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Adducts and Cyclometallated Derivatives of Palladium(II) with some 1,4-Benzodiazepin-2-ones. Crystal and Molecular Structure of *trans*-Dichlorobis[7-chloro-1-(cyclopropylmethyl)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one]palladium(II)

MARIA AGOSTINA CINELLU, MARIA LUISA GANADU, GIOVANNI MINGHETTI

Dipartimento di Chimica, Università di Sassari, Via Vienna 2, 07100 Sassari, Italy

FRANCO CARIATI

Dipartimento di Chimica Inorganica e Metallorganica, Università di Milano, CNR Center, Via Venezian 21, 20133 Milan, Italy

FRANCESCO DEMARTIN and MARIO MANASSERO

Istituto di Chimica Strutturistica Inorganica, Università di Milano, CNR Center, Via Venezian 21, 20133 Milan, Italy

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Abstract

The adducts *trans*-L_2PdCl_2 (**1**, L = Diazepam = 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one; **5**, L = Prazepam = 7-chloro-1-(cyclopropylmethyl)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one) were prepared by reaction of $PdCl_2$ or $(PhCN)_2PdCl_2$ with Diazepam and Prazepam, respectively.

In the adducts, the benzodiazepines act as monodentate ligands through the 4-nitrogen atom, as shown by the structure of compound **5**, determined by X-ray diffraction.

Two crystalline modifications have been characterized: **5a**, *trans*-$(Prazepam)_2PdCl_2/CHCl_3$ 1/1, monoclinic, space group $P2_1/n$, $a = 11.996(4)$, $b = 13.678(5)$, $c = 12.717(3)$ Å, $\beta = 98.83(2)$, $Z = 2$, $R = 0.032$; **5b**, *trans*-$(Prazepam)_2PdCl_2/CH_2Cl_2$ 1/1, monoclinic, space group $P2_1/c$, $a = 14.074(3)$, $b = 14.622(7)$, $c = 19.360(10)$ Å, $\beta = 100.04(3)$, $Z = 4$, $R = 0.076$.

Cyclometallated derivatives $[(L-H)PdCl]_2$, **2**, L = Diazepam and **6**, L = Prazepam, involving both C- and N-intramolecular coordination of the deprotonated ligands, have been obtained by reaction with $Na_2[PdCl_4]$ in ethanol solution. In the dimeric species **2** and **6**, the halide-bridge is easily split by reaction with Ph_3P or Tl(acac), to give [(L–H)-(Ph_3P)PdCl], (**3**, **7**) and [(L–H)Pd(acac)] (**4**, **8**) respectively.

Introduction

To comment on the therapeutic importance of the 1,4-benzodiazepines seems now to be superfluous. Closely linked with their use, or perhaps abuse, especially as tranquilizers, is the tremendous increase of the literature: a 'Handbook', published in 1982, lists something like 3778 references [1].

In spite of this, the interaction of the 1,4-benzodiazepines with transition metal ions has received relatively scanty attention, even if it is now common belief that the pharmacological activity of some drugs is improved by the presence of certain metal ions. Investigations in this field are likely to have been hindered, *inter alia*, by the difficulty in establishing the bonding mode of the ligands which may coordinate to a metal centre through several donor sites. Indeed different modes of coordination [2], including mono and bidentate behaviour, have been suggested mainly on the basis of infrared and electronic spectra.

Actually the structure in the solid state, as established by an X-ray analysis, has been described for two compounds only, namely $(L)_2CuCl_2$ (L = Diazepam) [2e, 2f] and $(L)AuCl_3$ (L = Prazepam) [3]. In both the copper(II) and gold(III) complexes, the benzodiazepine acts as a monodentate ligand through the 4-nitrogen atom. In addition the structure of a mercury(II) adduct, $(L)HgCl_2$ (L = Temazepam = 7-chloro-3-hydroxy-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one), has been described [4]. Here the ligand displays a more complex behaviour interacting with a dimeric ($HgCl_2$) unit through the 4-nitrogen atom, the keto oxygen and the 3-hydroxy group to give a polymeric structure.

As far as we know, X-ray evidences supporting other coordination modes have not been reported.

As a part of an investigation on the reactivity of 1,4-benzodiazepin-2-ones with metal ions having d^8

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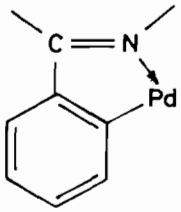
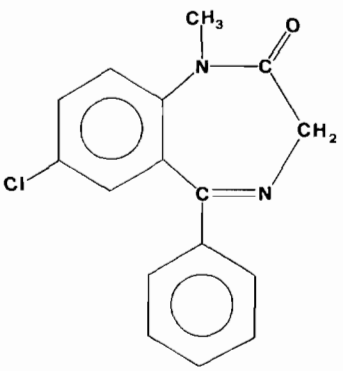
configuration, following our work on gold(III) derivatives, here we present the synthesis and structure of some $(L)_2PdCl_2$ adducts (**1**, **5**) as well as the synthesis of some organo-palladium derivatives, $[(L-H)PdCl]_2$ (**2**, **6**). In the latter compounds the deprotonated ligands are coordinated to the metal through the 4-nitrogen atom and the *ortho*-carbon atom of the 5-phenyl substituent. The reaction of these dimeric species with neutral (e.g. Ph_3P) and anionic ligands (e.g. acac) to give the monomers $[(L-H)(Ph_3P)PdCl]$ (**3**, **7**) and $[(L-H)Pd(acac)]$ (**4**, **8**) respectively, is consistent with the presence in the molecules of a stable C,N-five-membered ring

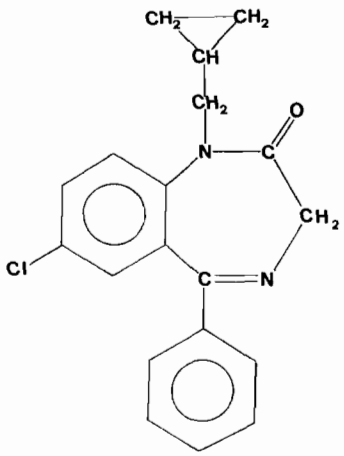


The compounds **2**–**4** and **6**–**8** are the first transition metal derivatives of 1,4-benzodiazepines where the ligand (i) acts as an anion, (ii) displays an endo-bidentate behaviour and (iii) gives rise to a metal–carbon bond. Owing to the presence of a palladium–carbon bond these molecules are potentially intermediates for new synthesis of 1,4-benzodiazepines functionalized on the *ortho*-carbon atom of the 5-phenyl ring. An investigation on this topic is in progress and will be reported elsewhere. A preliminary account of this work has been given [5].

