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Synthesis and Antitumor Activity of Aminomethylpiperidine Platinum(II) Complexes

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In order to examine the structure–activity relationship between the platinum complexes having a bidentate ligand as non-leaving group dichloro 2-aminomethylpiperidine Pt(II), $PtCl_2$(2-ampip), dichloro 3-aminomethylpiperidine Pt(II), $PtCl_2$-(3-ampip), and dichloro 2-aminomethylpyridine Pt(II), $PtCl_2$(2-ampy), were synthesized and tested against Leukemia L-1210 in CDF_1 mice. Structure of the complex of Pt(II) with 3-ampip is discussed on the basis of the data of ^{13}C nmr spectrum.

Experimental

2-ampip and 3-ampip were prepared by the reduction with sodium and alcohol of 2-ampy and 3-ampy, respectively. $PtCl_2$(2-ampip) and $PtCl_2$(2-ampy) were prepared by the general method of mixing equivalent moles of K_2PtCl_4 with ligands. *Anal.* calcd. for $PtCl_2$-(2-ampip): C, 19.0; H, 3.7; N, 7.4. Found: C, 19.1; H, 3.7; N, 7.3. IR data (δ_{NH_2} = 1578 cm^{-1}, and δ_{CH_2} = 1430 and 1452 cm^{-1}). *Anal.* calcd. for Pt-Cl_2(2-ampy): C, 19.3; H, 2.2; N, 7.5. Found: C, 19.2; H, 2.1; N, 7.4. IR data (ν_{ring} = 1635, 1490, 1450, and 1425 cm^{-1}, and δ_{NH_2} = 1580 cm^{-1}). $PtCl_2$(3-ampip) was prepared by the following method. 3-ampip (1 g) and K_2PtCl_4 (3.7 g) was dissolved in about 1.5 l of water and the solution was kept in the dark for a day. Dark orange precipitates were removed by filtration, and the filtrate was evaporated to about 100 ml. Dark orange solids that precipitated out were also removed by filtration, and the clear filtrate thus obtained was evaporated to dryness. Recrystallization of the residual solid from 0.1 *M* HCl solution gave pale yellow crystals. *Anal.* Calcd. for $PtCl_2$-(3-ampip): C, 19.0; H, 3.7; N, 7.4. Found: C, 19.2; H, 3.6; N, 7.4. IR data (δ_{NH_2} = 1582 cm^{-1} and δ_{CH_2} = 1430 and 1455 cm^{-1}). Pt(oxalato)(2-ampip) was prepared by the similar method reported previously [1]. *Anal.* calcd. for Pt(oxalato)(2-ampip)-

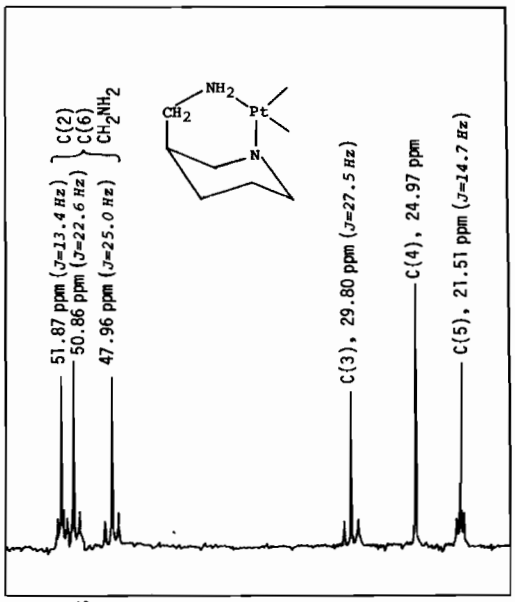

Fig. 1. ^{13}C nmr spectrum of $[Pt(NH_3)_2(3\text{-ampip})]Cl_2$.

(H_2O): C, 23.1; H, 3.9; N, 6.8. Found: C, 23.2; H, 3.8; N, 6.8. IR data ($\nu_{C=O}$ = 1700 and 1670 cm^{-1}, ν_{C-O} = 1375 cm^{-1}, and δ_{NH_2} = 1610 cm^{-1}).

Results and Discussion

The complexes prepared were characterized on the basis of their elemental analyses, IR, NMR, and conductivity data. The data of the equivalent conductivity indicated that all of the complexes are non-electrolytes. In the case of the chelation of 2-ampip with Pt(II), *cis* and *trans* structures are conceivable for $PtCl_2$(2-ampip), but sterically the *trans* structure is the preferred one [2]. In 3-ampip, the aminomethyl group is equatorial in the orientation, and this has been confirmed by the H-nmr spectrum which showed splitting due to geminal coupling in the resonance of the piperidine ring. Therefore, the chelation with Pt(II) requires the interconversion of the aminomethyl group from the equatorial to the axial conformation. When such a change occurs, 3-ampip is able to form a chelate. The nmr spectrum of $PtCl_2$(3-ampip) could not be measured because of its low solubility. Therefore, $[Pt(NH_3)_2(3\text{-ampip})]Cl_2$ was synthesized by the reaction of $PtCl_2$(3-ampip) with ammonia. Fig. 1 shows a ^{13}C nmr spectrum and J_{Pt-C} data for $[Pt(NH_3)_2(3\text{-ampip})]Cl_2$. Tentative assignment was made on the basis of the following consideration: 1) Three peaks on the upfield side in Fig. 1 are attributable to the C(3), C(4), and C(5) carbons.

