Synthesis and Antitumor Activity of Platinum Complexes Containing Neutral and Protonated Amino-olefin Ligands

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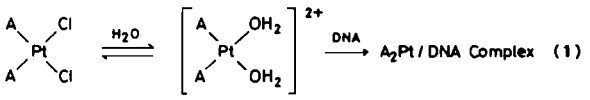
A series of compounds containing N-substituted allyl amines bound to platinum are reported. Under acidic conditions, compounds of the general formula (protonated amino-olefin)$PtCl_3$ are formed. Infrared and ^1H NMR spectroscopy establish that these complexes contain a protonated nitrogen and that the olefin is coordinated to platinum. Complexes containing neutral allyl amines are apparently dimeric, with bridging allyl amine. All of these complexes contain platinum–chloride bonds activated toward hydrolysis, and all were examined for potential antitumor activity. Most of the protonated ligand complexes exhibited significant cytotoxicity against both cis-*platinum sensitive and resistant L1210 Leukemia in cell culture. Neutral ligand complexes were, in all cases, less cytotoxic. Preliminary studies in mice demonstrate only marginal activity against L1210* in vivo.

Introduction

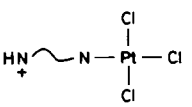
Although a vast number of platinum complexes have been screened for antitumor activity, virtually all have been of the form A_2PtX_2 where A is an amine (or A_2 a chelating diamine) and X an anionic ligand, typically chloride. Such compounds are direct analogs of the prototype antitumor platinum complex, *cis*-dichlorodiammineplatinum(II) (*cis*-$PtCl_2(NH_3)_2$ or PDD), available clinically as '*cis*-Platin' or 'Platinol'. Variations in the identity of the amine ligands lead to significant – but as yet unpredictable – variations in antitumor activity [1]. The amine ligands remain bound to platinum under biological conditions, and the variation in activity with variation in the amine is thus likely to result from differences in the thermodynamics of binding of the A_2Pt fragment to DNA. However, the activity of PDD and its analogs ultimately results from a two-step process (eqn. 1) involving initial loss of the anionic ligands.



(1)

A_2PtCl_2 enters the cell as the neutral complex, but at the low chloride ion concentration of the cell, equilibrium favors the hydrolyzed product, which once formed reacts rapidly with nitrogenous donor ligands such as DNA. The rate of this entire process is thus dictated by the rate of the initial hydrolysis reaction.

It is clear that it should be possible to vary the antitumor effectiveness of platinum complexes not only by altering the thermodynamics of platinum binding to DNA, but also by altering the rate at which the equilibrium of equation (1) is attained. The kinetics of this hydrolysis will be dictated by the *trans*-effect, that is, the ability of the ligand *trans* to the chloride to enhance its substitution reactions. Amines lie low in the *trans*-effect series, and consequently the equilibrium will be established only slowly. Our work centers on efforts to enhance antitumor activity by varying the substituents on platinum in such a fashion that the rate of equation (1) is enhanced. We have chosen to do this by replacing one of the amines by a ligand lying higher in the *trans*-effect series. As a practical matter, this restricts the ligand to anionic species, and we have generally used the chloride ion. Substitution of the neutral amine by an anionic chloride ion would lead to a negatively charged complex. In order to maintain overall complex neutrality (presumably necessary for cellular penetration) we have replaced the remaining amine with a positively charged ligand. One choice of positively charged ligand is a monoprotonated (or monoalkylated) diamine, which leads to complexes of type I. This complex offers not only the kinetic advantage of a chloride lying *trans*- to a good *trans*-director (the chloride ion) but also has a statistical advantage in that two different pairs of *cis*-chlorides can be lost.



I

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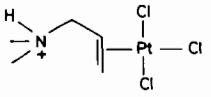
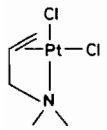
Our work using monoprotonated diamines has demonstrated that complexes of type I can in fact have significant antitumor activity [2]. These complexes are unique in that they represent a broad new class of antitumor active platinum complexes with a structure fundamentally different from PDD and its analogs. It seemed probable that similar complexes with other positively charged ligands should also exhibit antitumor activity. We report here the biological activity of complexes of type II, in which a monoprotonated amino-olefin is coordinated to platinum. This structure possesses the advantages of the type I complexes, but in addition there is a chloride ion which should be highly active toward substitution because it lies *trans* to the very good *trans*-effect ligand, the π-coordinated olefin.