Results and Discussion

In the belief that substituents can modify the behaviour of the ligands significantly, the investigation on the reaction with palladium(II) derivatives was restricted to two 1,4-benzodiazepin-2-ones, both having alkyl substituents on the 1-nitrogen atom, namely Diazepam and Prazepam.





By reaction (1), carried out at room temperature in chloroform solution

$$PdCl_2 + 2L \longrightarrow \textit{trans}\text{-}L_2PdCl_2 \quad (1)$$

(or $(PhCN)_2PdCl_2$)

the 1:2 adducts *trans*-(Diazepam)$_2$PdCl$_2$ (**1**) and *trans*-(Prazepam)$_2$PdCl$_2$ (**5**) were easily obtained in good yields. The adducts are non-electrolytes thus ruling out ionic isomers: in the IR spectra, one band alone, observed in the palladium–chlorine stretching region, is consistent with a *trans*-N_2PdCl_2 arrangement (Table I). In the range 1700–1550 cm^{-1}, the two strong absorptions assigned in the free ligands to the prevailing contribution of ν(C=O) and ν(C=N) respectively, are slightly shifted to higher (ν(C=O)) and lower (ν(C=N)) wavenumbers, as previously observed for the $(L)AuCl_3$ complexes.

The ^{1}H NMR spectra, recorded at room temperature in chloroform solution show the expected signals: by comparison with the spectra of the ligands [3, 6], they can be assigned to the protons of the two aromatic rings, which form an ABC and an AA′BB′C spin system, to the protons of the CH_2 group inside the heterocyclic ring and to those of the alkyl substituents on the 1-nitrogen atom, respectively. The overall pattern of the spectra are quite similar to those of the free ligands: in both **1** and **5**, only one set of signals is observed, consistent with equivalence in solution of the two coordinated 1,4-benzodiazepines and with the absence of any hindrance in the rotation around the palladium–ligand bond.

Upon coordination the resonances of the alkyl protons do not exhibit any significant shift: the resonance of the CH_2 group inside the ring appears as a typical AB quartet suggesting that the adducts have a fixed conformation even at room temperature. The H–H geminal coupling constants are larger than in the free ligands, as observed previously in some $(L)AuCl_3$ derivatives (Table II) [3].

TABLE I. Analytical[a] and IR Data

Compound	Melting point	C (%)	H (%)	N (%)	Cl (%)	ν(Pd–Cl)
trans-D_2PdCl_2 [b] (1)	285–287	51.50 (51.46)	3.62 (3.48)	7.45 (7.50)	19.10 (19.02)	335s [c]
$[(D\text{-}H)PdCl]_2$ (2)	no dec. up to 290	45.34 (45.11)	2.99 (2.82)	6.64 (6.58)	16.80 (16.66)	280m; 233s [d]
$[(D\text{-}H)(PPh_3)PdCl]$ (3)	248–250	59.18 (59.33)	4.08 (3.92)	4.66 (4.07)	11.60 (10.31)	310s [c]
[(D-H)Pd(acac)] (4)	148–149	51.94 (51.51)	4.16 (3.88)	5.47 (5.72)		
trans-P_2PdCl_2 (5)	285–287	55.28 (55.14)	4.24 (4.11)	6.65 (6.70)		335s [c]
$[(P\text{-}H)PdCl]_2$ (6)	no dec. up to 290°	50.26 (48.96)	4.00 (3.43)	6.08 (6.01)		282s; 236s [d]
$[(P\text{-}H)(PPh_3)PdCl]$ (7)	250–251	60.78 (61.01)	4.45 (4.26)	3.65 (3.84)		310s [c]
[(P-H)Pd(acac)] (8)	150–151	55.25 (54.41)	4.79 (4.34)	5.21 (5.25)		

[a]Calculated values in parentheses. [b]Pd%: found 14.00; calculated 14.25. [c]Terminal. [d]Bridging.

TABLE II. ^1H NMR Data[a]

Compound	Aromatic	$CH_2(3)$	$CH_3(1)$	CH_2–$\overline{CH}$–CH_2–$\overline{CH_2}$	CH_2–$\overline{CH}$–CH_2–$\overline{CH_2}$	CH_2–$\overline{CH}$–CH_2–$\overline{CH_2}$
Diazepam D	7.50 7.22	4.79, 3.75(10.8)	3.36			
trans-D_2PdCl_2 (1)	8.32 7.06	4.69, 3.63(12.6)	3.49			
$[(D\text{-}H)PdCl]_2$ (2)	7.78 7.05	5.07, 3.85(12.7)	3.41			
$[(D\text{-}H)(PPh_3)PdCl]$ (3)	7.61 6.29	5.85, 3.43(12.7)	3.06			
[(D-H)Pd(acac)] [c] (4)	7.70 7.06	5.18, 3.80(12.7)	3.38			
Prazepam P	7.50 7.21	4.76, 3.73(10.5)		4.19, 3.45(14.6)	0.83	0.14
trans-P_2PdCl_2 (5)	8.36 7.05	4.70, 3.68(12.6)		4.40, 3.48(14.6)	0.98	0.31
$[(P\text{-}H)PdCl]_2$ [b] (6)						
$[(P\text{-}H)(PPh_3)PdCl]$ (7)	7.94 6.50	6.10, 3.70(12.1)		4.11, 3.58(15.5)	0.89	0.17
[(P-H)Pd(acac)] [d] (8)	7.72 7.04	5.14, 3.79(12.2)		4.10, 3.48(21.0)	0.87	0.18

[a]In $CDCl_3$ solution at room temperature; the chemical shifts are reported in ppm (δ values), relative to TMS as internal standard, the J values (Hz) are in parentheses. [b] Insoluble in suitable solvents. [c]acac: 2.1, 2.09 (CH_3); 5.41 (CH). [d]acac: 2.1, 2.08 (CH_3); 5.41 (CH).

