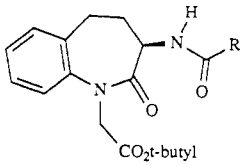

13 R = 2-naphthyl

14 R = 2-indolyl

Figure 3.

or from an electronic perturbation of the aromatic ring is currently being investigated.

In conclusion, we have determined the stereochemical preferences of the CCK receptor for the *R*(D) enantiomer of CR 1409 and related analogues and have proposed a functional identity between glutamate-derived CCK antagonists and the 3-amidobenzodiazepine series represented by L-364,718. Our initial efforts have resulted in the compound A-65,186 (**10**), which possesses both good potency at CCK type A receptors and high selectivity (700-fold) for type A over type B CCK receptors. Currently A-65,186 is being utilized for additional pharmacological and chemical investigations, the results of which will be forthcoming.[11]

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† This paper is dedicated to Professor Kenneth L. Rinehart, Jr. in honor of his 60th birthday.

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Articles

Analogues of Cisplatin Derived from Diaminodideoxytetritols. Synthesis and Activity against the ADJ/PC6 Plasmacytoma in Mice

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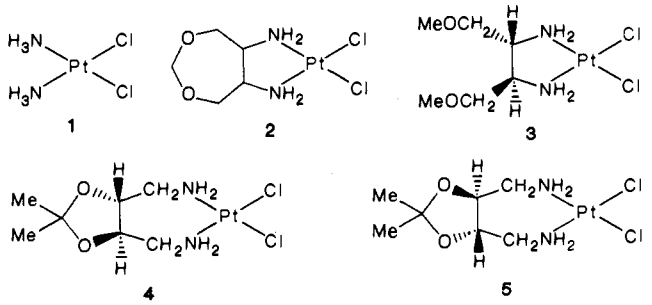
Four new analogues of the anticancer drug cisplatin have been prepared that contain a diaminodideoxytetritol derivative as the amine ligand moiety, and their activities have been measured against the ADJ/PC6 plasmacytoma in mice. Two of these compounds, the enantiomers of *cis*-dichloro(1,4-diamino-1,4-dideoxy-2,3-*O*-isopropylidenethreitol)-platinum(II), show a higher TI value than cisplatin when administered by intraperitoneal injection and, importantly, show significant antitumour activity when administered orally.

Continuing interest[1-4] in the development of analogues of the anticancer drug cisplatin (**1**), which, for example, are less toxic, have increased clinical efficacy and have a broader spectrum of activity than the parent compound, and recent reports[5,6] of analogues containing diamino carbohydrate derivatives, led us to prepare four new complexes **2–5**, each of which contain a diaminodideoxytetritol derivative in place of the amine ligands present in **1**. Our reasoning for this line of investigation hinged on the concept that subtle changes in the lipophilic–hydrophilic nature of such platinum complexes might lead to useful differences in their chemotherapeutic properties. Further, we reasoned that complexes that contained protecting groups on the organodiamine moiety that might be removed under particular physiological conditions, for example the acetal residues of **2**, **4**, and **5**, could have a novel type of anticancer action, especially if release were to be triggered within or close to the cancer cell. We report the synthesis of these platinum complexes and results of tests on the ADJ/PC6 plasmacytoma in mice.



† University of East Anglia.

‡ Johnson Matthey Technology Centre.

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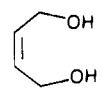
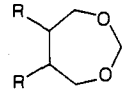
Synthesis

Preparation of complex **2** required the synthesis of *cis*-5,6-diamino-1,3-dioxepane (**11**), which has previously been made[7] from *cis*-butene-1,4-diol (**6**). The sequence of reactions involved acetalization of **6** with formaldehyde to give 1,3-dioxep-5-ene (**7**), hydroxylation of this alkene with potassium permanganate to afford 1,3-dioxepane-*cis*-5,6-diol (**8**), methanesulfonylation of the latter to give the corresponding dimesylate (**9**), displacement of the sulfonyloxy groups in the dimesylate by azide ion to give *cis*-5,6-diazido-1,3-dioxepane (**10**), and reduction of the diazide to diamine **11**. We found that cis-hydroxylation of **7** could be performed in higher yield (70%) by using the osmium tetraoxide/*N*-methylmorpholine *N*-oxide reagent[8] instead of the permanganate-based method originally reported,[7] which gave the diol **8** in only 50% yield. Reaction of the diamine **11** with potassium tetrachloroplatinate(II) afforded *cis*-dichloro(*cis*-5,6-diamino-1,3-dioxepane)platinum(II) (**2**) in 17% overall yield from the diazide.