II

In the absence of protonation, the neutral amino-olefin is, in principle, capable of coordination as a chelate ligand, utilizing both the olefin π-system and the nitrogen lone pair. This would produce a neutral complex of type III, which should also be activated toward the substitution reaction of equation (1), and, consequently, have potential as an antitumor agent. We report here the synthesis and antitumor activity of several compounds containing neutral and protonated amino-olefins. Although examples of both types of complex are known, there has been no previous report of their biological activity.



III

Results and Discussion

Characterization of Complexes

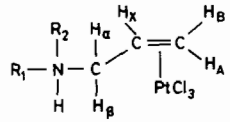
(Protonated amino-olefin)$PtCl_3$ complexes

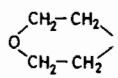
The direct reaction of an N-substituted allyl amine with potassium tetrachloroplatinate in acidic aqueous solutions leads directly to complexes having structure II. These compounds form as yellow crystals which are slightly soluble in dilute mineral acids but poorly soluble in common organic solvents. Analytical data clearly establish their formulation as protonated-ligand complexes. In particular, the Cl/Pt ratio of 3 requires a positive charge at some other point in the molecule.

A large number of similar complexes having the general formula (aminoolefin-H^+)$PtCl_3$ have been reported since their discovery in 1883. Denning and Venanzi [3] have summarized the history of such compounds, and were the first to suggest the structure which has now been conclusively demonstrated. A significant number of X-ray crystallographic studies have established that in each case the coordination environment at platinum is similar to that in Zeise's salt, *e.g.*, square-planar platinum coordination by three chlorides and the olefin π-system [4].

A sharp, weak band near 1495–1500 cm^{-1} in the infrared spectrum of each of these complexes (except for N-allyl aniline, where it is obscured by ligand absorptions), and the absence of absorptions near 1650 cm^{-1} demonstrates that the olefin is coordinated in each case. A broad, complex progression of absorptions spanning the region 3300–2800 cm^{-1} and below appears to be characteristic of the protonated amine, and serves to distinguish these complexes from the neutral ligand complexes discussed below. These infrared spectral results are in accord with the conclusions of Denning and Venanzi [3]. In the platinum–chlorine stretching region, infrared spectra again provide support, albeit somewhat ambiguous, for this structure. Goodfellow, *et al.* [5] have examined far infrared spectra of complexes having the form $[LPtCl_3]^-$. As they note, for a complex of C_{2v} symmetry (probably a reasonable approximation for the protonated aminoolefin complexes) three infrared active platinum–chloride stretching modes are expected. However, under the conditions which they used (tetraalkylammonium cation, 1,2-dichloroethylene solution) only two absorptions were observed. Thus, $[(ethylene)PtCl_3]^-$ exhibits strong absorptions at 330 and 309 cm^{-1}. This compound should serve as a good model for the protonated aminoolefin complexes, and indeed each of these compounds exhibits two strong absorptions, near 335 cm^{-1} and 305 cm^{-1}. However, in several of these compounds there is evidence for a third absorption. The higher energy band is generally broader and somewhat asymmetric, and in the cases of the N-ethyl- and N,N-dimethylallylamine complexes distinct shoulders are observed (at 345 and 341 cm^{-1}, respectively). In the case of the N-allylaniline complex, three distinct absorptions are observed, at 307, 322, and 338 cm^{-1}. Because absorptions near 322 cm^{-1} are absent in the other complexes, it is possible that the 322 cm^{-1} absorption must be assigned to some other mode in the N-allylaniline complex. The lower frequency mode is assigned to stretching of the platinum-chloride bond lying *trans* to the olefin, its decreased frequency resulting from the strong *trans*-influence of the coordinated olefin. Not surprisingly then, there is significant variation in the frequency of this absorption (from 296 to 316 cm^{-1}) as the identity of the *trans* ligand, the protonated amino-olefin, is varied. By

TABLE I. NMR Spectral Data for Protonated Amine Complexes*.