In contrast significant differences are observed in the aromatic region: the assignment of these signals and the coupling constants, as obtained by simulation of the ^1H spectra, are reported in Table III. With respect to the free ligand, a remarkable downfield shift is observed for the resonances due to the protons of the 5-phenyl substituent, and a moderate one, of the same sign, for the protons in 8. Unexpectedly the protons in **6** and in **9** are found to resonate at higher field.

Although the spectroscopic data (IR and NMR) on the whole provided some information on the nature of these molecules and indicated a *trans* distribution of the ligands around the palladium atom, they failed to establish the coordination mode of the benzodiazepines with certainty. Indeed the IR data do not appear to be a reliable criterion, owing to the complex pattern of the region where both the C=O and C=N stretching vibrations are observed, conjugated with each other: even the ^1H NMR spectra, do not provide convincing evidence on the nature of the metal–ligand bond. To settle the point, an X-ray diffraction determination of **5** was undertaken (see later): thus the coordination of the 1,4-benzodiazepin-2-ones in the adducts was revealed unambiguously to occur through the 4-nitrogen atom.

By reaction (1) we were unable to obtain adducts of Diazepam or Prazepam having other stoichiometries even in the presence of excess ligand or with a 1:1 ligand to metal molar ratio. 1:1 adducts of some 1,4-benzodiazepines, Diazepam included, $(L)MX_2$, (M = Pd, Pt; X = Cl, Br) have been described previ-

TABLE III. ^{1}H NMR Data – Aromatic Region[a]

Compound		6	8	9	2'	6'	3'	5'	4'	J_{8-9}	J_{8-6}	J_{9-6}	$J_{2'-3'}$	$J_{2'-4'}$	$J_{2'-6'}$	$J_{3'-4'}$	$J_{3'-5'}$	$J_{3'-6'}$	$J_{4'-5'}$	$J_{4'-6'}$	$J_{5'-6'}$
Diazepam	D	578.0	592.0	592.0	600.0	600.0	582.0	582.0	584.0	8.8	2.5	0.0	8.2	0.6	2.5	7.5	2.0	0.0	0.0	0.0	0.0
trans-D_2PdCl_2	1	565.4	602.6	580.0	665.9	665.9	624.3	624.3	615.0	8.8	2.5	0.0	8.2	0.6	2.5	7.5	2.0	0.0	0.0	0.0	0.0
$[(D-H)PdCl]_2$	2	565.4	602.6	580.0		621.0	608.0	613.0	618.0	8.8	2.5	0.0	0.0	0.0	0.0	8.8	2.5	0.4	2.5	2.5	8.8
[(D–H)Pd(acac)	4	571.0	596.0	582.0		617.0	603.0	609.0	615.0	8.8	2.5	1.25	0.0	0.0	0.0	2.7	0.0	0.0	3.0	1.5	3.0
Prazepam	P	577.5	592.0	593.0	600.0	600.0	588.5	588.5	586.0	8.3	3.3	0.6	8.2	0.8	2.0	7.9	1.7	0.0	0.0	0.0	0.0
trans-P_2PdCl_2	5	564.0	599.5	585.5	668.9	668.9	620.0	620.0	617.7	8.9	2.2	0.7	8.2	0.8	2.0	7.9	1.7	0.0	0.0	0.0	0.0
[(P–H)Pd(acac)]	8	570.0	604.0	582.0		625.5	607.0	615.0	621.0	8.8	2.5	2.0	0.0	0.0	0.0	3.0	2.7	0.0	3.0	1.5	3.0

[a]Chemical shifts in Hz downfield from TMS; coupling constants in Hz.

ously by Preti and Tosi [2c] and claimed to be dimers with terminal halides and bridging heterocyclic nitrogen ligands. In order to check the difference between the two series of complexes, attempts were made to obtain the 1:1 adducts according to the procedure of ref. 2c, *i.e.* by reaction of the tetrachloropalladate ion in ethanol/water solution. Under the exact experimental conditions of Preti and Tosi, *i.e.* at reflux, besides palladium black, a small amount of a yellow product, insoluble in ethanol, was obtained. To improve the yield of the yellow product, the experimental conditions were slightly modified, the reaction being carried out in ethanol at room temperature. By this method, with both the ligands, no adducts, either 1:1 or 1:2, were obtained: the yellow compounds, **2** (Diazepam) and **6** (Prazepam), were identified, on the basis of the analytical values, as (L–H)PdCl derivatives. The loss of the molecule of HCl, is likely to be favoured, *inter alia*, by the basic medium of the reaction (ethanol). The complexes **2** and **6** were supposed to be dimeric metallated derivatives of palladium involving C- and N-intramolecular coordination of the deprotonated ligands, with bridging chlorides:

To check the hypothesis, reactions of **2** and **6** with neutral and anionic ligands were carried out: in both cases displacement of the heterocyclic ligand was not observed. Indeed with triphenylphosphine (reaction (2))

$$[(L-H)PdCl]_2 + 2Ph_3P \longrightarrow 2[(L-H)(Ph_3P)PdCl] \quad (2)$$

and with thallium(I) acetylacetonate, Tl(acac) (reaction (3))

$$[(L-H)PdCl]_2 + 2Tl(acac) \longrightarrow 2[(L-H)Pd(acac)] + 2TlCl \quad (3)$$

the monomeric species **3**, **7** and **4**, **8** respectively, were isolated and characterized.

