Preparation, Characterization and Activity of Palladium(II) Halide Complexes with Diethyl 2-Quinolylmethylphosphonate (2-dqmp). X-Ray Crystal Structures of *trans*-[Pd(2-dqmp)$_2$X$_2$] (X = Cl or Br)†

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A series of new palladium(II) halide complexes with diethyl 2-quinolylmethylphosphonate (2-dqmp) were prepared and studied. Two types of square-planar palladium dihalide complexes, *trans*-[Pd(2-dqmp)$_2$X$_2$] with the N-bonded monodentate ligand and *cis*-[Pd(2-dqmp)X$_2$] where dqmp acts as a bidentate N,O-bonded chelate ligand, could be obtained by reaction of 2-dqmp with [PdX$_4$]$^{2-}$ (X = Cl or Br) in neutral methanolic–aqueous solution. The ion-pair salt complexes, [2-Hdqmp]$_2$[PdX$_4$], containing the protonated quinoline ligand as cation and the square-planar tetrahalogenopalladate complex as anion, were isolated upon treatement of the ethanolic–aqueous solution with HX. The new complexes were identified and characterized by elemental and thermogravimetric analysis, magnetic and conductometric measurements, and by infrared and ^{1}H NMR spectral studies. All were tested for cytostatic activity on KB and L1210 cell lines, but only [Pd(2-dqmp)$_2$Br$_2$] **2** displayed a significant anti-tumour effect in both systems. The molecular structures of the complexes [Pd(2-dqmp)$_2$X$_2$] (X = Cl, **1**; Br, **2**) were determined by single-crystal X-ray analysis. The crystals are triclinic, space group $P\bar{1}$, $Z = 2$, with other parameters: **1**, $a = 10.209(3)$, $b = 9.812(3)$, $c = 8.949(2)$ Å, $\alpha = 78.36(2)$, $\beta = 94.82(2)$, $\gamma = 111.60(2)°$, $R = 0.0598$, and $R' = 0.0648$ for 2982 observed reflections; **2**, $a = 10.502(3)$, $b = 9.405(3)$, $c = 9.009(3)$ Å, $\alpha = 72.00(2)$, $\beta = 103.96(2)$, $\gamma = 100.63(2)°$, $R = 0.0574$, and $R' = 0.0614$ for 2033 observed reflections. Each complex has a *trans* square-planar structure, the palladium being co-ordinated by two halogen and two nitrogen atoms and lying at a centre of symmetry.

There is currently considerable interest in palladium(II) complexes not only because of their great importance in organic synthesis[1] and various catalytic processes,[2] but also from a biological and pharmacological point of view. A large number of complexes containing platinum metals have been found effective in the treatment of some animal and human carcinomas.[3] Their biological and chemical activity is greatly influenced by the structure of the ligands co-ordinated to the metal ions. Therefore a great deal of research has been directed towards the complexes of ligands which are important in medical and biological systems.[4–6] This led us to investigate palladium complexes with organophosphorus ligands. Although it is well known that some organophosphorus compounds, in particular derivatives of various phosphonic acids, can exhibit antibiotic, antibacterial and antiviral activity,[7,8] the co-ordination chemistry of this class of phosphorus ligands has drawn relatively little attention.[9–12]

In this paper we report the synthesis and characterization of new palladium(II) halide complexes with diethyl 2-quinolylmethylphosphonate (2-dqmp). It would be expected that this chelate ligand binds in a bidentate manner *via* the quinoline nitrogen and the phosphoryl oxygen donor atoms, however it can also act as a monodentate ligand through the nitrogen, and in acidic media the quinolinium salts of tetrahalogenopalladate anions have been isolated. Monodentate co-ordination in *trans* square-planar complexes [Pd(2-dqmp)$_2$X$_2$] deduced spectroscopically was subsequently confirmed by a single-crystal X-ray diffraction study. The *in vitro* cytostatic activity of all the complexes was evaluated against KB and L1210 cell lines as a preliminary screening for their biological activity.

Experimental

Materials.—Diethyl 2-quinolylmethylphosphonate (2-dqmp), prepared as previously described,[13] was purified by distillation under reduced pressure. All other reagents and solvents were analytical grade products. The purification of methanol and dimethylformamide (dmf) was carried out by the standard techniques.[14,15]

Preparation of the Complexes.—[Pd(2-dqmp)$_2$Cl$_2$] **1**. To a stirred solution of 2-dqmp (0.346 g, 1.24 mmol) in methanol (2 cm^3) was added dropwise a solution of K$_2$[PdCl$_4$] (0.203 g, 0.6

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† *trans*-Dibromo- and *trans*-dichloro-bis(diethyl 2-quinolylmethylphosphonate-κ*N*)palladium(II).

Supplementary data available: see Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1991, Issue 1, pp. xviii-xxii.

mmol) in water (5 cm^3). The yellow precipitate formed was washed with water and methanol, and dried under vacuum over P_2O_5. Yield 0.314 g (70%).

[Pd(2-dqmp)$_2$Br$_2$] **2**. A mixture of $K_2[PdCl_4]$ (0.232 g, 0.71 mmol) and LiBr (0.370 g, 4.26 mmol) in water (5 cm^3) was stirred for 1 h before adding 2-dqmp (0.396 g, 1.42 mmol) in methanol (2 cm^3). An ochre precipitate (0.176 g, 60%) was separated and dried as for **1**.