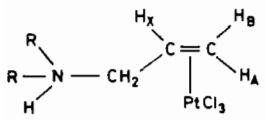
Compound No	R_1	R_2	Chemical Shifts, δ							Coupling Constants, (HZ)						
			δ_A	δ_B	δ_X	δ_{CH_α}	δ_{CH_β}	δ_{NH}	δ_R	J_{XB}	J_{XA}	J_{X-CH_α}	J_{X-CH_β}	$J_{\alpha-\beta}$	J_{Pt-X}	$J_{Pt-(A,B)}$
1a	H	H	4.34	4.38	4.92	3.28	3 68	8.56	–	7.7	12.5	5.5	5.5	–	63	59
2a	CH_3–	CH_3–	4 41	4.45	4.88	3.43	3.98	9.56	3.19	6.9	12 0	6.4	6.9	13.7	67	65
3a	H	CH_3CH_2–	4 36	4.38	4.87	3.36	3.80	9.03	1.40(t, J_{HH} = 7.3) 3.36(q)	7.7	13.3	–	–	–	66	56
4a	H		4 35	4.36	4.85	3 40	3.82	8.90, 9 12	~1.1–2.2(m)	7.3	12.9	6.9	6 9	–	63	58
5a	H		4.34	4.35	4.91	3.64	4.12	6.8	~7.35, 7.5(m)	8.2	12.9	6.5	6.5	13.5	67	58
6a			4 39	4.42	4.94	3.59	4.11	8.0(?)	3.51, 3.97(br)	6.9	11 2	6.6	6.6	13 7	67	58

*Complexes dissolved in DMF-d_7, with TMS as an internal reference.

contrast, the higher frequency mode, due to the pair of *trans* chlorides, is much less sensitive (ranging from 332 to 339 cm^{-1}) to variations in the identity of the olefinic ligand. The infrared spectra thus provide clear support for structure II in each case.

Although the solid state structures of compounds similar to these have been well established, there is surprisingly little information concerning solution properties. Thus, although a limited amount of electronic spectral data exists [3, 6], there have to our knowledge been no reports of nuclear magnetic resonance studies on such compounds, probably as a consequence of their rather poor solubility. We have found that all have sufficient solubility in N,N-dimethylformamide-d_7 to obtain well-defined ^1H NMR spectra. Our measurements confirm that the compounds retain their structural integrity in solution, and the evidence leading to that conclusion follows. Important chemical shifts and coupling constants for all compounds are given in Table I.

Several features in the NMR spectra of the protonated amino-olefin complexes demonstrate that the olefin is coordinated to platinum in dimethylformamide solution. The discussion that follows will deal specifically with allylamine, the simplest amino-olefin, and its complexes. It is clear, however, that similar considerations hold in all other cases examined. All of these compounds have the general structure shown:



For allyl amine (R = R′ = H) chemical shifts demonstrate both the amine protonation and olefin coordination to platinum. Thus, the amine proton resonance shifts from δ 1.47 (the exact position of this absorption is probably affected by traces of water present in the solvent) for the free amine to δ 8.56 in the complex, a shift characteristic of protonation. By contrast, the olefinic proton absorptions are all shifted to higher field. Thus, H_X shifts from δ 5.94 to δ 4.92; H_B shifts from δ 4.94 to δ 4,38; and H_A shifts from δ 5.13 to δ 4.34. (Assignments in all cases were made on the basis of chemical shifts and coupling constants. In each case, spectra were assumed to be first order.) An upfield shift of *ca.* 1 ppm is characteristic for olefinic protons upon coordination to platinum [7]. A decrease in the magnitude of olefinic proton-proton coupling constants is also suggestive of platinum coordination. Thus, J_{XA} changes from 17.2 Hz in the free amine to 12.5 Hz in the complex, and J_{XB} changes from 10.3 Hz in the free amine to 7.7 Hz in the complex. These changes are consistent with the expected rehybridization of the olefin toward a formal platinacyclopropane bonding description. We also observe platinum–proton coupling, of a magnitude appropriate for olefinic coordination [8]. Thus, J_{PtH_X} is a ca. 63 Hz and $J_{PtH_{A,B}}$ is *ca.* 59 Hz in the complex. These coupling constants were measured from satellites (^{195}Pt, I = 1/2, is 33% abundant) of the major peaks, and because of poor resolution in the satellites J_{PtH_A} and J_{PtH_B} could not be independently evaluated. The values in Table I are, consequently, only approximations.