The achievement of these mononuclear derivatives through a bridge-splitting reaction is fully consistent with the assumption of a deprotonated benzodiazepine acting as a chelating ligand: the splitting of a halide-bridge is typical of these systems and has been reported many times [7]. The spectroscopic data fit the formulation of the complexes **3**, **7** and **4**, **8**: particularly the IR spectra of **7** and **8** are in agreement with a chelating acetylacetonato.

The ^1H NMR spectra of the complexes **2**–**4** and **6**–**8** give evidence that the deprotonation of the ligands does not involve the CH_2 protons inside the ring or the protons of the alkyl substituents on the 1-nitrogen atom. Indeed none of these protons is missing. The CH_2 protons of the ring display, at room temperature, an AB system as in the adducts: however the resonance is shifted to lower fields and one of the protons is more shifted than the other so that the separation between the two sets of signals becomes larger than in the ligands or in the adducts. The overall pattern of the aromatic region is similar to that observed in the adducts: the intensity ratio shows the lack of one proton which is shown to be one of the protons of the 5-phenyl substituent (see Table III). On the basis of the spectroscopic data and of the pattern of reactivity, even in the absence of X-ray data, it is reasonable to assume that the metallation concerns one *ortho*-carbon atom of the 5-phenyl substituent, to give a series of complexes which contain a five-membered ring. For palladium derivatives, where the cyclometallation is assisted by the coordination of a nitrogen atom, such a ring is known to have a remarkable stability [7].

Complexes having this type of C- and N-intramolecular coordination are likely to be potential intermediates for the synthesis of 1,4-benzodiazepine-2-ones functionalized on the *ortho*-carbon atom of the 5 phenyl substituent. In this connection, it is noteworthy that the presence of certain substituents (e.g. Cl, F) in this position, is known to improve the activity of these drugs [8]: therefore investigations in this field (e.g. reaction with CO) are in progress.

Finally it is worth mentioning that the achievement of compounds **2** and **6** is accompanied by a second product, obtained in small yields: some evidence suggest that this is a monomeric complex, [(L–H)(L)PdCl], arising from a bridge-splitting reaction of the dimeric species, brought about by the neutral benzodiazepines. The latter compounds were not investigated further.

Description of the Structures: 5a and 5b

The structure of *trans*-(Prazepam)$_2$PdCl$_2$ has been solved and refined for two different crystalline modifications **5a** and **5b** (see 'Experimental') both containing a partially disordered clathrate solvent molecule, which is $CHCl_3$ in **5a** and CH_2Cl_2 in **5b**. In **5a** the complex molecule lies on a special position of space group $P2_1/n$ and therefore possesses a crystallographic centre of symmetry. The chloroform molecule is split into two pairs of 'half molecule' of equal weight (occupancy factors 0.50 each) in the proximity of another inversion centre of the space group. In **5b** the complex molecule lies in a general position of space group $P2_1/c$ and fairly approximates the idealized symmetry $\bar{1}$. The dichloromethane solvent molecules in **5b** exhibit a disorder quite similar to that of chloroform in **5a**. The results of the refinements are reported in Tables IV (for **5a**) and V (for **5b**). Figures 1 and 2 show perspective

TABLE IV. Fractional Atomic Coordinates for Non-hydrogen Atoms of **5a**

Atom	*x*	*y*	*z*
Pd	0.000	0.000	0.000
Cl(1)	0.05823(9)	0.15975(8)	−0.01857(9)
Cl(2)	−0.64017(8)	0.14369(9)	0.0499(1)
O(1)	0.0160(3)	0.1268(3)	0.2805(3)
N(1)	−0.1562(3)	0.1948(3)	0.2240(3)
N(4)	−0.1343(2)	0.0452(2)	0.0637(2)
C(2)	−0.0791(4)	0.1187(4)	0.2344(3)
C(3)	−0.1233(3)	0.0259(3)	0.1783(3)
C(5)	−0.2195(3)	0.0949(3)	0.0182(3)
C(6)	−0.4182(3)	0.1242(3)	0.0422(3)
C(7)	−0.4978(3)	0.1587(3)	0.0994(4)
C(8)	−0.4676(4)	0.2057(4)	0.1960(4)
C(9)	−0.3548(4)	0.2168(4)	0.2352(4)
C(10)	−0.2709(3)	0.1817(3)	0.1792(4)
C(11)	−0.3033(3)	0.1353(3)	0.0818(3)
C(12)	−0.2355(3)	0.1136(3)	−0.0980(3)
C(13)	−0.2732(4)	0.2038(3)	−0.1377(4)
C(14)	−0.2847(4)	0.2219(4)	−0.2461(4)
C(15)	−0.2609(4)	0.1511(4)	−0.3139(4)
C(16)	−0.2271(4)	0.0601(4)	−0.2756(4)
C(17)	−0.2128(3)	0.0402(3)	−0.1674(3)
C(18)	−0.1170(5)	0.2911(4)	0.2661(5)
C(19)	−0.1467(5)	0.3715(4)	0.1886(8)
C(20)	−0.0899(7)	0.3803(6)	0.0982(8)
C(21)	−0.0628(6)	0.4542(5)	0.1892(8)
CS	0.5540(8)	0.5065(8)	−0.0138(8)
Cl(1)S	0.5328(3)	0.4063(2)	0.0675(2)
Cl(2)S	0.6688(3)	0.5733(3)	0 0490(2)
Cl(3)S	0.4298(4)	0.5751(4)	−0.0343(3)

