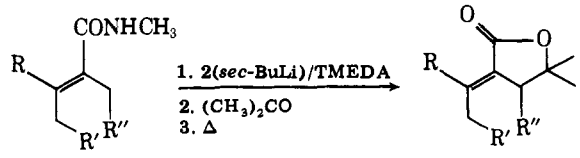
overall yield from **1** and **7**, respectively, a result which also provides chemical confirmation of the position of substitution.



1, R = H; R', R'' = CH_2CH_2 **10**, R = H; R', R'' = CH_2CH_2
7, R = CH_2CH_3; R' = CH_3; R'' = H **11**, R = CH_2CH_3; R' = CH_3; R'' = H

Specific activation of the β' position for metalation by the amide is indicated by the fact that cyclohexene is not metalated under similar conditions and that similar dimetalations of allyl and cyclopropyl carbinols generally require much more forcing conditions.[5]

Dimetalations of α,β-unsaturated secondary amides which lack a β' hydrogen have been reported to occur with proton loss from the γ carbon, a result which is consistent with the behavior of other α,β-unsaturated carbonyl derivatives.[6,7] Metalation of an α,β-unsaturated carbonyl system at the β' position seems to be precedented only by formation of a transient intermediate for a case in which γ protons are not present. Kauffmann et al. have found that *N,N*-diisopropyl-2-methylpropenamide undergoes allylic metalation prior to either self-addition or in situ addition to azobenzene on treatment with lithium diisopropylamide at −60 °C.[8,9] We have found that *N,N*-dimethylcyclohexenecarboxamide on treatment with *sec*-butyllithium–tetramethylethylenediamine under conditions for the metalation of **1** gives a mixture of products which appear to result from the expected additions and γ metalations. We also observe that *N*-methyl-2,3-dimethyl-2-butenamide appears to undergo substitution at more than one methyl group on treatment with *sec*-butyllithium–tetramethylethylenediamine at −78 °C in tetrahydrofuran and subsequent treatment with benzophenone.

In summary, we have found that directed lithiation and electrophilic substitution can be achieved selectively at the β' position of α,β-unsaturated secondary amides in the presence of γ and β protons. This result is useful for achieving carbon–carbon bond formation at a site in α,β-unsaturated carbonyl systems which has not been previously recognized as readily available for substitution. Moreover, the demonstration of a convenient, selective, and novel, directed metalation in a nonaromatic system by a group which is available for subsequent transformations could lead to development of a number of new synthons. Investigation of the apparent role of the amide as a strong complexing agent in directed metalations, extensions of other functionalities, and possibilities for more remote metalations are under further study.

Acknowledgment. We are grateful to the National Institutes of Health-Institute of General Medicine for support of this work.

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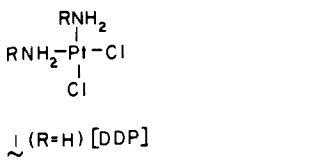
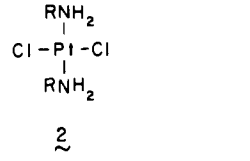
Antitumor Agents. Synthesis of Novel *cis*-Palladium Complexes and Their Action on Supercoiled DNA

Sir:

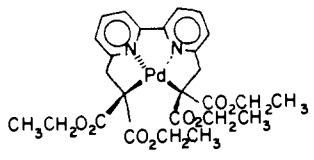
In 1969 Rosenberg et al. reported that *cis*-dichlorodiammineplatinum(II) (**1**) was the potential antitumor metal chelate;[1] currently **1** has worldwide application in the treatment of cancer.[1,2] However, owing to its severe nephrotoxicity, various analogues have been synthesized by ligand modification[3] to circumvent this limitation. In contrast to these cytotoxic platinum complexes, the palladium analogues were reported to be marginally active[4] and more recently demonstrated to be active against Landschutz ascites (in vitro and in vivo) and Sarcoma 180 systems in anticancer screening.[5] The antitumor properties of several related *cis*-$(amine)_2PtX_2$ complexes and the dramatic inactivity of the corresponding trans isomer have been shown throughout initial screening and clinical trials. To extend the ligand framework in these antitumor agents, we recently reported *trans*-**3**,[6] which possesses structural similarity to **2** but has two trans σ-carbon–palladium bonds. *We herein report the synthesis of the stable cis-organometallic reagent* **4**, *which contains two cis* σ*-palladium–carbon bonds making up a novel* [5.5.5] *fused-ring system*[7] *and has the ability to nick supercoiled DNA at low concentrations.*



1 (R=H) [DDP]



2



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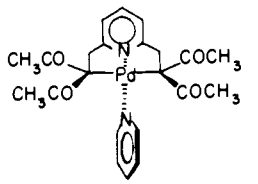

3

Treatment of 6,6′-dibromo-2,2′-bipyridyl with excess *n*-butyllithium in THF at −100 °C gave the dilithio intermediate, which upon treatment with *N,N*-dimethylformamide gave 6,6′-diformyl-2,2′-bipyridyl:[11] mp 236–237 °C. Reduction with sodium borohydride in absolute methanol gave the diol, which upon treatment with redistilled thionyl chloride afforded (45% overall) **5**: mp 157–158 °C. When a mixture of **5**, diethyl malonate, and anhydrous potassium carbonate in DMF was stirred at 25 °C for 12 h, the desired bis adduct **6**[12] [mp 55–56

