carefully into 100 ml of 1N HCl and was kept at 40 °C with stirring for 30 min. The two layers were separated and the organic layer was washed with aq NH_3 (1 N), water and brine, and was dried over Na_2SO_4. Evaporation of the solvent gave an 80–85% yield of crude product.

Compound **7** was made from 4-phenylbutylamine and the ester **2**: m.p. (from ethyl acetate–MeOH) 189–190 °C; IR (KBr) 3440, 3330(s), 3100, 3085, 2965, 1680(s), 1530(s), 760 cm^{-1}; NMR (acetone-d_6) δ 7.8 (1H, s, b, H-9), 6.95 to 7.5 (1H, aromatic), 4.1 to 3.95 (4H, m, H-1) and NH-CH_2), 3.55 (1H, d of d, H-3), 3.05 to 2.95 (1H, m, H_A-4), 2.85 to 2.7 (1H, m, H_B-4), 2.65 (2H, t, CH_2), 1.65 (4H, M, CH_2CH_2); mass spectrum (*m/e*) 347, 198, 171, (100), 155, 143, 115, 91.

Compound **10** was made from allylamine and the ester **2**: m.p. (toluene–MeOH) 208–209 °C; IR (KBr) 3360, 3265, 2900, 1655(s), 1645, 1520, 900, 765 cm^{-1}; NMR ($DCCl_3$) δ 7.45 to 6.95 (4H, m, aromatic), 6.0 to 5.8 (1H, m), 5.25 to 505 (2H, 2d, vinyl protons), 4.05 (2H, b, s, H-1), 3.9 (2H, d $J = 8.2$ Hz, allyl), 3.6 (1H, d of d, H-3) 3.05 and 2.7 (2H, 2 sets of m, H-4); mass spectrum (*m/e*) 255.31065 (calc. for $C_{15}H_{17}N_3O$: 255.1084) 255, 238, 171, 169 (100), 144, 143, 115, 83, 44, 41.

Preparation of Compound 8

Compound **7** (500 mg) was reduced under argon with $LiAlH_4$ (3 eq in 20 ml THF at 60 °C for 6 h). At the end of the reaction (TLC) the mixture was carefully quenched with 2 N HCl (100 ml) and was then kept at 40 °C for 6.5 h. The solution was made basic with NaOH and the aqueous layer was extracted with ethyl acetate. Drying and evaporation of the organic solvent and crystallization from cyclohexane–ethyl acetate afforded 375 mg (78.2%) of **8**: m.p. 127–128 °C; IR (KBr) 3500 (br), 3320, 2980, 1470, 1120, 920, 760, 735, 715 cm^{-1}. *Anal.* Calc. for $C_{22}H_{27}N_3$: C, 79.23; H, 8.16; N, 12.6. Found: C, 79.01; H, 8.43; N, 12.66%.

Preparation of the Pt(II) Complex 9

A solution of K_2PtCl_4 [207.5 mg (0.5 mmol) in 4 ml of water] was added dropwise to 184.48 mg (0.5 mmol) of the hypochloric salt of **8** in water (10 ml). The mixture was warmed to 60 °C and the pH was periodically adjusted to about 6 with 0.5 N NaOH. The off-white precipitate was isolated by filtration, washed with water, then with ethanol, and was dried *in vacuo* (60 °C, P_2O_5), to give 230 mg (77%) of **9**, m.p. 240 °C dec. *Anal.* Calc. for $C_{22}H_{27}N_3PtCl_2$: C, 44.07; H, 4.54; N, 7.01; Cl, 11.82. Found: C, 44.30; H, 4.68; N, 6.98; Cl, 11.69%.

Preparation of the Pt(II) Complex 11

A solution of $K[PtCl_3(C_2H_4)]$ [184.3 mg (0.5 mmol) in 8 ml acetone] was added to a solution of the amide **10** [127.5 mg (0.5 mmol) in 7 ml acetone]. The mixture was refluxed for 4 h, then concentrated. The precipitate formed was washed with water, ethanol and ether, and was dried *in vacuo* (60 °C, P_2O_5). A pale yellow powder (360 mg, 70%) was isolated, m.p. 265 °C (dec.): IR (KBr) 3360 (s, b) 1660, 1610, 740, 330 cm^{-1}; mass spectrum (FAB, matrix = 3-nitrobenzyl alcohol, solvent DMF), $M^+ = 522$.

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