TABLE V. Fractional Atomic Coordinates for Non-hydrogen Atoms of **5b**

Atom	*x*	*y*	*z*
Pd	0.2479(2)	0.1018(1)	0.2451(1)
ClA	0.3003(4)	0.1879(4)	0.3437(3)
ClB	0.1944(4)	0.0138(4)	0.1469(3)
Cl(2)A	−0.2807(4)	0.0447(5)	0.3478(3)
O(1)A	0.124(1)	0.348(1)	0.2142(8)
N(1)A	0.015(1)	0.303(1)	0.2808(7)
N(4)A	0.109(1)	0.133(1)	0.2506(8)
C(2)A	0.068(1)	0.289(2)	0.230(1)
C(3)A	0.062(2)	0.197(2)	0.195(1)
C(5)A	0.064(1)	0.108(1)	0.3002(9)
C(6)A	−0.106(1)	0.082(1)	0.319(1)
C(7)A	−0.194(1)	0.116(1)	0.327(1)
C(8)A	−0.215(2)	0.210(2)	0.318(1)
C(9)A	−0.148(2)	0.269(2)	0.301(1)
C(10)A	−0.056(1)	0.238(1)	0.294(1)
C(11)A	−0.032(1)	0.145(1)	0.3031(9)

(continued)

TABLE V. *(continued)*

Atom	x	y	z
C(12)A	0.101(1)	0.041(1)	0.355(1)
C(13)A	0.089(1)	0.054(2)	0.424(1)
C(14)A	0.127(2)	−0.012(2)	0.474(1)
C(15)A	0.174(2)	−0.086(2)	0.455(1)
C(16)A	0.190(2)	−0.100(2)	0.388(1)
C(17)A	0.153(2)	−0.040(2)	0.336(1)
C(18)A	0.032(2)	0.385(2)	0.326(1)
C(19)A	0.085(2)	0.367(2)	0.394(1)
C(20)A	0.080(2)	0.435(2)	0.452(2)
C(21)A	0.033(2)	0.344(2)	0.453(1)
Cl(2)B	0.7697(4)	0.1579(5)	0.1288(3)
O(1)B	0.372(1)	−0.145(1)	0.2767(7)
N(1)B	0.482(1)	−0.099(1)	0.2099(7)
N(4)B	0.387(1)	0.073(1)	0.2389(7)
C(2)B	0.425(1)	−0.086(2)	0.259(1)
C(3)B	0.433(1)	0.012(2)	0.291(1)
C(5)B	0.430(1)	0.096(1)	0.1886(9)
C(6)B	0.595(1)	0.118(1)	0.163(1)
C(7)B	0.683(1)	0.084(1)	0.1522(9)
C(8)B	0.707(2)	−0.006(2)	0.164(1)
C(9)B	0.638(2)	−0.063(2)	0.182(1)
C(10)B	0.548(1)	−0.034(1)	0.193(1)
C(11)B	0.527(1)	0.060(1)	0.1812(9)
C(12)B	0.384(1)	0.161(1)	0.1331(9)
C(13)B	0.332(1)	0.240(2)	0.153(1)
C(14)B	0.285(2)	0.294(2)	0.099(1)
C(15)B	0.284(2)	0.273(2)	0.029(1)
C(16)B	0.334(2)	0.196(2)	0.012(1)
C(17)B	0.381(2)	0.145(2)	0.064(1)
C(18)B	0.466(2)	−0.184(2)	0.166(1)
C(19)B	0.402(3)	−0.170(3)	0.099(2)
C(20)B	0.386(3)	−0.220(3)	0.040(2)
C(21)B	0.416(3)	−0.121(3)	0.041(2)
Cl(1)S	0.404(1)	0.500(1)	0.0146(9)
Cl(2)S	0.481(1)	0.623(2)	−0.065(1)
CS	0.525(5)	0.555(5)	0.004(3)

views of the two molecules. Due to the different quality of the diffracting crystals, the structure determination of **5a** is markedly more precise than that of **5b**, as shown by the standard deviations on the coordinates of corresponding atoms in Tables IV and V. However, individual bond lengths and angles for the complex molecule in **5b** are very similar to those found in **5a**, and in most cases statistically coincident within three e.s.d.s. A substantial difference is however present in the conformation of the cyclopropyl appendage, which will be discussed later. Apart from this point, we will limit ourselves to a discussion of the crystallographic results of **5a**, for which a list of selected bond lengths and angles is reported in Table VI, together with the average values for the corresponding parameters observed in the two independent molecules of the free Prazepam ligand [9].

Crystals of **5a** are built up of $(Prazepam)_2PdCl_2$ and $CHCl_3$ molecules, in the molar ratio 1/1, separated by normal van der Waals contacts. The solvent molecules are affected by the disorder previously described. The configuration around the Pd atom is strictly *trans* planar, as required by the crystallographic $\bar{1}$ symmetry (Fig. 1). Both the Pd–Cl, 2.317(1) Å and Pd–N, 2.009(3) Å, bond lengths are in the range usually found for similar single bonds in Pd(II) square planar complexes (see for instance Pd–Cl = 2.298(1) and Pd–N = 2.001(2) Å in $[PdCl_2\{\overline{N{=}N{-}N(Ph){-}CH{-}CH{-}(CH_2)_5{-}CH_2}\}_2]$ [10]. In $(Prazepam)AuCl_3$ [3] the Au–Cl (av. 2.270 Å) and Au–N (2.030(15) Å) bonds were, respectively, shorter and longer than the Pd–Cl and Pd–N bonds in the present molecule, and the Au–Cl bond *trans* to nitrogen (2.260(6) Å) was found to be slightly shorter than the other two (2.272(7) and 2.278(7) Å). This trend is in keeping with the covalent

