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Cyclometallated derivatives of palladium(II) with 1,4-benzodiazepin-2-ones. Crystal structure of (L-H)Pd(PPh_3)Cl · $CHCl_3$ (L = Prazepam: 7-chloro-1-cyclopropylmethyl-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one). Synthesis of isoindolo[2,1-d][1,4]benzodiazepine derivatives by reaction of $[(L\text{-}H)PdCl]_2$ species with carbon monoxide

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Abstract

The dimeric cyclometallated derivatives of palladium(II) $[(L\text{-}H)PdCl]_2$, **3** (L = **1**, Diazepam: 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one) and **4** (L = **2**, Prazepam: 7-chloro-1-cyclopropylmethyl-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one) react with triphenylphosphine to give the complexes (L-H)Pd(PPh_3)Cl, **5** (L = Diazepam) and **6** (L = Prazepam). The crystal structure of **6** was determined by X-ray crystallography. The palladium atom is in a square planar arrangement. The deprotonated ligand is bound to the metal through the 4-nitrogen and the *ortho*-carbon atom of the 5-phenyl substituent. The phosphorous and the chlorine atoms are *trans* to the nitrogen and the carbon atoms, respectively: Pd–N = 2.085(2), Pd–P = 2.263(1), Pd–Cl = 2.377(1), Pd–C = 2.009(3) Å.

The reaction of the dimeric derivatives $[(L\text{-}H)PdCl]_2$ with carbon monoxide was investigated. Under mild conditions (1 atm of CO, room temperature) the unstable (L-H)Pd(CO)Cl derivatives, **7** (L = Diazepam) and **8** (L = Prazepam) are formed, but at high pressure and temperature (60–100 atm of CO, 45–50 °C), extrusion of palladium occurs and tetracyclic derivatives having an isoindolo ring condensed on the 1,4-benzodiazepin-2-one system, **9–12**, are obtained.

Introduction

In recent years, we have described the reactions of some 1,4-benzodiazepin-2-ones having 5-phenyl substituents, (L), such as Diazepam (**D** = 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one) and Prazepam (**P** = 7-chloro-1-cyclopropylmethyl-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one) with several

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metal ions [1–3]. Adducts of gold(III) [1], palladium(II) [2] and gold(I) [3] have been synthesized and shown to contain the ligands bound via the 4-nitrogen atom. In addition, with 1-unsubstituted benzodiazepines, e.g. Nitrazepam (1,3-dihydro-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one) and Lorazepam (7-chloro-5-(*o*-chlorophenyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepin-2-one), neutral gold(I) derivatives, (**L**-H)Au(PPh_3), were obtained in which the hydrogen at the N(1) atom is replaced by the isolobal Au(PPh_3) unit [3].

During our investigations on the reactivity of Diazepam and Prazepam with palladium(II) derivatives [2], we observed that, besides the adducts, metallated derivatives, [(**L**-H)$PdCl]_2$, are formed. Spectroscopic evidence suggested that the deprotonated ligands are bonded to the metal through the 4-nitrogen and the *ortho*-carbon atom of the 5-phenyl substituent. The structure of this compound, which involves both C- and N-intramolecular coordination, has now been confirmed by an X-ray diffraction study of the complex [(**L**-H)Pd(PPh_3)Cl], **6**, (**L** = Prazepam), obtained by reaction of the dimeric derivative [(**L**-H)$PdCl]_2$, **4**, with triphenylphosphine.

In the chemistry of 1,4-benzodiazepin-2-ones with transition metal ions, these are the first species containing a metal–carbon bond. This prompted us to investigate some aspects of their reactivity, having in mind the possibility that the metallated species might be potential intermediates for achieving the synthesis of 1,4-benzodiazepin-2-ones with functional groups on the *ortho*-carbon atom of the 5-phenyl substituent. It is noteworthy that the presence of certain substituents in this position, is known to improve the activity of these drugs [4].

Here we describe the reactions of some of these organo-palladium species with carbon monoxide under a variety of conditions.

Some of this work has been previously communicated [5].

Results and discussion

The cyclopalladated derivatives [(**L**-H)$PdCl]_2$, **3** (**L** = **D** = Diazepam) and **4** (**L** = **P** = Prazepam) were prepared, as described previously, by reaction of the ligands with $Na_2[PdCl_4]$ (molar ratio 1 : 1) in ethanol [2]. To ascertain the nature of these almost insoluble species, the reactions with triphenylphosphine and thallium(I)acetyl acetonate were carried out to give the monomeric (**L**-H)Pd(PPh_3)Cl and (**L**-H)Pd(acac) complexes, respectively. The structure of the complex **6** (**P**-H)Pd(PPh_3)Cl (**P** = Prazepam) has now been determined by X-ray crystallography. General crystallographic information is presented in Table 1. Positional parameters and bond distances and angles are given in Table 2 and 3, respectively.

The molecular structure is shown in Fig. 1. Crystals of complex **6** contain discrete (**P**-H)Pd(PPh_3)Cl molecules and disordered $CHCl_3$ molecules in the molar ratio 1 : 1, separated by normal Van der Waals contacts. The refined model for the clathrated solvent consists of chloroform molecules sharing a common chlorine atom, with occupancies for the two disordered portions of the molecule of about 0.6 and 0.4, respectively. As expected, the palladium atom is in a nearly square planar environment, with the following small displacements ($Å \times 10^{-3}$) from the least-squares coordination plane: Pd 7(1), N(4) −27(5), C(13) 24(6), P −22(2) and Cl(1) 18(2). The Prazepam molecule acts as an anionic bidentate ligand, being coordinated to the metal center through the N(4) atom and the *ortho*-carbon atom C(13).