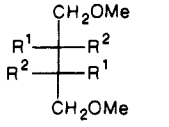


6

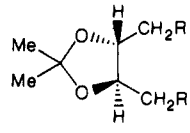
7



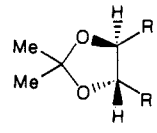
8: R = OH
9: R = OMs
10: R = N_3
11: R = NH_2



12: R^1 = OH; R^2 = H
13: R^1 = OMs; R^2 = H
14: R^1 = H; R^2 = N_3
15: R^1 = H; R^2 = NH_2



16: R = OH
17: R = OMs
18: R = N_3
19: R = NH_2



20: R = CN
21: R = CH_2NH_2
22: R = $CONH_2$

Ms = $MeSO_2$

The organic ligand in complex **3** is readily synthesized from 1,4-di-*O*-methyl-D-threitol (**12**), which can be made[9] in two steps from 3,4-*O*-isopropylidene-D-mannitol.[10] Methanesulfonylation of **12** gave the crystalline 2,3-dimesylate **13**, which underwent smooth reaction with sodium azide in *N*,*N*-dimethylformamide to afford an oil, characterized through its spectral properties as the 2,3-diazido compound **14**.[11] The diazide was reduced catalytically without further purification and the diamine **15** so produced was reacted with potassium tetrachloroplatinate(II) to give *cis*-dichloro(2,3-diamino-2,3-dideoxy-1,4-di-*O*-methyl-L-threitol)platinum(II) (**3**) in 37% yield from the diazide.

The enantiomeric pair of complexes **4** and **5** were prepared with 3,4-*O*-isopropylidene-D-mannitol[10] and 2,3-*O*-isopropylidene-L-tartaronitrile (**20**),[13] respectively, as chiral starting materials. Periodate cleavage of 3,4-*O*-isopropylidene-D-mannitol followed by borohydride reduction of the product gave[9] 2,3-*O*-isopropylidene-D-threitol (**16**), which was treated with methanesulfonyl chloride to afford 2,3-*O*-isopropylidene-1,4-bis-*O*-(methylsulfonyl)-D-threitol (**17**). Displacement of the methylsulfonoxy groups to give diazide **18** and catalytic reduction of the latter afforded diamine **19**, which was not isolated but was reacted immediately with potassium tetrachloroplatinate(II) to yield the complex **4**.

Reduction of 2,3-*O*-isopropylidene-L-tartaronitrile (**20**) with lithium aluminum hydride in diethyl ether gave, as a syrup, diamine **21**, which was reacted directly with potassium tetrachloroplatinate(II) to give the complex **5** in 14% overall yield from the dinitrile. This low yield was largely a result of a poor recovery of the diamine from the inorganic residues resulting from workup of the reduction mixture. The diamine **21** and, thereby, complex **5**, was also prepared by reduction of 2,3-*O*-isopropylidene-L-tartaramide (**22**). Through corresponding reactions in the D series, complex **4** may also be prepared from the readily available chiral pool provided by tartaric acid derivatives.

Table I. Activity of Cisplatin Analogues **2**–**5** against the ADJ/PC6 Plasmacytoma in Mice

compd	route	LD_{50},[a] mg kg^{-1}	ED_{90},[b] mg kg^{-1}	TI[c]
1	ip	13.0	1.6	8.1
2	ip	41.5	10	4.1
3	ip	17.7	<3.1	>5.7
3	po	660	150	4.4
4	ip	35	1.6	21.9
4	po	1100	9	122.2
5	ip	35	1.46	24.0
5	po	1130	26	43.5

[a] 50% lethal dose. [b] Inhibitory dose causing 90% tumor regression. [c] Therapeutic index = LD_{50}/ED_{90}.