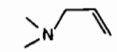
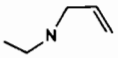
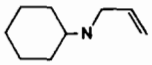
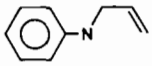
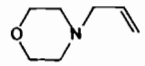
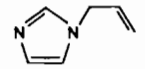
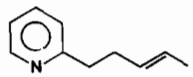
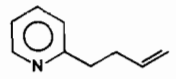
Further evidence for platinum coordination comes from the spectra of the methylene protons. In the free allyl amine, the methylene carbon is prochiral, and the methylene protons give rise to a single nmr absorption (coupled to H_X with $H_{CH_2H_X}$ = 5.2 Hz). Upon coordination of the olefin to platinum, however, the methylene protons become anisochronous, and give rise to an AB absorption pattern. Thus, the free amine resonance at δ 3.20 is replaced by absorptions at δ 3.68 and δ 3.28 in the complex. Such a net downfield shift is, of course, consistent with protonation of the adjacent amine. Although in several cases these inequivalent methylene absorptions are quite broad (*vide infra*), in others they are sufficiently sharp that accurate coupling constants can be extracted (Table I).

In every case, the protons bound directly to nitrogen give a broad absorption. These broad lines may be due to a number of factors, including quadrupolar relaxation effects, unresolved coupling and, most probably, chemical exchange processes. In two cases, however, two distinct amine proton signals are observed, suggesting that the nitrogen bound protons are nonequivalent. If so, this would again result from coordination of the olefin to platinum. Full understanding of these particular aspects of the nmr spectra requires much more detailed studies, currently in progress.

(Amino-olefin)$PtCl_2$ complexes

Neutralization of the (protonated amino-olefin)-$PtCl_3$ complexes with aqueous hydroxide, followed by extraction into chloroform, leads to yellow solids having the composition (amino-olefin)$PtCl_2$. Alternatively, at least in certain cases, identical materials can be prepared by the direct reaction of the amino-olefin with aqueous K_2PtCl_4. Once formed, these compounds are only poorly soluble in solvents which do not cause decomposition, and this fact has made their characterization elusive. Denning and Venanzi [3] have reported complexes of this form with N-ethylallylamine and N-octylallylamine, which they formulate as polymeric and dimeric, respectively. Apparently, a monomeric chelate complex having Structure III can not be formed because of the steric problems inherent in the formation of the 4 1/2-membered chelate ring. This would be consistent with similar observations on unsaturated ketone complexes of platinum [9, 10]. Based on their low solubility, we believe that the complexes we have prepared have

TABLE II. Cell Culture Activity for Protonated and Neutral Complexes of Allylamines

Allyl Amine, L	Protonated Ligand Complex, $(LH^+)PtCl_3$			Neutral Ligand Complex, $LPtCl_2$	
	Compound No.	I.D.$_{50}$(μg/ml)		Compound No.	I.D.$_{50}$
		L1210	L1210/PDD		L1210
	1a	3.0	5.0	1b	5
	2a	>10			
	3a	2.5	4.0	3b	>10
	4a	6	4.3	4b	7
	5a	8	27	5b	>10
	6a	>10			
	7a	>10			
				8b	>10
				9b	>10

oligomeric structures as well. Although Denning and Venanzi [3] were unable to reproduce the original report of an analogous compound with allylamine itself, we find that this compound is formed using the general preparative route.

Infrared spectra demonstrate conclusively that both the amine and the olefin are coordinated to platinum. Thus, for allylamine the free ligand NH stretching modes at 3370 and 3290 cm^{-1} [3] are shifted upon complexation to 3239 and 3197 cm^{-1}. Similarly, the free olefinic stretch at 1642 cm^{-1} [3] is replaced by a weak absorption at 1517 cm^{-1}, a shift characteristic of olefin coordination. Spectral interpretation in the far infrared is much more ambiguous. Denning and Venanzi [3] proposed an allylamine bridged dimeric structure incorporating *trans*-chlorides at platinum. A structure with *cis* chlorides would require that one chloride be *trans* to an olefinic ligand, and this would be expected to lead to a relatively low frequency platinum–chloride stretching mode. It is then tempting to interpret the spectra of certain of these compounds as favoring a *cis* geometry. Thus, (allylamine)$PtCl_2$ exhibits a band at 272 cm^{-1}, as well as bands at 320 and 342 cm^{-1}. Low frequency modes in the N-ethylallylamine (300 cm^{-1}) and allylurea (306 cm^{-1}) complexes may also favor a *cis* geometry. By contrast, complexes of allylimidazole, allylaniline, and N-cyclohexylallylamine exhibit two bands (or one dominant band with a clear shoulder) at *ca.* 340 and 330 cm^{-1}. These spectra clearly favor a *trans* geometry. In the absence of labeling studies which would allow more definitive assignments these data must be taken as inconclusive, although certainly supportive of Denning and Venanzi's original structural proposal in some cases.