Table 1

Crystallographic data

Formula	$C_{37}H_{31}Cl_2N_2OPPd \cdot CHCl_3$
F.w. (amu)	847.33
Crystal system	triclinic
Space group	$P\bar{1}$
a (Å)	13.217(7)
b (Å)	13.622(8)
c (Å)	12.513(6)
α (°)	108.41(1)
β (°)	113.56(1)
γ (°)	101.70(1)
U (Å^3)	1814(3)
Z	2
D_{calc} (g cm^{-3})	1.552
μ(Mo-K_α)(cm^{-1})	9.53
Min. transmission factor	0.83
Scan mode	ω
ω-scan width (°)	$1.2+0.35 \tan\theta$
θ-range (°)	3–23
Octants of reciprocal space explored	$\pm h, \pm k, +l$
Measured reflections	4163
Unique observed reflections with $I > 3\sigma(I)$	3412
Final R and R_w indices [a]	0.042, 0.055
No. of variables	459
ESD [b]	2.444

[a] $R = [\Sigma(F_o - k\,|\,F_c\,|)/\Sigma F_o]$, $R_w = [\Sigma w(F_o - k\,|\,F_c\,|)^2/\Sigma w F_o^2]^{1/2}$. [b] ESD $= [\Sigma w(F_o - k\,|\,F_c\,|)^2/(N_{obs} - N_{var})]^{1/2}$ $w = 1/(\sigma(F_o))^2$, $\sigma(F_o) = [\sigma^2(I) + (0.03I)^2]^{1/2}/2F_o$Lp.

The phosphine ligand is *trans* to the benzodiazepine nitrogen N(4) and the chlorine opposite to the metallated phenyl. A consequence of such an arrangement of ligands about the palladium atom is the long Pd–Cl bond (2.377(1) Å), in agreement with the large *trans*-influence of the carbon atom. For a comparison, the values found for Pd–Cl distances are in the range of ca. 2.24–2.45 Å [6], the upper values being observed for a chlorine *trans* to a σ-bonded carbon atom. The Pd–P bond length (2.263(1) Å) is comparable to that observed in $PdCl[C(O)C_9H_6N](PPh_3) \cdot PPh_3$ (2.267(2) Å) [7], which has a similar arrangement of ligands around the Pd atom, and the same is true for the Pd–N(4) bond [2.085(2) Å vs. 2.103(5) Å]. The five-membered palladacycle is essentially planar, with only minor distortions towards an envelope conformation (see Table 3, torsion angles). The seven-membered cycle of the Prazepam ligand is in the usual boat conformation and displays bond lengths and angles very close to those in *trans*-$PdCl_2$(Prazepam)$_2$ [2] and in the free ligand [8].

Besides triphenylphosphine, even carbon monoxide can split the chloride bridge in the dimeric species. Bubbling carbon monoxide into a suspension of complexes **3** or **4** in chloroform gave yellow solutions showing a strong absorption at 2120 cm^{-1} in the IR spectrum, which suggests a terminal palladium carbonyl species. Unfortunately, all the attempts to isolate the (L-H)Pd(CO)Cl derivatives **7** (L = Diazepam)

Table 2

Fractional atomic coordinates for non-hydrogen atoms with their e.s.d.'s in parentheses

Atom	x	y	z
Pd	0.03694(3)	0.31060(2)	0.19951(5)
Cl(1)	0.1177(1)	0.18619(9)	0.2674(2)
Cl(2)	0.3666(1)	0.9345(1)	0.6953(2)
Cl(3)	−0.0042(3)	0.6357(3)	0.4961(4)
Cl(4)	0.0172(2)	0.8306(2)	0.4505(3)
Cl(5)	−0.2052(3)	−0.3621(4)	0.3080(5)
Cl(6)	0.2059(6)	0.1817(7)	0.5824(8)
Cl(7)	0.1329(9)	0.3589(5)	0.589(1)
P	−0.1496(1)	0.17801(9)	0.0682(2)
O(1)	0.4236(3)	0.3908(3)	0.2912(5)
N(1)	0.4375(3)	0.5708(3)	0.3615(5)
N(4)	0.2013(3)	0.4442(3)	0.3193(5)
C(2)	0.3971(4)	0.4622(4)	0.3468(6)
C(3)	0.3157(4)	0.4398(4)	0.4001(6)
C(5)	0.1984(4)	0.5399(3)	0.3262(6)
C(6)	0.2899(4)	0.7304(4)	0.5025(6)
C(7)	0.3871(4)	0.8275(4)	0.5974(6)
C(8)	0.4984(4)	0.8387(4)	0.6166(7)
C(9)	0.5145(4)	0.7550(4)	0.5374(7)
C(10)	0.4188(4)	0.6565(4)	0.4411(6)
C(11)	0.3035(4)	0.6449(3)	0.4228(6)
C(12)	0.0857(4)	0.5373(3)	0.2357(6)
C(13)	−0.0092(4)	0.4304(3)	0.1558(6)
C(14)	−0.1124(4)	0.4251(4)	0.0613(6)
C(15)	−0.1236(4)	0.5183(4)	0.0427(6)
C(16)	−0.0324(4)	0.6207(4)	0.1200(6)
C(17)	0.0729(4)	0.6305(4)	0.2161(6)
C(18)	0.5168(5)	0.5978(5)	0.3093(7)
C(19)	0.4733(7)	0.6575(9)	0.229(1)
C(20)	0.527(1)	0.658(1)	0.139(1)
C(21)	0.567(2)	0.772(2)	0.282(2)
C(21A)	0.424(2)	0.562(2)	0.093(2)
C(111)	−0.1722(4)	0.0441(3)	0.0774(5)
C(112)	−0.1971(4)	−0.0543(4)	−0.0220(6)
C(113)	−0.2143(4)	−0.1527(4)	−0.0074(7)
C(114)	−0.2068(4)	−0.1518(4)	0.1042(7)
C(115)	−0.1819(5)	−0.0534(4)	0.2048(6)
C(116)	−0.1654(4)	0.0429(4)	0.1879(6)
C(121)	−0.1941(4)	0.1389(3)	−0.1006(6)
C(122)	−0.1192(4)	0.1037(4)	−0.1443(6)
C(123)	−0.1490(5)	0.0672(4)	−0.2721(6)
C(124)	−0.2523(6)	0.0674(4)	−0.3598(7)
C(125)	−0.3260(5)	0.1055(4)	−0.3182(6)
C(126)	−0.2981(4)	0.1403(4)	−0.1907(6)
C(131)	−0.2661(4)	0.2116(3)	0.0196(6)
C(132)	−0.3837(4)	0.1347(4)	0.0196(6)
C(133)	−0.4716(4)	0.1593(4)	0.0460(6)
C(134)	−0.4426(4)	0.2575(4)	0.1449(7)
C(135)	−0.3270(5)	0.3325(4)	0.2212(7)
C(136)	−0.2385(4)	0.3114(4)	0.1947(6)
C(200)	0.0769(9)	0.2721(9)	0.538(1)
C(201)	0.086(2)	0.209(1)	0.518(2)