Crystals of compounds **1** and **2** used for X-ray analysis were obtained by recrystallization from methanol.

[Pd(2-dqmp)Cl$_2$]·2H$_2$O **3**. A mixture of 2-dqmp (0.342 g, 1.22 mmol) and $Na_2[PdCl_4]$ (0.389 g, 1.32 mmol) in methanol (20 cm^3) was refluxed for 8 h under a stream of N_2. Solvent was partly removed from the filtered solution to give on cooling and addition of water (5 cm^3) an orange precipitate (0.330 g, 55%).

[Pd(2-dqmp)Br$_2$] **4**. By almost the same procedure, compound **4** was prepared by addition of $K_2[PdBr_4]$ (0.610 g, 1.21 mmol) in a mixture of methanol (30 cm^3) and water (5 cm^3) to a solution of 2-dqmp (0.311 g, 1.11 mmol) in methanol (5 cm^3). Yield 0.272 g (45%).

[2-Hdqmp]$_2$[PdCl$_4$]·2H$_2$O **5**. To a stirred solution of 2-dqmp (0.391 g, 1.44 mmol) in ethanol (5 cm^3) was added dropwise a solution of $K_2[PdCl_4]$ (0.274 g, 0.76 mmol) in water (8 cm^3) to which HCl (0.5 cm^3) had been added (1:1). The mixture was stirred for 2 h at 4 °C and the brown product precipitated (0.516 g, 85%).

[2-Hdqmp]$_2$[PdBr$_4$]·H$_2$O **6**. A mixture of $K_2[PdCl_4]$ (0.180 g, 0.55 mmol) in water (5 cm^3) and concentrated HBr (0.5 cm^3) was stirred for 1 h and then was slowly added to a stirred solution of 2-dqmp (0.282 g, 1.01 mmol) in ethanol (2 cm^3), giving a brown precipitate (0.433 g, 80%).

Physical Measurements and Analyses.—Melting points were determined on a hot-stage microscope and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer model 580B spectrophotometer using KBr pellets (4000–250 cm^{-1}) and Nujol mulls in polyethylene (400–200 cm^{-1}), ^{1}H NMR spectra on a JEOL FX90Q Fourier-transform spectrometer in CDCl$_3$ and [^{2}H$_7$]dimethylformamide with tetramethylsilane as an internal standard and a sweep width of 1200 Hz. Conductance measurements were carried out at room temperature using a CD 7A Tacussel conductance bridge for 10^{-3} mol dm^{-3} solutions in methanol and dimethylformamide. Magnetic susceptibilities in the solid state were measured at room temperature by the standard Gouy method using a Cahn-Ventron RM-2 balance and CuSO$_4$·5H$_2$O as the susceptibility standard. Thermogravimetric measurements were performed with a Cahn RG electromicrobalance applying a heating rate of 2° min^{-1} in an atmosphere of static air. Elemental analyses were performed in the Laboratory of Complex Compounds and Microanalytical Laboratory of the Rudjer Bošković Institute.

X-Ray Crystal Structure Determinations of [Pd(2-dqmp)$_2$-Cl$_2$] **1** *and* [Pd(2-dqmp)$_2$Br$_2$] **2**.—For both compounds data were collected on a Siemens AED diffractometer with ω–2θ scan, $\theta \leqslant 70$ with Cu-Kα radiation (nickel filtered).

Crystal data for compound **1**. $C_{28}H_{36}Cl_2N_2O_6P_2Pd$, M = 735.86, triclinic, space group $P\bar{1}$, a = 10.209(3), b = 9.812(3), c = 8.949(2) Å, α = 78.36(2), β = 94.82(2), γ = 111.60(2)°, U = 816.3(5) Å^3, Z = 2, crystal size 0.45 × 0.52 × 0.69 mm, F(000) = 752, μ(Cu-Kα) = 150.6 cm^{-1}.

Cell constants and an orientation matrix for data collection were obtained from a least-squares refinement of 29 reflections. 4012 Reflections were measured and 2982 with $I \geqslant 2\sigma(I)$ were used in the refinement. The intensity data were corrected for Lorentz, polarization and absorption effects. The structure was solved by the heavy-atom method and refined by full-matrix least squares. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located and refined in the last cycles isotropically.

The final cycle of refinement included 259 variable parameters with an agreement factor R of 0.0598 and R' 0.0648 [weighting scheme $w = 1/\sigma^2(F) + 0.115\,65F^2$]. Scattering factors were taken from SHELX 76,[16] anomalous dispersion factors from ref. 17, and all calculations were performed using the CRYSRULER package[18] on an IBM PC computer.

Crystal data for complex **2**. $C_{28}H_{36}Br_2N_2O_6P_2Pd$, M = 824.76, triclinic, space group $P\bar{1}$, a = 10.502(3), b = 9.405(3), c = 9.009(3) Å, α = 72.00(2), β = 103.96(2), γ = 100.63(2)°, U = 815.4(5) Å^3, Z = 2, F(000) = 824, μ(Cu-Kα) = 178.0 cm^{-1}.

The same procedure for data collection, solution and refinement was performed as for the chloro derivative. 2033 Observed reflections (out of 3098 measured) were used and the final agreement factors were R = 0.0574 and R' = 0.0614.