Although steric factors prohibit the formation of monomeric platinum complexes with allyl amines, it should be possible to generate complexes with structures analogous to III using amino-olefins with greater separation between donor sites. This has been done using, for example, 2-allylpyridines (II) and 2-vinylanilines [12]. To provide a monomeric reference for the (allylamine)$PtCl_2$ oligomers discussed above, we have prepared $PtCl_2$ complexes of 2-(3-butenyl)-pyridine and 2-(3-pentenyl)pyridine. These complexes are reported [13] to form as monomers, with the ligand chelating through the ring nitrogen and olefinic π-system to give a 6 1/2-membered ring. Infrared spectra support this structure.

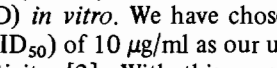
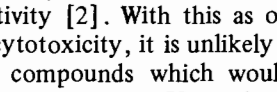
Biological Studies

The compounds prepared in this study have been evaluated as inhibitors of the growth of murine leukemic cells (L1210) and a PDD-resistant subline (L1210/PDD) *in vitro*. We have chosen a 50% inhibitory dose (ID_{50}) of 10 μg/ml as our upper-limit criterion for activity [2]. With this as our criterion for significant cytotoxicity, it is unlikely that we will fail to identify compounds which would subsequently prove to be active *in vivo*. Using this criterion, many of our compounds are found to be active *in vitro* (Table II). Several trends are apparent from these data. First, most of the protonated amine complexes have comparable cytotoxicity (the exceptions will be discussed shortly). Furthermore, most are approximately equitoxic to the sensitive and resistant cell lines. This suggests that there may be a significant difference in the mechanism of action of these compounds compared to PDD, since in PDD and many of its analogs there is a *ca.* 20-fold difference in activity toward these cell lines. The three protonated amine compounds with large values of ID_{50} are equivalent, and distinct from the other complexes, in that they are derived from tertiary amines. For simple PDD analogs there is significant evidence that complexes of primary and possibly secondary amines are much more active than complexes of tertiary amines [1]. This trend seems to be repeated here, but in this case the amine is not coordinated to platinum. Consequently, substitution at the amine is not expected to have any significant effect upon activity. The observation that the effect persists here should be accounted for in any discussion of the origin of the effect.

Although the neutral ligand complexes corresponding to each of the protonated ligand complexes could not be prepared, data is available for four such complexes. In general, cell culture activity is lower for these complexes, although in two cases activity is comparable for both the protonated ligand and neutral ligand complexes. Although this may be fortuitous, it is also possible that under biological conditions the two types of compound are interconvertible. Since the neutral ligand complexes are typically prepared by deprotonation of the protonated ligand complexes, it is conceivable that this deprotonation reaction occurs at physiological pH.

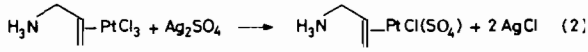
In an attempt to determine if the oligomeric nature of the neutral ligand complexes either enhanced or detracted from the antitumor activity, we examined complexes known to be monomeric, but with equivalent functionality. Complexes derived from 3-alkenyl-pyridines have sufficient separation between olefin and amine sites that chelation to platinum can occur with no serious steric problem. We have prepared complexes of 2-(3-butenyl)- and 2-(3-pentenyl) pyridine, which are known to be monomeric [13]. Neither of these complexes was found to be active in the cell culture screen. Consequently, it appears that oligomerization is apparently not a major obstacle to cytotoxicity.

TABLE III. Animal Test Results.