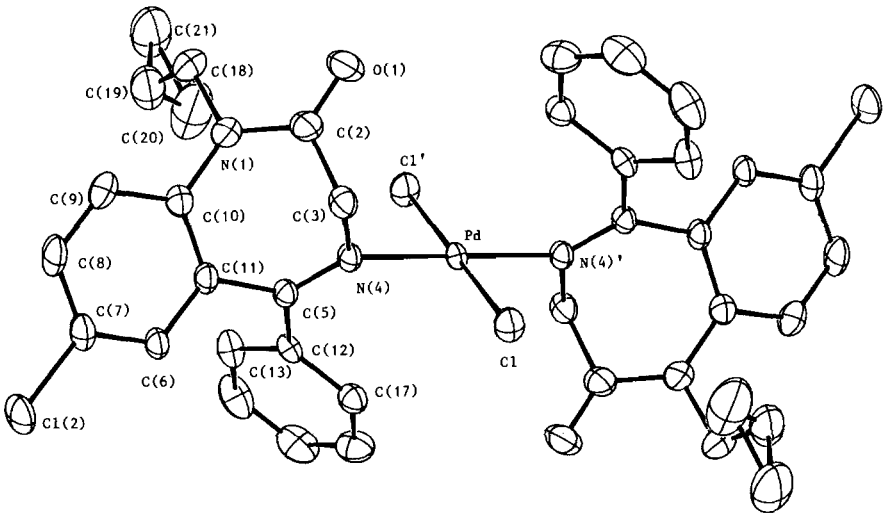


Fig. 1. ORTEP view of the $(Prazepam)_2PdCl_2$ molecule in crystals of compound **5a**.

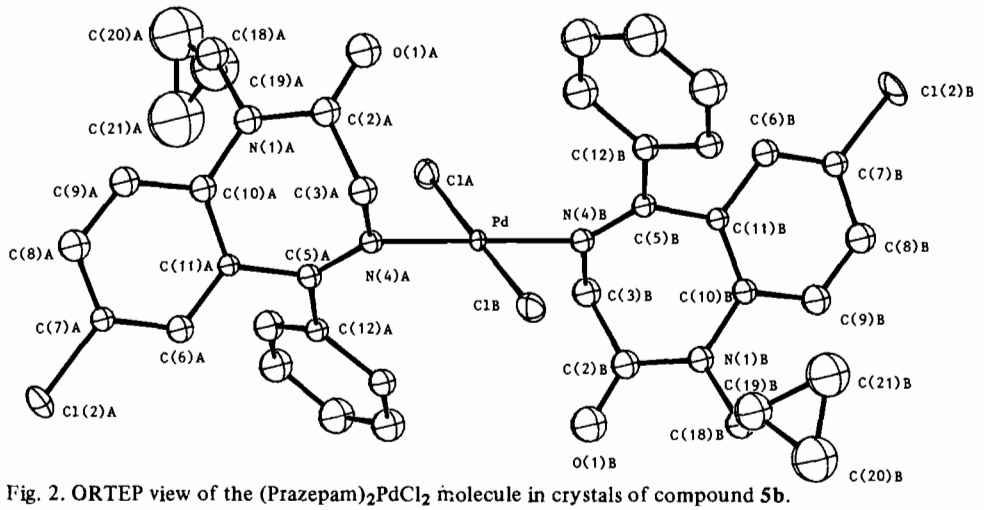


Fig. 2. ORTEP view of the $(Prazepam)_2PdCl_2$ molecule in crystals of compound **5b**.

TABLE VI. Selected Bond Distances (Å) and Angles (°) in **5a** and Prazepam[a]

	5a	Prazepam
Pd–Cl(1)	2.317(1)	
Pd–N(4)	2.009(3)	
N(1)–C(2)	1.385(6)	1.375
N(1)–C(10)	1.418(5)	1.423
N(1)–C(18)	1.471(7)	1.496
C(2)–O(1)	1.206(5)	1.209
C(2)–C(3)	1.511(6)	1.515
C(3)–N(4)	1.468(5)	1.462
N(4)–C(5)	1.289(5)	1.285
C(5)–C(11)	1.490(5)	1.497
C(5)–C(12)	1.482(5)	1.490
C(6)–C(11)	1.401(5)	1.404
C(6)–C(7)	1.370(5)	1.381
C(7)–Cl(2)	1.740(4)	1.749
C(7)–C(8)	1.385(6)	1.382
C(8)–C(9)	1.377(6)	1.374
C(9)–C(10)	1.404(6)	1.408
C(10)–C(11)	1.393(6)	1.398
C(12)–C(13)	1.382(5)	1.391
C(12)–C(17)	1.391(6)	1.400
C(13)–C(14)	1.386(7)	1.385
C(14)–C(15)	1.356(8)	1.381
C(15)–C(16)	1.376(7)	1.380
C(16)–C(17)	1.388(6)	1.394
C(18)–C(19)	1.483(11)	1.497
C(19)–C(20)	1.429(13)	1.441
C(19)–C(21)	1.514(10)	1.536
C(20)–C(21)	1.534(12)	1.538
Cl(1)S–CS	1.759(12)	
Cl(2)S–CS	1.741(11)	
Cl(3)S–CS	1.746(12)	
Cl(1)–Pd–N(4)	91.4(1)	
Cl(1)'–Pd–N(4)	88.6(1)	
Pd–N(4)–C(3)	112.9(2)	
Pd–N(4)–C(5)	127.7(3)	
C(2)–N(1)–C(10)	122.4(4)	123.0
C(2)–N(1)–C(18)	117.8(4)	118.8

(continued)