Additional material available from the Cambridge Crystallographic Data Centre comprises H-atom coordinates, thermal parameters and remaining bond lengths and angles.

In vitro *Cytostatic Evaluation.*—Two established cell lines, an epidermoid human carcinoma (KB)[19] and murine leukaemia (L1210)[20] were used for evaluation of the cytostatic effect. The KB cells were grown in a tissue culture flask (25 cm^3) with Eagle's Minimal Essential Medium (mem) supplemented with 10% new-born calf serum and 1% non-essential amino acids. The medium was buffered with *N*-tris(hydroxymethyl)methyl-2-aminoethanesulphonic acid (3 mmol), *N,N*-bis(2-hydroxyethyl)-2-aminoethanesulphonic acid (3 mmol), *N*-(2-hydroxyethyl)piperazine-*N'*-2-ethanesulphonic acid (3 mmol) and *N*-tris(hydroxymethyl)methylglycine (3 mmol).[21] The doubling time was *ca.* 24 h. For the *in vitro* assay the cells in logarithmic growth phase were fed again 24 h before testing. The cells were treated for 5 min at 37 °C with a 0.05% 1:250 trypsin solution, suspended in mem to obtain a concentration of 10^5 cells cm^{-3} and seeded in Leighton tubes. The samples were allowed to incubate for 24 h at 37 °C. Cell growth was estimated by counting the viable cells which were detached from the glass surface with trypsin solution. The L1210 cells were maintained as suspension cultures in RPMI 1640 medium[22] supplemented by 10% fetal calf serum. Under these conditions the doubling time was *ca.* 12 h. For the cytostatic assay the cells were seeded in Leighton tubes at 2 × 10^4 cells cm^{-3} in the exponential phase of growth. The compounds were added after seeding.

The compounds were dissolved or suspended immediately before use in sterile dimethyl sulphoxide (dmso). Further dilutions were performed with the growth medium to the desired drug concentration. The final solvent concentration in culture medium (0.5% in every tube) was tested for non-cytotoxicity. At least five concentration levels were used for each compound and each concentration was tested in triplicate. The incubation was carried out at 37 °C for 72 h, the time interval during which exponential growth occurs. Cell growth was estimated by counting the viable cells.

The cytostatic activity was evaluated as the growth inhibition percentage of the cells present in the treated tubes with respect to the controls and was expressed as the concentration of the complex in μg cm^{-3} (ID$_{50}$) at which the cells showed a 50% inhibition of growth in relation to the control values. The procedure was described earlier.[4]

Results and Discussion

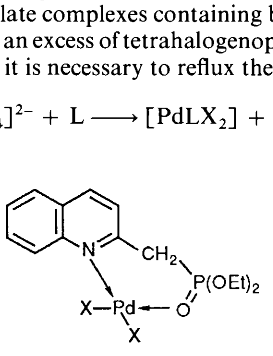
Synthesis and Properties.—Diethyl 2-quinolylmethylphosphonate, a ligand with two potential donor atoms, quinoline nitrogen and phosphoryl oxygen, can form palladium halide complexes with 1:2 and 1:1 metal-to-ligand ratios, as well as salts with the protonated ligand as cation and tetrahalogenopalladate complexes as anions. Different reaction conditions are needed to obtain these compounds.

The 1:2 complexes containing mutually *trans* N-bonded monodentate ligand molecules were formed according to equation (1) by reaction in neutral methanolic–aqueous

$$[PdX_4]^{2-} + 2L \longrightarrow [PdL_2X_2] + 2X^- \quad (1)$$

solution at room temperature, where X = Cl or Br, L = 2-dqmp. The 1:1 chelate complexes containing bidentate 2-dqmp were obtained with an excess of tetrahalogenopalladate complex [equation (2)] and it is necessary to reflux the reaction mixture

$$[PdX_4]^{2-} + L \longrightarrow [PdLX_2] + 2X^- \quad (2)$$



3 X = Cl
4 X = Br

for a few hours in order to induce phosphoryl oxygen co-ordination. In acidic ethanolic–aqueous medium when an excess of HX was present in the reaction solution the salt complexes were obtained according to equation (3). The ligand

$$[PdX_4]^{2-} + 2L + 2HX \longrightarrow [HL]_2[PdX_4] + 2X^- \quad (3)$$

is protonated forming a quinolinium cation, while the square-planar tetrahalogenopalladate complex acts as its counter ion.

All the novel complexes prepared together with the analytical and molar conductance data are presented in Table 1. Their spectral data (IR and ^{1}H NMR) are summarized in Tables 2 and 3. The complexes are all diamagnetic as expected for the square-planar stereochemistry involving palladium(II) ion. Spectral and structural studies confirm this. Complexes **1**–**4** are yellow to ochre, crystalline and stable in the solid state and in solution over a long period. From the very low molar conductance (below 6 S cm^2 mol^{-1}) it is concluded that these complexes are non-electrolytes in dmf and methanol solutions and are true molecular addition compounds.

The tetrahalogenopalladate complexes **5** and **6** are brown to reddish brown crystalline compounds, stable in the solid state and in non-polar solvents. In polar solvents they are slowly decomposed to the 1:2 dihalogenopalladium complexes and with heating this process is accelerated. The high conductivities measured in methanol of about 200 S cm^2 mol^{-1} confirm their ion-pair structure and the values obtained are comparable with those of 2:1 electrolytes.[23] However, their molar conductance in dmf is considerably lower than expected for 2:1 electrolytes, especially for complex **5**, indicating a considerable association in the less-polar dmf, whereas in methanol these ion-pair complexes are completely dissociated.