Antitumor Activity

The compounds **2**–**5** were screened for antitumor activity against ADJ/PC6 tumor[14] subcutaneously implanted into female Balb-C mice.[16,17] Compound **2** was administered intraperitoneally (ip) and compounds **3**–**5** were administered both intraperitoneally and orally (po). Four dose levels of the compounds were used (5, 25, 125, and 625 mg per kg) and six animals were used per dose level. Results are given in Table I, and figures for ip administered cisplatin (**1**) are given for comparison.

These compounds are representative of a largely neglected class of diamine platinum complexes, in which the ligand is of a type that presents many possibilities for introducing subtle structural variations in the search for

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(11) Inversion of configuration is assumed during the azide displacement reaction in keeping with all previous observations on similar reactions and by analogy with the reported[12] azide reaction on the ditosylate of 1,4-di-*O*-methyl-L-threitol.
(12) Seebach, D.; Kalinowski, H. O.; Bastani, B.; Crass, G.; Daum, H.; Dorr, H.; Du Preez, N. P.; Ehrig, V.; Langer, W.; Nussler, C.; Oei, H.; Schmidt, M. *Helv. Chim. Acta* **1977**, *60*, 301.
(13) Briggs, M. A.; Haines, A. H.; Jones, H. F. *J. Chem. Soc., Perkin Trans. 1* **1985**, 795.
(14) This tumor has been used as a predictor of the clinical utility of a number of platinum compounds against ovarian cancer.[15] As a solid tumor implanted subcutaneously and exposed to systemic drug it offers considerable advantage over the more commonly used ip/ip rodent leukemias such as the L1210 and P338 tumors.
(15) Wilkinson, R.; Cox, P. J.; Jones, M.; Harrap, K. R.; *Biochemie* **1978**, *60*, 851.
(16) Potter, M.; Robertson, C. L. *J. Natl. Cancer Inst.* **1960**, *25*, 847.
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platinum drugs showing novel antitumor properties. The importance of this series of compounds is enhanced by the inclusion of the two cisplatin analogues 4 and 5, which belong to a class virtually ignored[1-4] by previous workers in the field, that is one of analogues that may contain a seven-membered chelate ring.[18,21] Further, the enantiomeric relationship of 4 and 5 makes a comparison of their activities particularly interesting, in view of the known dependence of antitumor activity of Pt(II) and Pt(IV) complexes containing a 1,2-diaminocyclohexane ligand on the chirality of the diamine.[23]

Compounds 2 and 3, delivered intraperitoneally, both show TI values comparable to that of cisplatin (1), and the same is true for 3 delivered orally, although in this case it is noticeable that the toxicity and efficacy, as measured by the LD_{50} and ED_{90} values, respectively, are lower than in the other cases.

Both of the complexes 4 and 5 administered intraperitoneally show similar TI values that are greater than that of 1 and, more importantly, they both show significant activity by the *oral* route. In the latter case, the chirality of the ligand appears to influence the TI values, complex 4 being the most active, with TI equal to 122.

The LD_{50} and ED_{90} values for 4 and 5 are both increased in going from the ip to the oral route. This increase could be due in part to the incomplete absorption of the platinum compounds. If this were the only factor, then the same TI would be expected for both routes. However, the decrease in toxicity after oral dosing is much greater than the decrease in activity so that the oral route proves to be a method of decreasing the toxicity of these drugs. It is not yet known whether this effect is due to different species being present after dosing, an altered distribution of platinum, or a different pharmacokinetic profile.

In the development of a third generation of cisplatin-type anticancer drugs, oral activity is of prime interest.[4] Further work is in progress with compounds related to 4 and 5 in an attempt to exploit their promising antitumor activity.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 257, 297, or 557 grating spectrometer and ^1H NMR spectra were measured at 60 MHz with a JEOL PMX60SI spectrometer for solutions in deuteriochloroform with TMS as internal standard. Optical rotations were recorded at ambient temperature with a Perkin-Elmer 141 polarimeter.