TABLE VI. *(continued)*

	5a	Prazepam
N(1)–C(2)–O(1)	123.0(4)	122.5
N(1)–C(2)–C(3)	113.9(4)	114.5
O(1)–C(2)–C(3)	123.0(4)	122.9
C(2)–C(3)–N(4)	106.8(3)	108.0
C(3)–N(4)–C(5)	119.0(3)	117.5
N(4)–C(5)–C(11)	120.4(3)	123.4
N(4)–C(5)–C(12)	120.7(3)	118.4
C(11)–C(5)–C(12)	118.8(3)	118.3
C(7)–C(6)–C(11)	119.9(4)	119.4
Cl(2)–C(7)–C(6)	119.5(4)	119.0
Cl(2)–C(7)–C(8)	119.0(3)	119.1
C(6)–C(7)–C(8)	121.5(4)	121.9
C(7)–C(8)–C(9)	118.7(4)	119.2
C(8)–C(9)–C(10)	121.3(4)	120.9
N(1)–C(10)–C(9)	118.7(4)	119.0
N(1)–C(10)–C(11)	122.4(4)	121.6
C(9)–C(10)–C(11)	118.9(4)	119.3
C(10)–N(1)–C(18)	119.7(4)	118.2
C(5)–C(11)–C(6)	118.2(3)	118.7
C(5)–C(11)–C(10)	122.2(3)	121.8
C(6)–C(11)–C(10)	119.6(4)	119.7
C(5)–C(12)–C(13)	120.2(4)	120.8
C(5)–C(12)–C(17)	120.0(3)	120.4
C(13)–C(12)–C(17)	119.8(4)	118.9
C(12)–C(13)–C(14)	120.0(4)	120.5
C(13)–C(14)–C(15)	120.5(4)	120.4
C(14)–C(15)–C(16)	120.1(4)	119.9
C(15)–C(16)–C(17)	120.1(5)	120.3
C(12)–C(17)–C(16)	118.8(4)	120.1
N(1)–C(18)–C(19)	113.1(5)	109.9
C(18)–C(19)–C(20)	120.1(6)	124.2
C(18)–C(19)–C(21)	117.4(7)	118.7
C(20)–C(19)–C(21)	62.8(6)	62.1
C(19)–C(20)–C(21)	61.3(6)	62.1
C(19)–C(21)–C(20)	55.9(5)	55.9
Cl(1)S–CS–Cl(2)S	108.4(6)	
Cl(1)S–CS–Cl(3)S	108.1(6)	
Cl(2)S–CS–Cl(3)S	112.5(7)	

[a]Average of two independent molecules, ref. 9.

radius of Pd(II) being slightly larger than that of Au(III), and with the *trans* influence of the Prazepam nitrogen donor atom being comparable, or even slightly lower, than that of a chloride ion.

The metal-coordinated Prazepam ligand is in the usual boat conformation and displays bond lengths and angles very close to those found in the free molecule (see Table VI). This similarity had been observed previously, although to a minor extent, in (Prazepam)$AuCl_3$ [3], whose structure determination was however affected by a lower precision. The C(5)–N(4) distance (1.289(5) Å) is typical of a C–N double bond: it falls into the range 1.27–1.29 Å found in the crystal structures of six different 1,4-benzodiazepin-2-ones, listed in ref. 11, and is statistically coincident with the C(5)–N(4) distance of 1.285 Å found in free Prazepam: this confirms the view that Pd and N(4) are involved in a pure sigma bond, without any contribution coming from the C(5)–N(4) π-system. The N(1)–C(2) and C(10)–N(1) distances are 1.385(5) and 1.418(5) Å, respectively, to be compared with the average values observed in the free ligand, 1.375 and 1.423 Å. Both these values are shorter than expected for a C–N single bond, in keeping with a partial electron delocalization along the whole O(1)–C(2)–N(1)–C(10) fragment, deriving from a conjugation of the N(1) lone pair with the C=O π-system and from an extension of the aromatic character of the chlorophenyl ring.

The conformational parameters of the Pd-coordinated Prazepam are also very similar to those of the free molecule [9]. Table VII lists some selected least-squares planes for **5a** and the corresponding dihedral angles for **5a**, **5b** (first molecule), the free ligand (first molecule), and (Prazepam)$AuCl_3$ [3]. Table VIII reports selected torsion angles for the same compounds.

TABLE VII. Least-squares Planes through Selected Groups of Atoms in the Form $Ax + By + Cz + D = 0$ (Compound **5a**)

Plane	Atoms	*A*	*B*	*C*	*D*
(i) Equations of planes					
1	C(5) C(11) C(10) N(1)	0.0892	0.8761	−0.4739	−0.7925
2	C(5) N(1) C(2) N(4)	0.7042	0.5879	−0.3982	1.1938
3	N(4) C(3) C(2)	−0.9489	0.3156	−0.0023	−1.8402
4	C(10) N(1) C(18) C(2) O(1) C(3)	0.4068	0.2731	−0.8717	2.6771
5	C(6) C(7) C(8) C(9) C(10) C(11) C(5) N(1)	0.0807	0.8775	−0.4728	−0.8230
6	N(1) C(18) C(19)	0.9282	−0.1342	−0.3470	3.4792

Plane	Atoms
(ii) Distances (Å × 10^3) of selected atoms from planes	
4	C(10) −71, N(1) 11, C(18) 68, C(2) −19, O(1) −66, C(3) 77
5	C(6) 5, C(7) −6, C(8) −2, C(9) 1, C(10) 3, C(11) 9, N(1) −3, C(5) −7

Planes	I[a]	II[b]	III[c]	IV[d]
(ii) Dihedral angles (°) between selected pairs of planes for Prazepam in different crystal structures				
1–2	40.0	36.6	41.1	36.7
2–3	61.2	62.3	58.3	58.4
4–5	133.2	135.1	132.5	137.7
5–6	83.0	85.5	99.7	100.4

[a]Present work, **5a**. [b]Prazepam, ref. 9, first molecule. [c]Present work, **5b**, first molecule. [d](Prazepam)$AuCl_3$, ref. 3.

TABLE VIII. Selected Torsion Angles (°)

	I[a]	II[b]	III[c]	IV[d]
N(4)–C(3)–C(2)–N(1)	69.7	73.9	67.7	66.8
C(3)–C(2)–N(1)–C(10)	9.3	3.3	10.3	8.8
C(2)–N(1)–C(18)–C(19)	130.3	118.5	103.1	101.3
C(10)–N(1)–C(18)–C(19)	−52.5	−59.1	−75.1	−84.2
N(1)–C(18)–C(19)–C(20)	−71.8	−77.0	160.7	158.0
N(1)–C(18)–C(19)–C(21)	−144.6	−149.5	91.5	93.2

[a]Present work, compound **5a**. [b]Prazepam, ref. 9, first molecule. [c]Present work, compound **5b**, first molecule. [d](Prazepam)$AuCl_3$, ref. 3.