Table 3

Selected bond lengths (Å) and angles (deg.) with e.s.d.'s in parentheses

Bond lengths			
Pd–N(4)	2.085(2)	Pd–P	2.263(1)
Pd–Cl(1)	2.377(1)	Pd–C(13)	2.009(3)
N(1)–C(10)	1.413(5)	N(1)–C(2)	1.391(5)
C(2)–C(3)	1.504(7)	C(3)–N(4)	1.471(4)
N(4)–C(5)	1.288(4)	C(5)–C(11)	1.482(4)
C(11)–C(10)	1.414(5)	C(11)–C(6)	1.371(5)
C(6)–C(7)	1.381(5)	C(7)–C(8)	1.359(6)
C(8)–C(9)	1.370(6)	C(9)–C(10)	1.387(5)
C(7)–Cl(2)	1.732(4)	C(5)–C(12)	1.451(5)
C(12)–C(13)	1.425(4)	C(13)–C(14)	1.372(5)
C(14)–C(15)	1.387(5)	C(15)–C(16)	1.367(5)
C(16)–C(17)	1.373(5)	C(17)–C(12)	1.397(5)
C(2)–O(1)	1.209(5)	N(1)–C(18)	1.485(6)
C(18)–C(19)	1.50(1)	C(19)–C(20)	1.55(1)
C(19)–C(21)	1.52(2)	C(20)–C(21)	1.75(3)
C(19)–C(21A)	1.54(2)	C(20)–C(21A)	1.44(2)
P–C(111)	1.836(4)	P–C(121)	1.806(5)
P–C(131)	1.812(4)		
Bond angles			
N(4)–Pd–P	174.44(7)	Cl(1)–Pd–C(13)	172.49(9)
P–Pd–Cl(1)	92.98(3)	Cl(1)–Pd–N(4)	92.34(8)
N(4)–Pd–C(13)	80.2(1)	P–Pd–C(13)	94.51(9)
Pd–C(13)–C(12)	112.2(2)	C(13)–C(12)–C(5)	116.0(3)
C(5)–N(4)–Pd	115.1(2)	C(2)–N(1)–C(10)	120.5(4)
N(1)–C(10)–C(11)	121.2(3)	C(10)–C(11)–C(5)	121.8(3)
C(11)–C(5)–N(4)	121.3(3)	C(5)–N(4)–C(3)	118.4(3)
N(4)–C(3)–C(2)	108.7(4)	C(3)–C(2)–N(1)	115.7(4)
C(3)–C(2)–O(1)	123.0(4)	N(1)–C(2)–O(1)	121.3(5)
N(4)–C(5)–C(12)	115.6(3)	C(11)–C(5)–C(12)	123.0(3)
C(6)–C(11)–C(10)	119.1(3)	C(11)–C(6)–C(7)	120.3(3)
C(6)–C(7)–C(8)	120.9(4)	C(7)–C(8)–C(9)	120.0(3)
C(8)–C(9)–C(10)	120.6(4)	C(9)–C(10)–C(11)	119.1(4)
C(6)–C(7)–Cl(2)	119.2(3)	C(8)–C(7)–Cl(2)	119.9(3)
C(2)–N(1)–C(18)	118.2(4)	N(1)–C(18)–C(19)	110.6(5)
C(5)–C(11)–C(6)	119.0(3)	C(10)–N(1)–C(18)	120.5(3)
Selected torsion angles			
C(13)–Pd–N(4)–C(5)	8.5	N(4)–Pd–C(13)–C(12)	−6.2
C(10)–N(1)–C(2)–O(1)	−171.7	C(10)–N(1)–C(2)–C(3)	10.4
C(2)–N(1)–C(10)–C(11)	−53.8	Pd–N(4)–C(5)–C(12)	−8.6
C(3)–N(4)–C(5)–C(11)	−6.7	N(1)–C(2)–C(3)–N(4)	69.1
N(4)–C(5)–C(12)–C(13)	3.2	N(4)–C(5)–C(11)–C(10)	48.2
N(1)–C(10)–C(11)–C(5)	4.4	C(5)–C(12)–C(13)–Pd	3.9
C(2)–N(1)–C(18)–C(19)	130.9	C(10)–N(1)–C(18)–C(19)	−58.7
N(1)–C(18)–C(19)–C(20)	−163.1	N(1)–C(18)–C(19)–C(21)	120.9
N(1)–C(18)–C(19)–C(21A)	−107.2		

and **8** (L = Prazepam), were unsuccessful, since only the starting products **3** and **4** could be recovered upon evaporation of the solvent. The same result was obtained from reactions at room temperature under high CO pressure (75 atm).