All the 2-dqmp complexes are insoluble in water, partly soluble in alcohols, and soluble in a number of non-polar solvents as well as in solvents of co-ordinating ability like dmf and dmso. Generally, the bromide complexes are more soluble than the corresponding chlorides, as are the dihalogeno- compared to the tetrahalogeno-complexes. The structures of the complexes were deduced mainly from their IR and ^{1}H NMR spectra.

Infrared Spectra.—In general, the IR spectra of the complexes are very complicated and a complete assignment of all the absorption bands is not possible, although a careful study can lead to some important structural conclusions. The frequencies associated with the characteristic functional groups for the free 2-dqmp ligand and its palladium complexes are presented in Table 2. In going from the free ligand to the complexes the most significant differences are related to the various modes of the quinoline-ring vibrations. Upon co-ordination of the quinoline nitrogen in both types of dihalogenopalladium complexes, $[PdL_2X_2]$ and $[PdLX_2]$, the bands due to the stretching modes of the quinoline C=C and C=N bonds in the region of 1600–1500 cm^{-1} are slightly shifted to higher frequencies suggesting co-ordination of the ligand in the molecular form.[24] On the other hand the bands attributed to the in-plane and out-of-plane ring deformation vibrations of C=N which occur for the free ligand at 620 and 398 cm^{-1}, respectively, are shifted in the complexes to higher frequencies by *ca.* 20 cm^{-1}. In the spectra of complexes containing the N-bonded monodentate quinoline ligand, **1** and **2**, the characteristic ligand bands attributed to the phosphonic ester groups remain almost at the same position as for the free ligand. In the far-IR region the spectra show one band for Pd–X and one band for Pd–N stretching, as expected for the *trans*-square-planar complexes in D_{2h} stereochemistry.[25,26]

The spectra of $[PdLX_2]$-type complexes **3** and **4** are consistent with the assumption that in these complexes 2-dqmp acts as a bidentate ligand. Besides the previously described changes in the quinoline ring-stretching vibrations, as a result of the co-ordination of quinoline nitrogen, the absorption which corresponds to the P=O stretching is shifted by *ca.* 20 cm^{-1} towards lower frequencies supporting also the co-ordination of the phosphoryl group to the palladium(II) ion.[9,27] On the other hand the position and the multiplicity of the metal–halogen stretching bands are in agreement with a *cis* orientation of the terminal halogens. Therefore, with regard to the metal–anion stretching modes, a *cis*-square-planar C_{2v} stereochemistry can be proposed for these palladium complexes.

The ν(Pd–N) vibrations appear around 270 cm^{-1} in the same region as for the $[Pd(2\text{-dqmp})_2X_2]$ complexes, but as here they are more intense and broad it may be presumed that there is overlap of the Pd–N and Pd–O stretching vibrations.

As expected, in the spectra of the tetrahalogenopalladate complexes there is no evidence for palladium co-ordination to the 2-dqmp ligand. There is a small shift to lower frequencies of the bands ascribed to the stretching vibrations of the quinoline ring and no change in the deformation vibrations of the C–N group. Instead, the absorption attributed to the protonated quinoline nitrogen appears as a strong band at 1660 cm^{-1} and two broad bands of medium intensity around 2580 and 2080 cm^{-1}. The presence of the lattice water is indicated by the rather intense bands in the range 3400–3200 cm^{-1}. The phosphoryl stretching vibration is shifted to lower frequencies by *ca.* 20 cm^{-1} due to the water presumably hydrogen bonded to the phosphoryl oxygen. In the far-IR region the spectra show a band at a position expected for compounds containing square-planar $[PdX_4]^{2-}$ anions with D_{4h} stereochemistry.[28,29]

Proton NMR Spectra.—Chemical shifts and coupling constants for the free ligand and its complexes are given in Table 3. Fig. 1 shows the ^{1}H NMR spectra of 2-dqmp and its dibromopalladium complexes **2** and **4**. The spectrum of free 2-dqmp shows that the two ester groups are equivalent.[13] Only one triplet is found for the methyl protons and two closely spaced quartets for the methylene protons of the $POCH_2CH_3$ group. Protons of the PCH_2 group appear as a doublet and the aromatic region has an unresolved multiplet. In the spectra of the complexes there is a downfield shift for all kinds of protons relative to the uncomplexed ligand. The most pronounced change was observed for the protons adjacent to the ligation site, which may be related to a decrease in the electron density in the aromatic ring following the electron-withdrawing effect of complexation,[6] and to the magnetic anisotropy of the metal.[30–33] In both types of dihalogenopalladium complexes, **1**–**4**, there was a downfield shift of about 2.5 ppm for aromatic proton H(8) and a shift of 1.6–2.0 ppm for the PCH_2 protons. On the basis of X-ray data for the 1:2 complexes **1** and **2** it is evident that these protons closely approach the d^8 square-planar palladium atom above the co-ordination plane. The resonances of the PCH_2 protons in these complexes appear as two doublets, as could be expected from two rotational isomers with different magnetic environments. Since the high-field signal is more intense than that observed at lower field, it could be concluded that these two