1,3-Dioxepane-*cis*-5,6-diol (8). A mixture of water (40 mL), acetone (20 mL), *N*-methylmorpholine *N*-oxide (14.81 g, 0.13 mol), and osmium tetraoxide in 2-methyl-2-propanol (2 mL of a 5% by weight solution) was stirred at room temperature under nitrogen. To this mixture was added 1,3-dioxep-5-ene[24] (7) (10 g, 0.1 mol), the temperature of the reaction mixture being maintained near 25 °C with the aid of an ice bath, and the mixture was then stored for 12 h. Sodium dithionite (0.5 g) and Kieselguhr (5 g) were then added, and after stirring of the reaction mixture for 10 min, it was filtered through a Kieselguhr pad, and the latter was washed with acetone (3 × 20 mL). The combined filtrate and washings were neutralized with 6 M sulfuric acid, and acetone was removed under reduced pressure. The resulting solution was extracted continuously with ethyl acetate for 24 h and the extract, after drying ($MgSO_4$), was concentrated under reduced pressure to give the syrupy diol (9.44 g, 70%). Anal. ($C_5H_{10}O_4$) C, H.

***cis*-5,6-Bis[(methylsulfonyl)oxy]-1,3-dioxepane (9).** Treatment of diol 8 (1.78 g, 13.3 mmol) in pyridine (10 mL) with methanesulfonyl chloride (9.13 g, 79.7 mmol) in the usual manner gave, after recrystallization of the product from ethyl acetate–light petroleum, the diester (2.6 g, 67%), mp 127–128 °C (lit.[7] mp 129–131 °C). Anal. ($C_7H_{14}O_8S_2$) C, H, S.

***cis*-Dichloro(*cis*-5,6-diamino-1,3-dioxepane)platinum(II) (2).** To a solution of *cis*-5,6-bis[(methylsulfonyl)oxy]-1,3-dioxepane (9) 0.826 g, 2.85 mmol) in *N,N*-dimethylformamide (41 mL) was added sodium azide (1.04 g, 16 mmol), and the mixture was heated under reflux for 5 h. The cooled reaction mixture was diluted with dichloromethane (165 mL) and filtered, and the filtrate washed with water (2 × 80 mL) and dried ($MgSO_4$). Concentration of the organic solution afforded crude *cis*-5,6-diazido-1,3-dioxepane (10) (0.38 g, 73%): IR (film) 2110 cm^{-1} (N_3); ^1H NMR δ 3.55–4.16 (6 H, complex, 2 CH_2 + 2 CH), 4.75 (2 H, br s, OCH_2O). This material was dissolved in methanol (50 mL) and hydrogenated at a slight overpressure of hydrogen over 5% palladium on charcoal catalyst (0.2 g) until TLC indicated all starting material had been consumed. The catalyst was removed by filtration, and the filtrate was concentrated to a clear syrup (0.094 g, 0.7 mmol, 34% based on expected diamine 11). Without purification this material was dissolved in water (5 mL) and a solution of potassium tetrachloroplatinate(II) (0.23 g, 0.55 mmol) was added with stirring. On storage overnight at 2 °C a yellow precipitate formed, from which the supernatant liquor was removed with a pipet. The solid was washed successively with water, ethanol, and diethyl ether and finally was dried over phosphorus pentoxide to give the complex 2 (0.11 g, 50% based on K_2PtCl_4, 17% based on diazide 10): IR (KBr) 3500, 1580, 1455, 1445, 1285, 1255, 1180, 1130, 1100, 1070, 1045, 1030, 995, 990, 925, 780, 740, 615, 440, 320, and 315 (Pt–Cl) cm^{-1}. Anal. ($C_5H_{12}Cl_2N_2O_2Pt$) C, H, Cl, N.

2,3-Bis-*O*-(methylsulfonyl)-1,4-di-*O*-methyl-D-threitol (13). 1,4-Di-*O*-methyl-D-threitol (12)[9] (1 g, 6.6 mmol) was treated with methanesulfonyl chloride (3.108 g, 27 mmol) in pyridine in the usual manner and the product recrystallized from ethanol to give the diester (1.86 g, 91%): mp 39.5–41.5 °C; $[\alpha]_D$ +21.6° (c, 1.64 in ethanol). Anal. ($C_8H_{18}O_8S_2$) C, H, S.