When the reaction was carried out in 1 : 1 chloroform–ethanol solution under

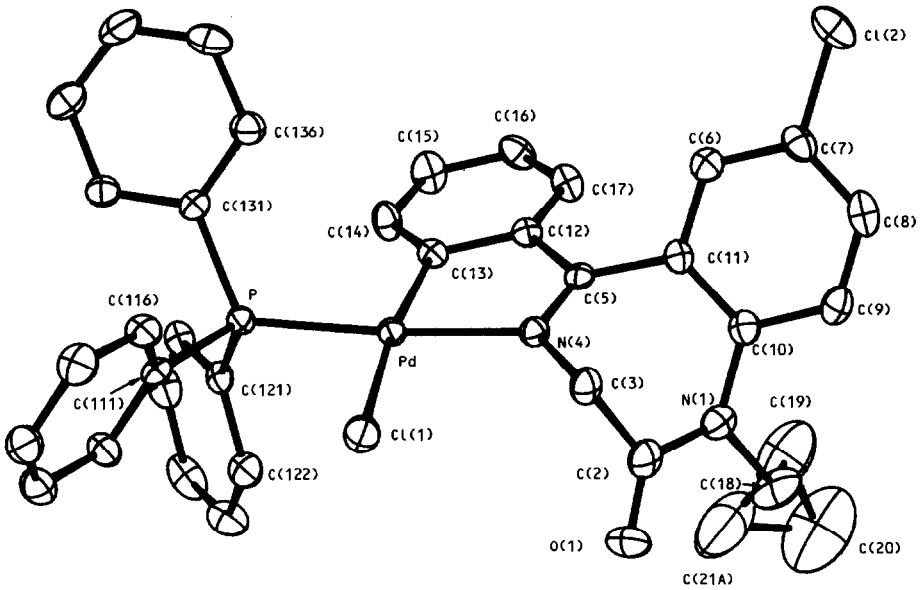
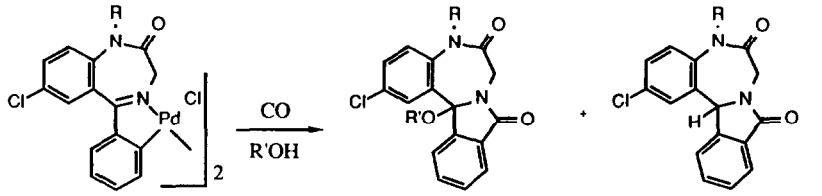


Fig. 1. ORTEP drawing of compound **6**. Thermal ellipsoids are drawn at 30% probability.

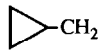
more vigorous conditions (60–100 atm and 45–50 °C) there was a quite different outcome: palladium separated as a black precipitate and a mixture of organic products was formed. With complex **3**, this mixture consists of three products, the first of which was identified by ^{1}H NMR and MS as 2-*N*-methylamino-5-chlorobenzophenone, **1a** (R = CH_3), formed in small amounts (5–10%) from the acidic cleavage of the benzodiazepine ring. The other two products, **9a** and **11**, were formed in about a 3 : 2 ratio. The more abundant of them, **9a**, was characterized by the presence of an ethoxy group in the ^{1}H NMR.

Compound **9a** is by far the predominant product when the high pressure carbonylation is carried out in absolute ethanol, and due to its low solubility in ether it can be isolated in 50–60% yield. Its most significant spectroscopic features are: in the IR, two carbonyl absorptions at 1705 and 1665 cm^{-1} and the absence of C=N stretching vibrations; in the ^{1}H NMR, the ABX_3 pattern of the methylene protons of the ethoxy group and the preservation of the AB system of the benzodiazepine ring. The presence of a quaternary sp^3 carbon at 93.9 ppm in the ^{13}C NMR was decisive for assigning to this product the structure of 2-chloro-13*b*-ethoxy-5-methyl-9*H*-isoindolo-[2,1-*d*]-5,6,8,13*b*-tetrahydro-7*H*-[1,4]-benzodiazepine-6,9-dione, **9a** (R′ = C_2H_5) (Scheme 1). This assignment is consistent with the presence of an asymmetric carbon atom and is supported by the MS spectrum, which shows the molecular ion at *m/z* 356 and the base peak at *m/z* 311, corresponding to the loss of an ethoxy group.

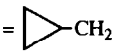
The second product, **11**, which can be separated from the first one by flash chromatography, is obtained more conveniently (60% isolated yield) when the carbonylation is carried out in 1 : 1 methanol–chloroform. When absolute methanol was employed, a mixture was obtained from which compound **11** and the methoxy derivative **9b** (2 : 3 ratio) were isolated.