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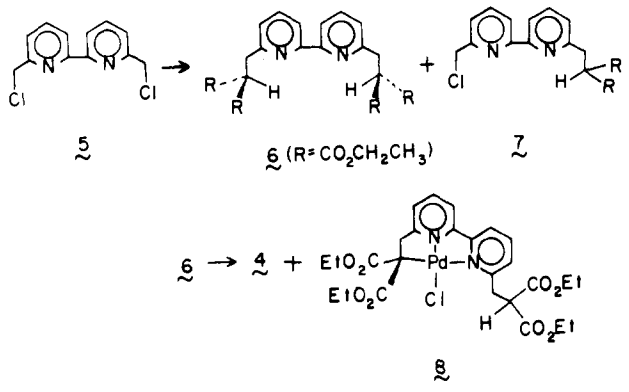
°C; 35%, NMR (200 MHz, CD_2Cl_2) δ 1.22 (t, J = 7.3 Hz, CH_3, 12 H), 3.45 (d, J = 7.7 Hz, py CH_2, 4 H), 4.15 (m, CH_2, 8 H), 4.22 (t, J = 7.7 Hz, CH, 2 H), 7.18 (d, J = 7.6 Hz, 5-py H, 2 H), 7.70 (dd, J = 7.6, 7.8 Hz, 4-py H, 2 H), 8.24 (d, J = 7.8 Hz, 3-py H, 2 H); MS m/e 500 (M^+ 17.0); IR ($CHCl_3$) 1738 (C=O) cm^{-1}] and a monoadduct **7** [1.3%; MS m/e 376 (M^+ 11.9)] were isolated. An anhydrous ethanol solution of sodium ethoxide was added dropwise to a THF solution of $PdCl_2(PhCN)_2$ and **6**. After 12 h at 25 °C the resultant con-



centrate was recrystallized from benzene and diethyl ether to give (25%) complex **4**, as yellow needles:[12] mp 230–232 °C dec; NMR (CD_2Cl_2) δ 1.21 (t, J = 7.2 Hz, CH_3, 12 H), 3.90 (s, py CH_2, 4 H), 4.14 (m, CH_2CH_3, 8 H), 7.49 (d, J = 7.8 Hz, 5-py H, 2 H), 7.64 (d, J = 7.8 Hz, 3-py H, 2 H), 7.91 (t, J = 7.8 Hz, 4-py H, 2 H); IR ($CHCl_3$) 1729 (C=O) cm^{-1}. In addition, mass spectrum of **4** exhibited a parent-ion isotope pattern centered at m/e 604 in accord with the proposed structure. A second complex was isolated (5.5%), recrystallized (benzene–petroleum ether), and spectrally shown to be **8**:[12] mp 187–189 °C dec.

Evidence supportive of the [5.5.5] system in **4** is based on spectral data. In view of the sharp NMR spectrum for **7**, palladium is diamagnetic and thus possesses a (distorted) square planar configuration.[13] The completely symmetrical configuration is confirmed by the NMR first-order pattern and the syn orientation of the bipyridyl moiety is indicated by the pyridine-H_3 chemical shift (δ 7.64). This value of δ 7.64 is in accord with an anticipated upfield shift (~1 ppm)[14] caused by the anti (**6**, δ_{H_3} 8.24) to syn conformational change coupled with a downfield shift (~0.3 ppm) resultant to metal-N coordination.[15] The 16-line multiplet at δ 4.14 for the ethyl methylene protons is caused by the diastereotopic environment imposed by the rigid metal-centered ring system.

As a basis for future investigations, it was of interest to learn if these new cis palladium reagents, which replaced the metal-halide bonds in **1** with metal-carbon bonds, would introduce lesions into purified DNA. We have used superhelical phage PM2 DNA in an assay system[16] based on filtration through nitrocellulose filters, in which denatured DNA or DNA containing single-stranded regions is selectively retained. Preliminary investigations have focused on determining if during the course of action of **4** single-stranded nicks in DNA are produced. As shown in Table I, it appears that one mechanism of action of **4** results in the creation of nicks of DNA. The cis geometry in **4** is obviously critical since the corresponding trans compound **3** is ineffective. The initial ligand **6** is also inactive. That only the cis form is active is not unreasonable in light of the results obtained on studies of the platinum complexes, in which only the cis form is effective as an antitumor drug.[1,2] An observation not depicted in Table I is that the nicking activity of **4** is dependent on temperature (twofold decrease at 25 °C) and the time of reaction.

In conclusion, it appears that *selected cis palladium organometallics may act in a manner similar to that of the known intercalating antitumor platinum drugs.* Currently, we are investigating ligand and metal modifications and their subsequent activity with DNA.

Table I. Supercoiled Phage PM2 DNA Nicked by Palladium Compounds[a]

concn, μM of added compd	nicks introduced, fmol		
	cis-**4**	*trans*-**3**	**6**
7	10	2	
14	36	2	
22	80	2	
40			<2

[a] Reaction mixtures (0.05 mL) contained 130 fmol of PM2 [^{3}H]DNA molecules, Tris (25 mM), pH 7.5, $MgCl_2$ (10 mM), and the palladium compound as indicated and then were incubated at 37 °C for 5 min. Procedures for the detection of activity and quantification of nicks introduced by added palladium compounds have been previously described.[16]

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