Table 1 Analytical[a] and physical data for the palladium halide complexes

Complex	Colour	M.p.[b]/°C	Analysis (%) Pd	C	H	N	P	Halogen	Λ_M[c]/S cm^2 mol^{-1}
1 $[Pd(2\text{-}dqmp)_2Cl_2]$	Pale yellow	200–207	14.8 (14.5)	45.6 (45.7)	4.7 (4.9)	3.9 (3.8)	8.2 (8.4)	9.7 (9.6)	1.7, *d*
2 $[Pd(2\text{-}dqmp)_2Br_2]$	Ochre	195–202	12.9 (12.9)	40.5 (40.8)	4.2 (4.4)	3.2 (3.4)	7.2 (7.5)	19.4 (19.4)	2.1, 5.1
3 $[Pd(2\text{-}dqmp)Cl_2]\cdot 2H_2O$	Ochre	111–113	21.1 (21.6)	34.4 (34.1)	4.7 (4.6)	2.7 (2.8)	6.4 (6.3)	14.1 (14.4)	1.6, *d*
4 $[Pd(2\text{-}dqmp)Br_2]$	Ochre-brown	122–124	19.2 (19.5)	31.1 (30.8)	3.5 (3.3)	2.4 (2.6)	5.2 (5.7)	29.0 (29.3)	1.8, 4.2
5 $[2\text{-}Hdqmp]_2[PdCl_4]\cdot 2H_2O$	Hazel	89–90	12.5 (12.6)	40.2 (39.8)	4.9 (5.0)	3.2 (3.3)	7.4 (7.3)	16.5 (16.8)	70.3, 217.0
6 $[2\text{-}Hdqmp]_2[PdBr_4]\cdot H_2O$	Reddish brown	125–127	10.7 (10.6)	33.6 (33.5)	3.8 (4.0)	2.6 (2.8)	6.1 (6.2)	32.1 (31.8)	91.9, 192.1

[a] Calculated values are given in parentheses. [b] With decomposition. [c] At room temperature in *ca.* 1×10^{-3} mol dm^{-3} dimethylformamide and methanol solutions. [d] Too insoluble for measurements.

Table 2 Selected infrared spectroscopic data (cm^{-1})[a]

Compound	ν(OH)[b]	ν(NH$^+$)	ν(C=C), ν(C=N)	ν(P=O)	δ(PO–C)	ν(P–OC)	δ(C=N)[c]	δ(C=N)[d]	ν(Pd–X)[e]	ν(Pd–N)
2-dqmp	—	—	1621w–m 1601s 1570s 1564w–m	1270s (sh) 1258vs 1240s (sh)	1160w 1125w	1055vs 1030vs	620w	398w	—	—
1	—	—	1621m 1607m–s 1571w–m 1514s	1278s 1260vs 1241s	1164w 1155w	1051vs 1022vs	642w	420w–m	352m	272w–m
2	—	—	1621w–m 1604m–s 1570w–m 1512s	1265s (sh) 1252s	1164w 1150 (sh)	1050vs 1022vs	641w	417w	321w (br)	270w–m
3	3460m (br)	—	1621m 1607s 1570w–m 1514vs	1241s (br) 1221s (sh)	1164m 1148w	1050vs 1022vs	641w 630 (sh)	417w	350m 320m	276m (br)[f]
4	—	—	1620m 1605m–s 1570w–m 1514vs	1242s (br) 1221s (sh)	1166m 1148w	1050vs 1023vs	641w 630 (sh)	416w	310w 267w–m (br)	267m (br)[f]
5	3430s 3318m 3220m	2570m (br) 2090m (br) 1660s	1628w 1602m 1551w 1500w–m	1261vs 1220s	1162w 1135w	1050vs 1020vs	620w	397w	325m–s	—
6	3468m 3300m 3201w	2580m (br) 2085w–m(br) 1654s	1603s 1551w–m 1500m	1256m 1242s 1218vs	1155m 1135w	1050vs 1020vs	620w	397w	252m	—

[a] As KBr pellets. Abbreviations: v = very, s = strong, m = medium, w = weak, br = broad and sh = shoulder. [b] From H_2O. [c] In-plane quinoline ring deformation. [d] Out-of-plane ring deformation. [e] X = Cl or Br. [f] Overlapped with ν(Pd–O) absorption.

isomers are not equally abundant. Protons of the ethylene ester groups and of the other aromatic protons which are further from the ligation site exhibit a downfield shift of only 0.20–0.25 ppm compared to the free ligand. Our measurements are in good agreement with the results reported for some palladium complexes of various 2-substituted pyridine or quinoline ligands.[31]

The spectra of the 1:1 dihalogenopalladium complexes **3** and **4** are more complicated than those obtained for the 1:2 complexes and the extent of the downfield shift for some protons is also slightly increased. The complexity may arise from the molecular dissymmetry caused by the distorted co-ordination around the metal on formation of a six-membered chelate ring. The resonances of the methyl protons are doubled indicating a magnetically different environment for the protons of the two ethylene groups: two triplets separated by 2.7 Hz are found for the methyl protons, and an unresolved multiplet for the methylene protons. The PCH_2 region has a multiplet at about δ 5.3, and the resonances of the aromatic protons appear as multiplets with similar downfield shifts as obtained for the 1:2 complexes of 2-dqmp.