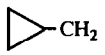
3 R = CH_3

4 R = 

9 R = CH_3

10 R = 

11 R = CH_3

12 R = 

a R' = CH_3CH_2

b R' = CH_3

c R' = $(CH_3)_2CH$

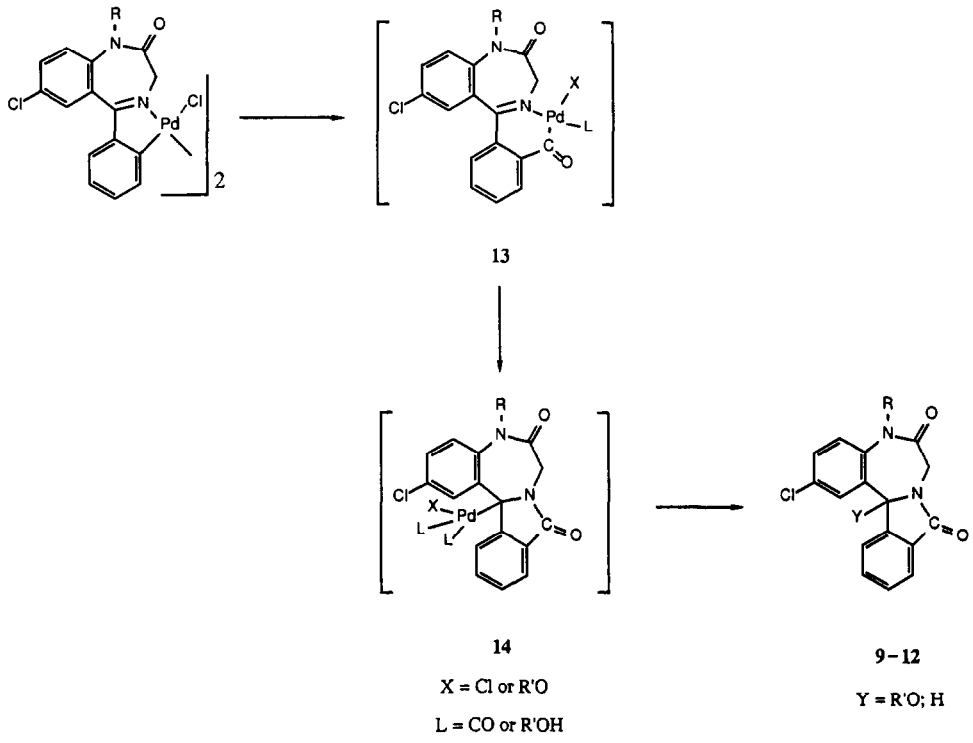
Scheme 1

Making allowance for the differences due to the absence of the alkoxy substituent, in particular for the absence of the quaternary sp^3 carbon, the overall spectroscopic data are rather similar to those of compound **9a**. The presence of an isolated proton resonance at 5.70 δ (singlet) and of a monoprotonated carbon at 59.51 δ, allowed the structure **11** to be confidently assigned to this product. This attribution is supported by the MS spectrum, which shows $[M^+]$ at m/z 312.

The reactions of complex **4** with CO under pressure gave similar results. In absolute ethanol the predominant product, isolated in 50% yield, was the corresponding ethoxy derivative **10a**. In 1 : 1 methanol–chloroform solution, the derivative **12** can be separated in pure form with a 45% yield. In contrast, the methoxy derivative **10b** was not isolated in pure form, although it was detected (NMR criterion). In both the reactions a small amount (5–10%) of 2-*N*-cyclopropylmethylamino-5-chlorobenzophenone **2a** (R = c-$C_3H_5CH_2$) was also formed. Additionally, in the case of ethanol, a palladium-containing product was present. Analytical and spectroscopic evidence indicates that this last product is a species containing the benzodiazepine moiety as a neutral ligand [2].

The formation of alkoxy substituted derivatives **9** and **10** in the carbonylation of five-membered cyclopalladated complexes, supported by nitrogen coordination, is not novel since it has been observed even under mild conditions (room temperature and atmospheric pressure of CO) with palladium complexes derived from open chain nitrogen ligands such as azobenzene or benzylidenimines [9]. It has been assumed that compounds such as **9** and **10** are produced through the intermediacy of two labile palladium derivatives, the cyclic acyl complex **13** and the σ-alkyl complex **14** [10] (Scheme 2). To the best of our knowledge, however, no direct experimental evidence for this reaction path has been produced in the case of five-membered palladacycles.

We have recently provided some support for this hypothesis in the case of carbonylation of a six-membered cyclopalladated complex derived from a benzylbipyridine ligand [11]. In that work, we were able to detect and to intercept an intermediate seven-membered acyl palladium complex. In spite of the rather drastic reaction conditions required for promoting the carbon monoxide insertion, in the

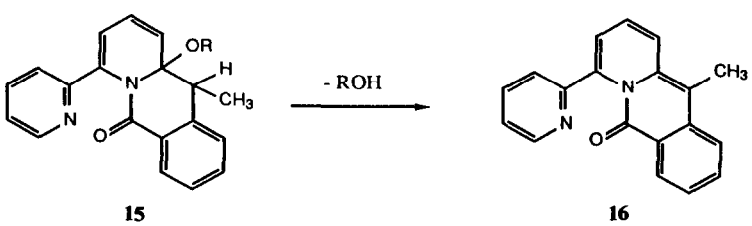


Scheme 2

absence of ethanol, it was stable enough to be isolated and characterized. When ethanol was present, the acyl complex sufferred contraction of the seven-membered cyclometallated ring, with metal extrusion, to give a benzoquinolizinone derivative **16**. The formation of the latter product can reasonably occur through an alkoxy substituted derivative **15**, analogue to **9** and **10**, that easily eliminates a molecule of ethanol to attain the most favourable arrangement of the double bond system (Scheme 3).

Except for this similarity, the behaviour of palladated benzodiazepines towards carbon monoxide is substantially different from other nitrogen based cyclic complexes in two aspects.