Compound	Structure	Dose, mg/kg	%T/C
3a		10	98
		20	98
3b		10	105
		20	107
		50	93

As representative samples, the complexes (protonated N-ethylallylamine)$PtCl_3$ and (N-ethylallylamine)$PtCl_2$ have been given a preliminary screening for antitumor activity *in vivo*. The complexes were administered intraperitoneally to mice with L1210 leukemia (Table III). At the dosage used, neither compound exhibited significant antitumor activity. In fact, the decreased value of %T/C for compound 3b suggests that at higher doses, drug toxicity is overwhelming any carcinostatic effect. We are forced to conclude that although these compounds are indeed cytotoxic, they do not have significant antitumor effect at acceptable levels of host toxicity.

None of these compounds are particularly water soluble. Consequently, we considered that the poor *in vivo* activity might reflect poor water solubility, rather than inherent molecular inactivity. In order to test this hypothesis, we prepared the sulfate derivative of (protonated allylamine)$PtCl_3$ by reaction 2:



Unfortunately, we were unable to prepare an analytically acceptable product by this route, although the material which we isolated is probably predominantly the desired material. This impure sulfate complex is readily water soluble but, like its insoluble chloride analogs, appears to be inactive *in vivo*.

Summary

We have prepared a unique series of platinum complexes and have examined them for antitumor activity. These complexes all contain an olefin coordinated to platinum, and consequently the ligand lying *trans* to these olefins should be activated toward hydrolysis reactions. The complexes exhibit modest cytotoxicity in the cell culture screen, but exhibit no significant antitumor activity in mice.

Experimental Section

Chemistry

Allylamines were purchased from Pfaltz and Bauer, Inc., and were used without further purification. Allylimidazole was purchased from Fluka and K_2PtCl_4 was purchased from Matthey-Bishop, Inc. (2-(3-pentenyl)pyridine was a generous gift from Reilly Tar and Chemical Corp. Elemental analyses on platinum complexes were performed by Integral Microanalytical Laboratories, Inc., Raleigh, NC. Infrared spectra of the complexes (as KBr pellets) were measured in the range 260–4000 cm^{-1} using a Nicolet 6000 Fourier transform infrared spectrophotometer. NMR spectra were measured using dimethylformamide-d_7 as solvent with TMS as an internal solvent. Proton spectra were recorded at 250 MHz with a Bruker WM250 pulsed Fourier-transform nuclear magnetic resonance system.

2-(3-Butenyl)pyridine

The general procedure of Brown and Murphey [14] as modified to produce 4-alkenylpyridines [15] was extended to the 2-alkenylpyridine series. Sodium amide in ammonia was produced as previously described [16] using sodium metal (8.0 g, 0.35 mol) in 250 ml ammonia. To this gray solution was added 2-picoline (31.3 g, 0.35 mol) over 1 hour and a dark red solution developed. 3-Bromopropene (42.3 g, 0.35 mol) was added over 1/2 hour and stirring was continued for 7 hours. After the ammonia had evaporated, water was added and the organic material extracted with ether. The ether layers were combined, dried over anhydrous magnesium sulfate, and reduced in volume by rotary evaporation to give 40.8 g of a dark yellow brown liquid. Fractional distillation produced three fractions. The first, b_{10} 78–82° (17.2 g, yield 37%) a clear colorless liquid N_D^{22} 1.5074, was identified as 2-(3-butenyl)pyridine by comparison of physical properties and spectra [13, 17, 18]. The second fraction b_{10} 96–102° (12.4 g, yield 34%) appears to be mainly 4-(2-pyridyl)-1,6-heptadiene, the diaddition product of allylbromine and 2-picoline. The residue is a mixture of triaddition products.

Platinum complexes of the neutral and protonated allyl amines were prepared using the same fundamental routes described by Denning and Venanzi [3]. Reaction of the allyl amines with K_2PtCl_4 in hot aqueous HCl gave protonated ligand complexes in good yield as yellow, crystalline solids. Analytical data are presented in Table IV. Deprotonation of these complexes in a $CHCl_3/H_2O$ suspension led, in some cases, to the neutral ligand complexes. Analytical data for those compounds are indicated in Table V. Complexes of 2(3-butenyl)- and 2(3-pentenyl)pyridines were prepared by reaction of the alkenylpyridine with Zeise's dimer, $[PtCl_2(C_2H_4)]_2$, in diethyl ether.