Since the tetrachloropalladate complex **5** is sparingly soluble or is unstable in some organic solvents, a satisfactory ^1H NMR spectrum in $[^2H_7]$dmf could be obtained only for the corresponding tetrabromo complex **6**. The extent of the downfield shifts for most protons decreases with respect to the dihalogenopalladium complexes due to the lack of palladium co-ordination to the quinoline ligand.

X-Ray Studies of $[Pd(2\text{-}dqmp)_2Cl_2]$ **1** *and* $[Pd(2\text{-}dqmp)_2Br_2]$ **2**.—The atomic coordinates for complexes **1** and **2** are given in Tables 4 and 5, selected bond distances, angles and torsion angles in Table 6. Perspective views of these two molecules with the atom numbering scheme are shown in Figs. 2 and 3.

The complexes have a *trans* configuration. The co-ordination

Table 3 Proton NMR (δ, *J*/Hz) data[a]

Compound	
2-dqmp	1.26 [t, 6 H, *J*(HH) 7.1, CH_3], 3.60 [d, 2 H, *J*(PH) 22.1, PCH_2], 4.06, 4.19 [dq, 4 H, *J*(HH) 7.0, *J*(PH) 7.9, $POCH_2$], 7.3–8.1 (m, 6 H, aryl H)
1	1.38 [t, 12 H, *J*(HH) 7.1, CH_3], 4.30 (m, 8 H, $POCH_2$), 5.21, 5.35 [dd, 4 H, *J*(PH) 21.8, PCH_2], 7.57–8.32 (m, 10 H, aryl H), 10.57, 10.65 [dd, 2 H, aryl H(8)]
2	1.38 [t, 12 H, *J*(HH) 7.0, CH_3], 4.30 (m, 8 H, $POCH_2$), 5.16, 5.33 [dd, 4 H, *J*(PH) 21.5, PCH_2], 7.51–8.35 (m, 10 H, aryl H), 10.44, 10.52 [dd, 2 H, aryl H(8)]
3	1.39, 1.42 [dt, 6 H, *J*(HH) 7.3, CH_3], 3.87–4.55 (m, 4 H, $POCH_2$), 5.01–6.13 (m, 2 H, PCH_2), 7.56–8.36 (m, 5 H, aryl H), 10.55 [m, 1 H, aryl H(8)]
4	1.36, 1.39 [dt, 6 H, *J*(HH) 7.3, CH_3], 3.76–4.51 (m, 4 H, $POCH_2$), 4.67–5.74 (m, 2 H, PCH_2), 7.53–8.33 (m, 5 H, aryl H), 10.59 [m, 1 H, aryl H(8)]
6[b]	1.30 [t, 12 H, *J*(HH) 7.0, CH_3], 4.18 (m, 8 H, $POCH_2$), 5.15 (br s, 4 H, NH^+, OH),[c] 5.18 [d, 4 H, *J*(PH) 21.9, PCH_2], 7.62–8.63 (m, 10 H, aryl H), 9.30 [d, 2 H, aryl H(8)]

[a] Spectra recorded in $CDCl_3$ unless otherwise specified: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, dq = doublet of quartets, m = multiplet and br = broad. [b] Recorded in heptadeuteriated dmf. [c] D_2O-exchangeable protons.

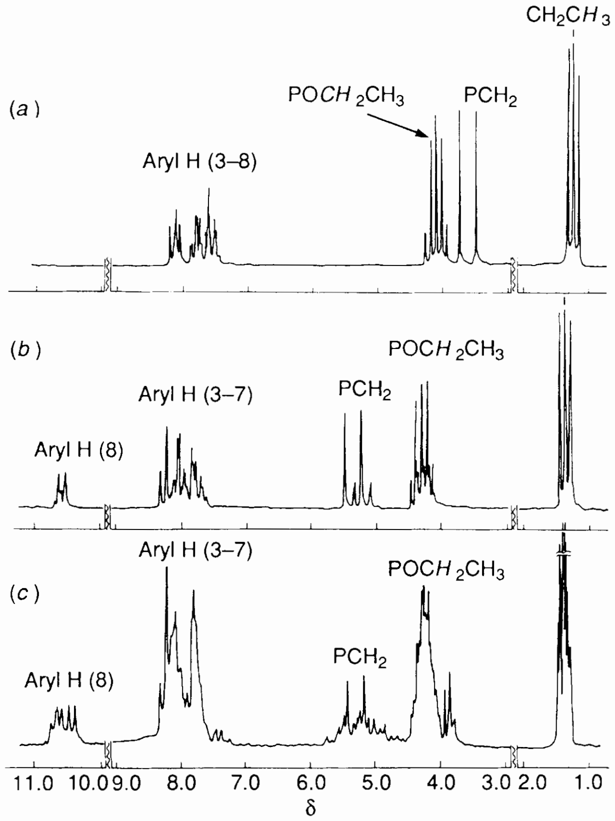


Fig. 1 Proton NMR spectra of 2-dqmp (*a*) and its dibromopalladium complexes **2** (*b*) and **4** (*c*)

about palladium, which is situated on the crystallographic centre of symmetry, is essentially square planar as expected. The 2-dqmp molecule is bonded to palladium through its nitrogen atom. The Pd–N bond distances [2.054(4) for **1** and 2.064(7) Å for **2**] are similar to the values obtained in dichloro[2,2-bis(pyrazolyl)propane]palladium(II) of 2.030(3) Å,[34] in *trans*-dichlorobis(cyclohexylamine)palladium(II) of 2.058(2) Å,[35] and in dichlorobis(3,5-dimethylpyrazole)palladium(II) of 2.008(4) Å.[36] We can also compare the Pd–Cl bond length of 2.303(1) Å with those cited in the literature: 2.297(1),[34] 2.304(1),[35] 2.293(2) and 2.299(2) Å.[36] The angle N–Pd–Cl is 89.1(1)°.