First, when **3** and **4** are carbonylated in the presence of an alcohol, the putative acyl palladium intermediate fails to give even a trace of the corresponding ester. In contrast, esters were reported to be obtained, in good to excellent yields, by



15 **16**

Scheme 3

Table 4

^{1}H NMR spectral data [a]

Compound	Aromatic	CH_2	CH_3	CH_2–CH(CH$_2$–CH$_2$)	CH_2–CH(CH$_2$–CH$_2$)	CH_2–CH(CH$_2$–CH$_2$)	CH	O–CH_2–CH_3	O–CH_2–CH_3	NH
		JAB		*JAB; JAX*				*JAB; JAX*		
Diazepam, D, 1	7.70–7.30	4.80, 3.74 (10.8)	3.34							
1a	7.66–6.66		2.96 (5.12)							8.47
9a	7.94–6.90	4.52, 3.54 (12.80)	3.38					3.33, 2.79 (8.0; 7.03)	1.05	
11	8.05–6.94	4.75, 3.56 (13.5)	3.50				5.70			
Prazepam, P, 2	7.86–7.08	4.64, 3.95 (10.25)		4.15, 3.40 (14.22; 7.0)	0.96	0.24				
2a	7.70–6.63			3.10 (6.7)	1.26	0.63				8.59
10a	7.98–6.91	4.53, 3.57 (12.80)		3.93, 3.43 (14.22; 6.6)	1.25	0.44		3.38, 2.81 (8.8; 7.0)	1.05	
12	8.00–6.95	4.70, 3.50 (13.2)		4.30, 3.44 (14.2; 7.2)	1.0	0.3	5.83			

[a] Chemical shifts in ppm (δ) downfield from TMS; coupling constants (J) in Hz; $CDCl_3$, r.t.

Table 5

^{13}C NMR spectral data

Compound	OCH_2CH_3	R [a]	CH_2	OCH_2CH_3	CH	C	Aromatic CH	Aromatic C	CO
Diazepam, D, 1		35.04	57.16			169.07	122.77; 128.6; 129.65; 130.08; 130.88; 131.67	129.44; 130.22; 138.40; 142.80	170.08
1a		34.85					122.48; 128.42; 129.43; 129.9; 130.67; 131.43	129.3; 130.08; 138.15; 142.58	169.9
9a	14.98	37.0	45.0	58.10		93.9	124.34; 124.48; 126.42; 127.03 130.28; 130.70; 132.95	129.44; 130.13; 132.02; 133.45; 141.21	166.14 166.23
11		36.37	46.02		59.51		124.12; 124.54; 124.76; 126.30 129.54; 130.22; 132.13	131.28; 132.94; 133.60; 140.30; 141.31	166.06 166.35
Prazepam, P, 2		3.23; 4.76 10.22 51.31	57.26			169.05	124.53; 128.62; 129.42; 129.79 130.77; 131.46	129.92; 132.05; 138.56; 141.63	168.92
2a		3.8 10.63 48.07					113.36; 128.41; 129.07; 131.32 134.22; 134.95	118.34; 129.21; 131.07; 140.02	150.44
10a	15.19	4.60; 5.17 10.43 54.77	45.49	58.36		94.26	124.50; 124.56; 126.62; 127.37 130.10; 130.75; 133.00	132.15; 132.66; 133.63; 140.23; 141.53	166.11 166.24
12		3.65; 3.95 10.01 53.11	45.86		59.44		124.0; 124.66; 125.67; 126.07; 129.42; 130.11; 132.47	131.97; 133.16; 133.57; 140.24; 140.29	165.92 165.97

[a] R = CH_3: **1**; **1a**; **9a**; **11**. R = CH_2–CH(–CH_2–CH_2–): **2**; **2a**; **10a**; **12**.

carbonylation of cyclopalladated benzylidenimines [9], particularly when performed in the presence of a base such as triethylamine. In our case, in the presence of such a base, the only significant effect is to reduce the extent of the acidic cleavage of the benzodiazepine ring.

These results parallel those we observed for the six-membered palladacycle previously mentioned, and seem to indicate a general behaviour for cyclopalladated complexes containing a ring sp^2-nitrogen as the donor atom. The rigid disposition determined by the ring constraint seems to make the carbonyl group of the intermediate acyl complex more prone to attack by the internal nucleophilic nitrogen than by the external nucleophile, the alcohol. Alternatively, coordination of the alcohol to the palladium atom may be prevented.

The second and more significant difference in the reactivity towards carbon monoxide, between ours and other palladium complexes, concerns the species **11** and **12**. As far as we know, molecules of this kind have not been isolated previously in the carbonylation of cyclopalladated complexes. In principle, they may arise from protonation of the intermediate **14** previously invoked. This does not seem to be the case, however, since their formation was not suppressed, or their yield reduced, when the carbonylation was carried out in the presence of an acidic scavenger such as triethylamine.

An alternative possibility is that **11** and **12** may originate from a hydride transfer to the coordinated benzodiazepine ligand either from an alcohol or, better, from an alkoxy group bound to the metal. This hypothesis is in keeping with the well known ability of transition metal complexes to promote H-transfer reactions to suitable unsaturated substrates when alcohols are used as hydrogen donors. Owing to more favourable thermodynamics, the rate of these reactions should increase when propan-2-ol is used in place of methanol as the hydrogen source. Unfortunately, the opposite was true in our case (see Experimental) and consequently the latter hypothesis could not find any experimental support.

Further work aimed at clarifying this point is in progress.

Experimental

Elemental analyses were performed with a Perkin–Elmer Analyzer 240B. Infrared spectra were recorded with Perkin–Elmer 1310 and 983 photometers. ^1H and ^{13}C NMR spectra were recorded with a Varian XL 200 or a Varian VXR 5000. The mass spectra were obtained with a VG 7070 EQ instrument under EI conditions (70 eV). Ligands **1** and **2** were provided by Roche and Parke–Davis, respectively. The palladium complexes $[(L\text{-}H)PdCl]_2$, **3** and **4** were prepared as described previously [2].