***cis*-Dichloro(2,3-diamino-2,3-dideoxy-1,4-di-*O*-methyl-L-threitol)platinum(II) (3).** A solution of dimethanesulfonate 13 (3.74 g, 12.2 mmol) in *N,N*-dimethylformamide (50 mL) was heated under reflux in the presence of sodium azide (5.39 g, 83 mmol) for 2 h, and the cooled solution was then diluted with dichloromethane (100 mL) and filtered. The filtrate was washed with water (2 × 50 mL), dried, and concentrated to afford crude 2,3-diazido-2,3-dideoxy-1,4-di-*O*-methyl-L-threitol (14) (1.19 g, 49%): IR (film) 2110 cm^{-1} (N_3); ^1H NMR δ 3.36 (6 H, s, OCH_3), 3.58 (6 H, br s, 2 CH_2 + 2 CH). A portion (0.88 g, 4.4 mmol) of the material dissolved in methanol (50 mL) was reduced in the presence of 5% palladium on carbon (0.3 g) under a slight overpressure of hydrogen to give, after concentration of the filtered solution, a syrup (0.47 g, 3.17 mmol, 72% based on the expected diamine 15). To a stirred solution of this material in water (2 mL) was added a solution of potassium tetrachloroplatinate(II)

(18) Confirmation of the presence of a seven-membered ring in these compounds must await further study, since a polymeric structure cannot be ruled out at present. A seven-membered chelate ring in a bidentate complex of platinum is relatively uncommon. Romeo and co-workers have prepared[19] a 1,4-diaminobutane complex, chloro(dimethyl sulfoxide)(1,4-diaminobutane)platinum(II) chloride, the molecular structure of which has been determined in the crystalline state by X-ray analysis.[20] The preparation of this chelate, by reacting 1,4-diaminobutane with a suspension of *cis*-[$Pt(DMSO)_2Cl_2$] in methanol, also affords a second product, μ-(1,4-diaminobutane)bis[dichloro(dimethylsulfoxide)platinum(II)], in which two $Pt(DMSO)Cl_2$ residues are bridged by the diamine.

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(21) A patent application[22] made after completion of our work, regarding the use of platinum complexes obtained from 1,4-diaminobutane and its *C*-alkyl derivatives as antitumor agents, points to the potential importance of this type of compound in this area of chemotherapy. The compounds had lower renal and vomiting toxicities than those of cisplatin.

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(1.33 g, 3.2 mmol) in water (4 mL) and the resultant mixture was stored overnight at 2 °C, leading to formation of a yellow precipitate. The latter was collected, washed with water, ethanol, and diethyl ether and dried to give the complex **3** (0.67 g, 51%); IR (Nujol) 3260, 3170, 1570, 1220, 1190, 1160, 1150 (br), 1060, 1010, 1000, 960, 915, 850, 770, 755, 720, 650 cm^{-1}. Anal. ($C_6H_{16}Cl_2N_2O_2Pt$) C, H, Cl, N.

2,3-*O*-Isopropylidene-1,4-bis-*O*-(methylsulfonyl)-D-threitol (17). 2,3-*O*-Isopropylidene-D-threitol (**16**) (5.1 g, 0.031 mol), prepared[9] from 3,4-*O*-isopropylidene-D-mannitol, was dissolved in pyridine (40 mL) and treated with methanesulfonyl chloride (26.64 g, 0.233 mol) to yield, after crystallization of the reaction product from ethanol, the diester **17** (6.6 g, 66%): mp 83–85 °C; $[\alpha]_D$ +19.6° (c, 1.4 in acetone) [lit.[25] mp 85.5–86.5 °C; $[\alpha]_D$ +21.9° (c, 2 in acetone)]. Anal. ($C_9H_{18}O_8S_2$) C, H, S.