Table 4 Atomic fractional coordinates (× 10^4) for complex **1**

Atom	*X/a*	*Y/b*	*Z/c*
Pd	0	0	0
Cl	−2208(1)	−1420(1)	−764(1)
P	−2125(1)	3074(1)	163(1)
O(1)	−3357(5)	1651(4)	−188(5)
O(2)	−2716(5)	3511(5)	1500(5)
O(3)	−1606(4)	4235(4)	−1170(5)
N	−840(3)	−63(4)	2031(4)
C(2)	−1135(4)	1086(4)	2302(4)
C(3)	−1734(5)	1014(5)	3697(5)
C(4)	−1998(4)	−235(5)	4805(5)
C(5)	−1879(5)	−2749(5)	5684(5)
C(6)	−1513(6)	−3891(6)	5412(6)
C(7)	−934(7)	−3761(6)	4004(6)
C(8)	−690(6)	−2492(5)	2881(5)
C(9)	−1076(4)	−1317(4)	3142(4)
C(10)	−1665(4)	−1445(5)	4558(4)
C(11)	−751(5)	2490(5)	1117(5)
C(12)	−3738(9)	1399(9)	−1751(10)
C(13)	−4838(11)	2023(13)	−2411(14)
C(14)	−3854(8)	4078(9)	1231(9)
C(15)	−4508(8)	3940(14)	2658(11)

Table 5 Atomic fractional coordinates (× 10^4) for complex **2**

Atom	*X/a*	*Y/b*	*Z/c*
Pd	0	0	0
Br	1789(1)	−1239(1)	1954(1)
P	3435(4)	3375(3)	−2368(4)
O(1)	4725(14)	3193(17)	−918(17)
O(2)	3455(10)	2368(9)	−3463(11)
O(3)	3472(12)	4959(9)	−3134(13)
N	813(7)	2009(7)	509(8)
C(2)	1624(12)	2961(10)	−358(12)
C(3)	2161(18)	4374(12)	−72(18)
C(4)	1788(21)	4780(14)	1076(18)
C(5)	546(19)	4158(13)	3238(16)
C(6)	−326(15)	3142(15)	4065(15)
C(7)	−775(14)	1775(14)	3800(13)
C(8)	−404(12)	1392(12)	2620(12)
C(9)	425(10)	2383(9)	1697(9)
C(10)	935(15)	3748(12)	2011(15)
C(11)	1958(16)	2482(15)	−1677(17)
C(12)	4706(56)	1848(31)	−147(81)
C(13)	6066(31)	1907(26)	1277(32)
C(14)	4342(28)	2810(28)	−4558(32)
C(15)	4172(51)	1764(39)	−5420(38)

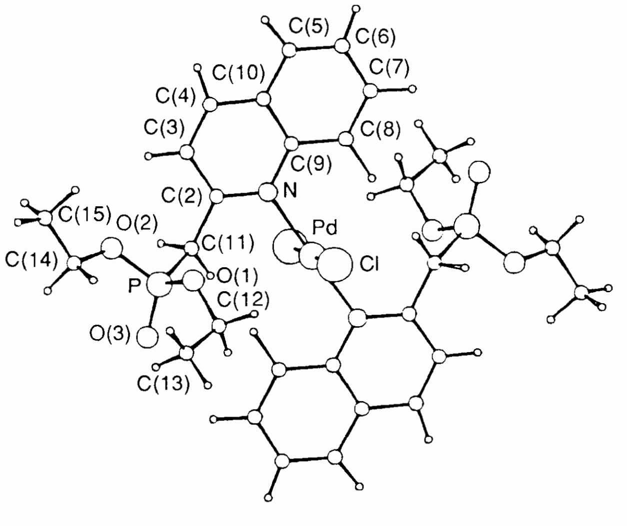


Fig. 2 Perspective drawing of complex **1** with the atom numbering scheme

Table 6 Selected bond distances (Å), angles (°) and torsion angles (°) for complexes **1** and **2**