X-Ray data collection and structure determination

Suitable crystals for X-ray structure examination were obtained by slow evaporation of a $CHCl_3$–n-hexane solution of compound **6**. The data were collected on an Enraf–Nonius CAD-4 diffractometer at room temperature with Mo-K_α radiation ($\lambda = 0.71073$ Å). During the data collection a quick decay of the crystal was observed, and amounted to about 60%, evaluated on F_o at the end of the data collection. The diffracted intensities were corrected for Lorentz, polarization and

absorption (empirical correction) [12], but not for extinction. Scattering factors and anomalous dispersion corrections for scattering factors of non-hydrogens atoms were taken from ref. 13. The structure was solved by Patterson and Fourier methods and refined by full-matrix least-squares, minimizing the function $\Sigma w(F_o - k \mid F_c \mid)^2$. All the calculations were performed on a PDP11/73 computer using the SDP-Plus Structure Determination Package [14].

Anisotropic thermal factors were refined for all the non-hydrogen atoms of the complex molecule and for the chlorine atoms of the clathrated solvent. Hydrogen atoms were introduced in the model at calculated positions with C–H = 0.95 Å, and not refined.

The final difference Fourier synthesis showed maxima residuals of 0.6 e/Å^3 close to the disordered solvent molecule and the cyclopropyl moiety. The high thermal parameters of the latter indicate that a percentage of disorder also involves the cyclopropyl fragment.

Tables of structure factors; a table of temperature factors and tables of calculated positions for hydrogen atoms are available from the authors.

Reaction of the complexes [(L-H)PdCl]$_2$, 3 (L = Diazepam) and 4 (L = Prazepam) with CO at room temperature

Compound **3** or **4** (ca. 200 mg) was suspended in chloroform (10 ml) and CO was bubbled at room temperature with stirring. After ca. 1 hour, a yellow solution was obtained: IR spectrum ($CHCl_3$) 2120 cm^{-1}, **7** (L = Diazepam); 2120 cm^{-1}, **8** (L = Prazepam). Attempts to isolate the (L-H)(CO)PdCl complexes, **7** and **8** by concentration, failed: the yellow solids which were recovered were identified as the starting compounds **3** and **4**, respectively.

The same result was obtained from reactions at ambient temperature and at high pressure (75 atm of CO).

Reaction with carbon monoxide under high pressure. General procedure

A Pyrex bottle containing a suspension of **3** or **4** in a solvent was placed in a stainless steel autoclave. After removal of the air the vessel was pressurized with CO (60–100 atm) and then rocked at 45–50 °C for several hours. At the end of the reaction the CO was released and the mixture worked up.

Reaction of [(D-H)PdCl]$_2$, 3, with CO in EtOH

A suspension of compound **3** (208 mg; 0.24 mmol) in 95% EtOH (12 ml) was subjected to the general procedure described above for 30 hours under 60 atm of CO at 50 °C, after which the mixture consisted of a yellow solution and palladium black. The solution was filtered and evaporated to dryness, and the residue extracted with n-hexane. The n-hexane extract was evaporated to dryness: yellow crystals were obtained and identified as 2-*N*-methylamino-5-chloro-benzophenone, **1a** (10 mg; 0.04 mmol; 8.3%) mass spectrum: *m/z* 245.

The white residue, insoluble in n-hexane, was taken up with $CHCl_3$ and neutralized with K_2CO_3 under stirring, then filtered and concentrated to small volume. Addition of n-hexane gave a white product which was filtered off; a second crop was obtained by slow evaporation of the mother solution.

9a, (100 mg; 0.28 mmol) yield 58%, m.p. 209–211 °C. Mass spectrum: *m/z* 356. IR (nujol; cm^{-1}): 1705 vs, 1665 vs.

*Reaction of [(P-H)PdCl]$_2$, **4**, with CO in EtOH*

A suspension of compound **4** (250 mg; 0.27 mmol) in 95% EtOH (10 ml) was subjected to the general procedure described above for 40 hours under 100 atm of CO at 45°C, after which the mixture consisted of a pale-yellow solution and palladium black. The solution was filtered and evaporated to dryness, and the residue extracted with diethyl ether. Slow evaporation of the ether solution gave white crystals of **10a**, (107 mg; 0.27 mmol) yield 50%, m.p. 153–154°C. Mass spectrum: *m/z* 396. IR (nujol; cm^{-1}): 1690 vs, 1665 vs; ($CHCl_3$): 1700 vs, 1665 vs.

A yellow residue, insoluble in diethyl ether, was crystallized from $CHCl_3$–Et_2O and identified as the adduct $(L)_2PdCl_2$: yield 21%, m.p. 285–287°C [2]. Anal. found: C, 52.17; H, 4.24; N, 6.30. Calc. for $C_{38}H_{34}Cl_4N_4O_2Pd \cdot 1/2CHCl_3$: C, 52.11; H, 3.89; N, 6.31%. IR (nujol; cm^{-1}): 1675vs, 1590 s. 339 s.

*Reaction of [(D-H)PdCl]$_2$, **3**, with CO in MeOH / $CHCl_3$*

A suspension of **3** (200 mg; 0.23 mmol) in MeOH–$CHCl_3$ (1:1; 12 ml) was subjected to the general procedure described above for 31 hours under 60 atm of CO at 45–50°C, after which the mixture consisted of a green solution and palladium black. The solution was filtered and evaporated to dryness.

The residue was dissolved in $CHCl_3$ and neutralized with K_2CO_3 under stirring, then filtered and evaporated to dryness. Treatment with n-hexane gave a yellow solution and a white precipitate. The solution was filtered and the product was purified by chromatography on a column (10 × 1.5 cm) of silica gel (Merck 80–300 mesh) with $CHCl_3$ as the eluent. Yellow crystals, obtained by slow evaporation of the eluate, were identified as 2-*N*-methylamino-5-chlorobenzophenone, **1a**.