***cis*-Dichloro(1,4-diamino-1,4-dideoxy-2,3-*O*-isopropylidene-D-threitol)platinum(II) (4).** A solution of the diester **17** (3 g, 9.4 mmol) in *N*,*N*-dimethylformamide (100 mL) was heated under reflux in the presence of sodium azide (4.9 g, 75 mmol) for 3 h. The solution was cooled, diluted with dichloromethane (150 mL), filtered, and washed with water (2 × 50 mL). Concentration of the dried solution gave crude 1,4-diazido-1,4-dideoxy-2,3-*O*-isopropylidene-D-threitol (**18**) (1.3 g, 65%): IR (film) 2110 (N_3), 1385, 1375 cm^{-1} (Me_2C); ^1H NMR δ 1.44 (6 H, s, Me_2C), 3.28–3.64 (4 H, complex, 2 CH_2), 3.96–4.16 (2 H, complex, 2 CH). A solution of a portion of this product (1.13 g, 5.3 mmol) in methanol (50 mL) was hydrogenated under a slight overpressure of hydrogen in the presence of 5% palladium on carbon (0.2 g) until TLC indicated all starting material had been consumed. The suspension was filtered and the filtrate was concentrated to a syrup (0.61 g, 3.8 mmol, 72% based on the expected diamine **19**). To a solution of this product in water (10 mL) was added a solution of potassium tetrachloroplatinate(II) (1.58 g, 3.8 mmol) in water (10 mL), and the mixture was stored overnight at 2 °C, affording a pale yellow precipitate. The supernatant liquor was removed, and the residue was washed successively with water, ethanol, and diethyl ether. It was then dried over phosphorus pentoxide to give the complex (**4**) (0.97 g, 60%): IR (KBr) 3450 (br), 3210, 1595, 1460, 1450, 1380, 1370, 1215, 1160, 1070, 870, 510 (weak, Pt–N), 335 and 325 (Pt–Cl). Anal. ($C_7H_{16}Cl_2N_2O_2Pt$) C, H, Cl, N.

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***cis*-Dichloro(1,4-diamino-1,4-dideoxy-2,3-*O*-isopropylidene-L-threitol)platinum(II) (5).** (a) To a suspension of lithium aluminum hydride (1.3 g, 0.034 mol) in diethyl ether (40 mL) was added a solution of 2,3-*O*-isopropylidene-L-tartaronitrile (**20**)[13] (1 g, 6.57 mmol). The suspension was stirred for 4 h at room temperature, after which time water (1.3 mL) was added followed at 5-min intervals by a 15% sodium hydroxide solution in water (1.3 mL) and then water (3.9 mL). The suspension was filtered and the filtrate dried and concentrated to a syrup (0.27 g, 1.69 mmol, 26% based on the expected diamine **21**). Without further purification the product was dissolved in water (5 mL), and a solution of potassium tetrachloroplatinate(II) (0.76 g, 1.8 mmol) in water (10 mL) was added with stirring. After storage overnight at 2 °C, supernatant liquor was removed from the pale orange precipitate that had formed, and the solid was washed with water, ethanol, and diethyl ether and was then dried over phosphorus pentoxide to give the complex **5**. Anal. ($C_7H_{16}Cl_2N_2O_2Pt$) C, H; N: calcd, 6.6; found, 6.1; Cl: calcd, 16.6, found, 15.9.

(b) 2,3-*O*-Isopropylidene-L-tartaramide[13] (**22**) (9.0 g, 48 mmol) was placed in a Soxhlet thimble and extracted into a refluxing suspension of lithium aluminum hydride (4.5 g, 118 mmol) in tetrahydrofuran (300 mL). Refluxing was continued for 6 h and the suspension was then stirred at room temperature overnight. Water (5 mL) was then added dropwise to the stirred mixture, followed by 15% aqueous sodium hydroxide (5 mL) and then water (15 mL). The mixture was filtered, the solids were washed with tetrahydrofuran (200 mL), and the combined filtrates were concentrated to afford the crude diamine **21** as a pale brown oil (6.5 g, 85%). A solution of potassium tetrachloroplatinate(II) (13.66 g, 32.9 mmol) in water (138 mL) was filtered and to it was added a solution of the crude diamine (6.5 g, 40.6 mmol) in water (10 mL). The mixture was stirred overnight and the pale orange precipitate was collected by filtration, washed sequentially with water, ethanol, and diethyl ether, and dried to give **5**: IR (KBr) 3450 (br), 3210, 1600, 1460, 1455, 1385, 1375, 1220, 1160, 1070, 870, 510 (weak Pt–N), 335, and 325 (Pt–Cl). Anal. ($C_7H_{16}Cl_2N_2O_2Pt$) C, H, Cl, N.

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