	1	**2**
Pd–X	2.303(1)	2.435(1)
Pd–N	2.054(4)	2.064(7)
P–O(1)	1.564(4)	1.632(13)
P–O(2)	1.581(6)	1.570(12)
P–O(3)	1.454(4)	1.433(8)
P–C(11)	1.794(5)	1.778(17)
O(1)–C(12)	1.465(10)	1.240(34)
O(2)–C(14)	1.446(11)	1.436(33)
N–C(2)	1.339(6)	1.321(13)
N–C(9)	1.374(5)	1.390(13)
X–Pd–N	89.1(1)	89.7(2)
O(1)–P–O(2)	103.6(2)	110.0(6)
O(1)–P–O(3)	114.2(2)	105.5(7)
O(1)–P–C(11)	107.7(2)	111.6(7)
O(2)–P–O(3)	116.7(2)	115.5(5)
O(2)–P–C(11)	101.8(2)	98.6(6)
O(3)–P–C(11)	111.8(2)	115.8(7)
P–O(1)–C(12)	121.9(4)	108.6(21)
P–O(2)–C(14)	121.0(4)	120.6(12)
Pd–N–C(2)	121.9(2)	119.9(6)
Pd–N–C(9)	118.3(2)	119.1(5)
P–C(11)–C(2)	119.2(3)	117.6(10)
X–Pd–N–C(2)	−101.0(3)	94.0(7)
X–Pd–N–C(9)	80.2(3)	−90.3(6)
O(2)–P–O(1)–C(12)	140.0(5)	−59.0(3)
O(3)–P–O(1)–C(12)	12.1(6)	176.0(3)
C(11)–P–O(1)–C(12)	−112.6(6)	50.0(3)
O(1)–P–O(2)–C(14)	−69.2(6)	−75.0(2)
O(3)–P–O(2)–C(14)	57.1(6)	44.0(2)
C(11)–P–O(2)–C(14)	179.1(5)	168.0(1)
O(1)–P–C(11)–C(2)	−40.6(4)	56.0(1)
O(2)–P–C(11)–C(2)	68.0(4)	172.0(1)
O(3)–P–C(11)–C(2)	−166.8(4)	−64.0(1)
P–O(1)–C(12)–C(13)	−91.0(8)	−179.0(2)
P–O(2)–C(14)–C(15)	161.5(6)	−179.0(2)
N–C(2)–C(11)–P	115.3(4)	−158.2(9)
C(3)–C(2)–C(11)–P	−67.5(5)	22.0(2)

X refers to Cl in complex **1** and Br in complex **2**.

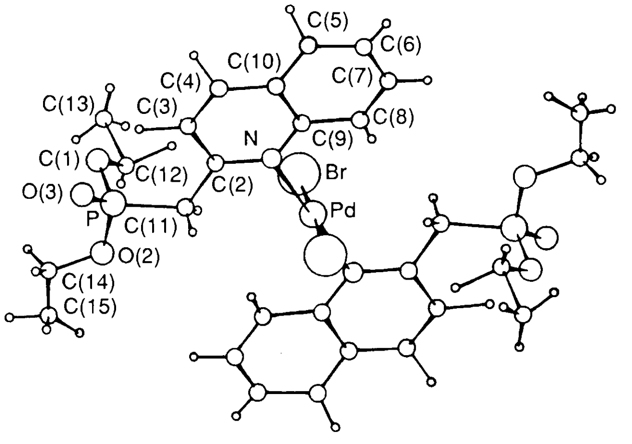


Fig. 3 Perspective drawing of complex **2** with the atom numbering scheme

The C–C bond lengths in the quinoline ring average 1.400(7) and 1.39(2) Å in **1** and **2**, respectively. The C–N distances are slightly different: N–C(2) is 1.339(6) in **1** and 1.32(1) Å in **2**, while N–C(9) are 1.374(5) and 1.39(1) Å. The quinoline moiety in both complexes is planar with deviations from the plane of ⩽0.024 Å and is approximately perpendicular to the plane of the Pd, N and Cl atoms. From Figs. 2 and 3 as well as from the torsion angles given in Table 6, the orientation of the two diethyl ester groups around the phosphorus atom is remarkably different for these two complexes.

Table 7 *In vitro* cytostatic activity of the complexes

	ID_{50}*/μg cm^{-3}	
Complex	KB cells	L1210 cells
1	47.74 (6.49×10^{-5})	57.20 (7.77×10^{-5})
2	10.51 (1.27×10^{-5})	2.76 (3.30×10^{-6})
3	25.23 (5.12×10^{-5})	5.68 (1.15×10^{-5})
4	23.07 (4.22×10^{-5})	7.08 (1.30×10^{-5})
5	167.40 (1.99×10^{-4})	44.29 (5.25×10^{-5})
6	35.15 (3.57×10^{-5})	3.00 (3.00×10^{-6})

* Molar concentration of the complex is given in parentheses.

Biological Activity.—In Table 7 are listed the results obtained by screening the new complexes for antitumour activity. The inhibitory activities are expressed as the concentrations of the complex required to inhibit growth by 50% (ID_{50}). The smaller ID_{50} values signify higher cytostatic activity. All the examined complexes exhibit a certain inhibitorial effect. In general the L1210 cell line appears to be more responsive than the KB cell line. Only the dibromopalladium complex **2** displays a considerable anti-tumour effect in both test systems. While for the chelate 1:1 dihalogenopalladium complexes **3** and **4** there are no significant differences in activity between the chloro and bromo derivative, both the 1:2 dibromo- and tetrabromo-palladium complexes, **2** and **6**, are more effective than their chloro analogues against both cell lines. This may partly be due to the higher solubility of the bromide complexes. In addition, the low activity of the tetrachloropalladate complex **5** is most probably also a reflection of the lower dissociation rate for this ion-pair complex in the examined solvent system. All the complexes exhibit smaller activity than does cisplatin, *cis*-$[Pt(NH_3)_2Cl_2]$, for which the molar ID_{50} values against KB and L1210 cells are 0.37×10^{-6} and 0.65×10^{-6} mol dm^{-3}, respectively. These values were determined under the same experimental conditions as those used for the examined palladium complexes which are particularly interesting in view of their non-toxicity.

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