The white residue, insoluble in n-hexane, was extracted with diethyl ether: white crystals were formed by slow evaporation of the solution. **11**, (70 mg; 0.22 mmol) yield 48%, m.p. 255–256°C. Mass spectrum: *m/z* 312. IR (nujol; cm^{-1}) 1689 vs, 1666 vs.

*Reaction of [(P-H)PdCl]$_2$, **4**, with CO in MeOH / $CHCl_3$*

A suspension of **4** (250 mg; 0.27 mmol) in MeOH/$CHCl_3$ (1:1; 12 ml) was subjected to the general procedure described above for 31 hours under 100 atm of CO at 45–50°C, after which the mixture consisted of a green solution and palladium black. The solution was filtered and evaporated to dryness. The residue was dissolved in $CHCl_3$ and neutralized with K_2CO_3 under stirring. After filtration and reduction to small volume, the solution was flash chromatographed on a column (25 × 2.0 cm) of silica gel (230–400 mesh ASTM) using n-hexane/ethyl-acetate (1:1) as eluent. Three products were separated:

The first eluted (R_f 0.74 on silica gel plates) was identified as 2-*N*-cyclopropyl-methylamino-5-chlorobenzophenone, **2a**, (20 mg; 0.07 mmol) yield 13%; mass spectrum: *m/z* 285.

The second eluted (R_f 0.40) was a 5:1 mixture of prazepam and **10b** (by ^{1}H NMR). **10b**, ^{1}H NMR ($CDCl_3$, δ): 2.93, s, O-CH_3; 3.55, 4.54 (13 Hz), AB, CH_2; 6.93–7.93, aromatics.

The third eluted (R_f 0.27), after removal of solvent, was taken up with $CHCl_3$/n-hexane: white crystals separated by slow evaporation of the solvent. **12**, (85 mg; 0.24 mmol) yield 45%; m.p. 135–136°C. Mass spectrum: *m/z* 352. IR (nujol; cm^{-1}): 1700 vs, 1668 vs.

Reaction of [(D-H)PdCl]$_2$, 3, with CO in i-PrOH

A suspension of **3** (200 mg, 0.47 mmol) in i-PrOH (12 ml) and NEt_3 (0.5 ml) was subjected to the general procedure described above for 30 hours under 100 atm of CO at 45–50 °C, after which the mixture consisted of a pale-green solution and palladium black. The solution was filtered and evaporated to dryness. Treatment of the residue with diethyl ether gave a solution and a yellow precipitate. The precipitate was crystallized from $CHCl_3$–Et_2O and identified as the adduct $(L)_2PdCl_2$: yield 13%, m.p. 286–287 °C [2]. The solution was evaporated to dryness and then flash chromatographed on a column (25 × 1.0 cm) of silica gel (230–400 mesh ASTM) using n-hexane/ethylacetate (1 : 1) as eluent. The major product (87 mg; R_f 0.19) was an unresolved mixture of **11** and **9c** (molar ratio 1 : 5) (by ^1H NMR).

9c, ^1H NMR ($CDCl_3$, δ): 1.03, d, 1.24, d, O-CH(CH_3)$_2$; 4.88 (6.3 Hz), sept, O-CH(CH_3)$_2$; 3.48, s, N-CH_3; 3.82, 4.80 (10 Hz), AB, CH_2; 6.97–7.86, aromatics.

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References

1 (a) G. Minghetti, C. Foddai, F. Cariati, M.L. Ganadu, M. Manassero, Inorg. Chim. Acta, 64 (1982) L235; (b) G. Minghetti, M.L. Ganadu, C. Foddai, M.A. Cinellu, F. Cariati, F. Demartin, M. Manassero, Inorg. Chim. Acta, 86 (1984) 93.
2 M.A. Cinellu, M.L. Ganadu, G. Minghetti, F. Cariati, F. Demartin, M. Manassero, Inorg. Chim. Acta, 143 (1988) 197.
3 M.A. Cinellu, S. Stoccoro, G. Minghetti, A.L. Bandini, F. Demartin, Inorg. Chim. Acta, 168 (1990) 33.
4 L.H. Sternbach, J. Med. Chem., 22 (1979) 1.
5 G. Minghetti, S. Gladiali, M.A. Cinellu, S. Stoccoro, Fifth IUPAC Symposium on Organometallic Chemistry directed towards Organic Synthesis, OMCOSV, Florence, Italy, October 1989, Abstract PS1-46.
6 G.P. Palenik, T.J. Giordano, J. Chem. Soc., Dalton Trans., (1987) 1175.
7 A. Albinati, C.G. Anklin, F. Ganazzoli, H. Ruegg, P.S. Pregosin, Inorg. Chem., 26 (1987) 503.
8 G. Brachtel, M. Jansen, Cryst. Struct. Commun., 10 (1981) 669.
9 A. Albinati, P.S. Pregosin, R. Ruedi, Helv. Chim. Acta, 68 (1985) 2046.
10 J.M. Thompson, R. Heck, J. Org. Chem., 40 (1975) 2667.
11 M.A. Cinellu, S. Gladiali, G. Minghetti, J. Organomet. Chem., 363 (1989) 401.
12 A.C. North, D.C. Phillips, F.S. Mathews, Acta Crystallogr., A24 (1968) 351.
13 International Tables for X-ray Crystallography, Vol. IV, Kynoch Press, Birmingham, U.K., 1974.
14 B.A. Frenz and Associates, Inc., SDS Plus Version 1.0, Enraf–Nonius, Delft, Netherlands, 1980.