TABLE I. Antitumor Screening Results of Platinum Complexes of Aminomethylpiperidine and Related Compounds. Test tumor: L-1210, 10^5 cells/mouse, ip-ip, CDF_1 mice (6 mice/group); antitumor active: T/C (%) $\geqq$125.

	T/C (%)			
Dose (mg/kg)/day	50	25	12.5	6.25
$PtCl_2$(2-ampip)	–	150[a]	152[a]	142[a]
$PtCl_2$(3-ampip)	–	127[b]	133[b]	127[b]
$PtCl_2$(2-ampy)	–	127[a]	121[a]	111[a]
Pt(oxalato)(2-ampip)	186[a]	155[a]	134[a]	–
Pt(oxalato)(2-ampip)	238[b]	201[b]	164[b]	–

[a]Administered day 1 and 5. [b]Administered day 1, 5, and 9.

2) Coupling constant of ^{195}Pt with C(4) should be too small to be detected because of four bond coupling. 3) A peak of the C(3) is expected to be most downfield among these three peaks because of the α-effect of the aminomethyl group and the inductive effect of the nitrogen atoms, and it should be accompanied by ^{195}Pt satellite peaks. 4) The γ-effect of the aminomethyl group should have the peak of the C(5) moved to upfield. This peak should also contain ^{195}Pt satellite peaks. 5) Three peaks on the downfield side in Fig. 1 are attributable to the resonance of the aminomethyl, C(1), and C(6) carbons, but assignment of these three peaks may be difficult because of complicated steric factors. Determination whether the Pt(II) complex of 3-ampip has formed a six membered chelate ring or not can be made by the J_{Pt-C} coupling constant. There should be detected five Pt–C couplings, three are geminal couplings and two are vicinal couplings, for the chelate compound as is shown in Fig. 1. Each of the three peaks on the downfield side contains satellite peaks due to $^2J_{Pt-C}$, indicating coordination of Pt(II) to the nitrogen atoms of the piperidine ring and the aminomethyl group.Molecular model shows that the dihedral angle (ϕ) of Pt–N–C(6)–C(5) is about 60°. The $^3J_{Pt-C(5)}$ is 14.7 Hz which agrees with $^3J_{Pt-C}$ with $\phi = 60°$ [2, 3]. According to the multipath mechanism [2], the $^{3,3}J_{Pt-C(3)}$ is expected to be twice as much as the $^3J_{Pt-C(5)}$ because the dihedral angles of Pt–N–C(2)–C(3) and Pt–NH_2CH_2–C(3) are almost 60°, respectively. The observed $^{3,3}J_{Pt-C(3)}$ is 27.5 Hz which agrees with the expected coupling constant. These data indicate that the Pt(II) complex of 3-ampip forms a chelate through the nitrogen atoms of the aminomethyl group and the piperidine ring.

All the complexes tested showed antitumor activity as indicated in Table I, but their activities are not especially high when compared with those of the Pt(II) complexes of 1,2-cyclohexanediamine [4]. The piperidine ring of $PtCl_2$(3-ampip) is almost perpendicular to the chelate ring, while the piperidine ring of $PtCl_2$(2-ampip) is almost coplanar to the chelate ring. In the screening system of using Leukemia L-1210, the antitumor activity of $PtCl_2$(*trans*-1,2-cyclohexanediamine) was much more effective than that of $PtCl_2$(*cis*-1,2-cyclohexanediamine). The steric structure of $PtCl_2$(*trans*-1,2-cyclohexanediamine) and $PtCl_2$(*cis*-1,2-cyclohexanediamine) is similar to that of $PtCl_2$(2-ampip) and $PtCl_2$(3-ampip), respectively.

The antitumor activity of $PtCl_2$(2-ampip) is much more effective than that of $PtCl_2$(3-ampip), and this result is similar to the correlation between the activity and stereochemistry of the Pt(II) complexes of 1,2-cyclohexanediamine. In antitumor active $PtCl_2$(ethylenediamine), change of the dichloro groups with oxalate led to the appearance of neuromuscular toxicity [5]. On the other hand, the same modification in the Pt(II) complexes of 1,2-cyclohexanediamine led to higher antitumor activity, and especially it had very high therapeutic index against Sarcoma 180 ascites system [1]. In this work, change of the dichloro groups of $PtCl_2$(2-ampip) with oxalate led to the appearance of higher antitumor activity.

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