Biological Studies

Mouse leukemic L1210 cell lines were maintained in McCoy's 5A Medium containing 10% fetal calf serum (Grand Island Biological Co., Grand Island, NY). L1210/0 cells were highly sensitive (ID_{50} = 0.05 μg/ml) to PDD. Compounds to be tested were dissolved in distilled water; compounds that were poorly soluble in water were also prepared in suspension. Stock solutions were prepared at constant ratios up to 500 times that required in the growth medium so that 10 μl of stock solution could be added to 5 ml of inoculated growth medium. Cells were inoculated into media at a concentration of approximately 1×10^5 cells/ml and allowed to grow for 96 hours in 5% CO_2 at 37°. Controls cells grew to a density of 1 to 1.5×10^6 cells/ml as measured by use of an electronic cell counter (Coulter Counter, Model ZF).

To evaluate the activity of compounds against L1210 *in vivo*, the following procedure was employed. L1210 cells (1×10^6 suspended in 0.1 ml of physiological saline solution) were inoculated i.p. into BDF_1 mice (20–22 gm) and drug treatment (i.p.) initiated 24 hours after inoculation of leukemic cells. Drugs were dissolved or suspended in 0.3% hydroxypropylcellulose in saline ('Klucel'; obtained from the National Cancer Institute, NID, Bethesda, MD). Animals that received no drug treatment died between 7 and 9 days after inoculation of L1210 cells. All animals were housed in central animal facilities having controlled temperature, relative humidity and photoperiods.

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TABLE IV. Analytical Data for Complexes of the Type $(LH^+)PtCl_3$.

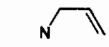
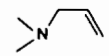
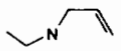
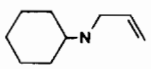
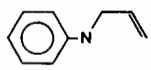
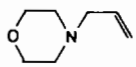
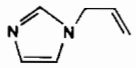
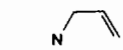
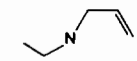
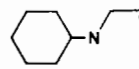
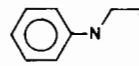
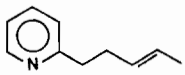
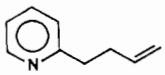
Compound No	L	Empirical Formula	%C		%H		%N		%Cl	
			Calc	Fd.	Calc.	Fd.	Calc.	Fd.	Calc	Fd.
1a		$C_3H_8Cl_3NPt$	10.0	10.12	2.14	1.67	–	–	–	–
2a		$C_5H_{14}Cl_3NPt$	15 44	15.39	3.34	2.52	–	–	–	–
3a		$C_5H_{12}Cl_3NPt$	15.48	15.39	3.10	2.78	–	–	–	–
4a		$C_9H_{19}NCl_3Pt$	24.51	24.44	4.08	3.84	3.17	3.03	23.95	23.98
5a		$C_9H_{12}NCl_3Pt$	24.85	24.87	2.76	2.51	3.22	3.01	24.28	24.27
6a		$C_7H_{14}NCl_3Pt$	19.55	19 57	3.25	2.96	3.25	3.23	24.74	24.61
7a		$C_6H_9N_2Cl_3Pt$	17.54	17.56	2.19	1.89	6.82	6.67	25.94	25.56

TABLE V. Analytical Data for Compounds of the Type $[LPtCl_2]$.

Compound No.	L	Empirical Formula	%C		%H		%N		%Cl	
			Calc.	Fd.	Calc.	Fd.	Calc.	Fd.	Calc.	Fd.
1b		$C_3H_7Cl_2NPt$	11.14	11.31	2.16	1.93	4.33	4.15	21.98	21.68
3b		$C_5H_{11}Cl_2NPt$	17.04	17.26	3.4	3.12	3.97	3.87	20.17	20.24
4b		$C_9H_{17}Cl_2NPt$	26.66	26.79	4.19	4.15	3.45	3 27	17.53	18.06
5b		$C_9H_{11}Cl_2NPt$	27.06	27.31	2.75	2.76	3.50	3.27	17.79	17.37
8b		$C_{10}H_{13}Cl_2NPt$	29.05	28.61	3 14	3 10	3.38	3.22	17.19	18 79
9b		$C_9H_{11}Cl_2NPt$	27 06	27 00	2 75	2 83	3.50	3 32	17 79	17 91

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