The conformation of the cyclopropyl moiety deserves a wider discussion. We can compare the stereochemical parameters of six crystallographically independent Prazepam molecules, as found in four crystal structure determinations, *i.e.* those of the free ligand (two independent molecules) [9], (Prazepam)-$AuCl_3$ (one molecule) [3], compound **5a** (one molecule), and compound **5b** (two independent molecules). The conformations displayed by the cyclopropyl moiety in the six molecules, although not identical, can be roughly divided into two groups, both represented in Fig. 3. Figure 3a shows the conformation of the Prazepam ligand found in **5a**, which is similar to that of both the independent molecules of the free ligand, whereas Fig. 3b shows the conformation of the ligand in **5b** (first independent molecule), which also appears, with minor differences, in the second molecule of **5b** and in (Prazepam)$AuCl_3$. It is noteworthy that, when atoms C(20) and C(21) are ignored, the conformations of the Prazepam ligand are very similar in all the six molecules described. In particular, the plane of the atoms N(1)–C(18)–C(19) is in all cases approximately perpendicular to the best plane of phenyl ring C(6)–C(11), and it seems likely that this is due to the need of minimizing intramolecular non-bonded repulsions. However, in the three molecules represented in Fig. 3a, atoms C(20) and C(21) are displaced from the N(1)–C(18)–C(19) plane in the same direction as the C(2)–C(3)–N(4) fragment; in contrast, in the three molecules represented by Fig. 3b, atoms C(20) and C(21) are on the side of the N(1)–C(18)–C(19) plane where the C(6)–C(11) phenyl ring is located. In other terms, the torsion angle concerning atoms N(1), C(18), C(19) and the midpoint of vector C(20)–C(21) is negative in the three molecules represented by Fig. 3a and positive in those represented by Fig. 3b. It may be concluded that the overall conformations of the cyclopropyl fragments are very similar in molecules belonging to the same group, but markedly different among molecules of different groups. It also seems likely that the difference in energy between the two kinds of conformations must be small as far as intramolecular effects are concerned, either conformation being adopted in a particular crystal on the grounds of packing forces. Thus, on changing the solvent molecules in crystals of **5a** and **5b**, the two different conformations are adopted. The conformation represented by Fig. 3a has been suggested to be present in chloroform solution of the free Prazepam on the basis of ^{13}C NMR LIS investigations [12].

Experimental

The ligands Diazepam and Prazepam were provided by Roche and Parke-Davis respectively. They were used without further purification.

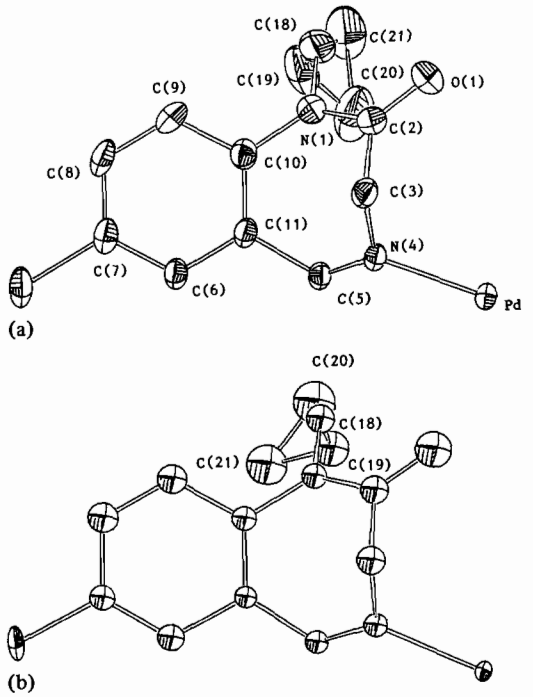


Fig. 3. Projection of a fragment of the Prazepam molecule onto the best plane of the C(6)–C(11) phenyl ring in compounds **5a** (a) and **5b** (b), showing the different conformations of the cyclopropyl moiety.

Analytical and other data are reported in Table I. ^1H NMR data in Tables II and III. Infrared spectra were recorded with Perkin-Elmer 1310 and 983 photometers using Nujol mulls. ^1H NMR spectra were recorded at 80 MHz using a Varian CFT-20 spectrometer, at room temperature (298 K).

Synthesis of the Adducts, trans-L_2PdCl_2, (1 and 5)

Typically, a solution of the ligand (1 mmol) in chloroform was added to a suspension of $PdCl_2$ (or a solution of $(PhCN)_2PdCl_2$) in the same solvent (molar ratio metal to ligand 1:2). The mixture was stirred for 48 h at room temperature. The yellow solution, after filtration, was concentrated to small volume: addition of diethyl ether gave the crude product, which was crystallized from chloroform/diethyl ether. Yield *ca.* 95%.

Synthesis of the Metallated Derivatives, [(L–H)PdCl]$_2$ (2 and 6)

A solution of the ligand (*ca.* 300 mg) in ethanol was added to a solution of $Na_2[PdCl]_4 \cdot 0.33H_2O$ in the same solvent (molar ratio 1:1). The solution was stirred for 48–72 h at room temperature: the yellow precipitate was filtered off, washed with ethanol and diethyl ether and then crystallized from chloroform/diethyl ether. Yield *ca.* 90%, **2** and **6**. The mother ethanol solution was concentrated to small volume and diethyl ether was added: a yellow precipitate was

TABLE IX. Crystal Data and Intensity Collection Parameters

	5a	5b
Formula	$C_{39}H_{35}Cl_7N_4O_2Pd$	$C_{39}H_{36}Cl_6N_4O_2Pd$
Formula weight (amu)	946.31	911.88
Crystal system	monoclinic	monoclinic
Space group	$P2_1/n$	$P2_1/c$
a (Å)	11.996(4)	14.074(3)
b (Å)	13.678(5)	14.622(7)
c (Å)	12.717(3)	19.360(10)
β (°)	98.83(2)	100.04(3)
U (Å^3)	2062(2)	3923(5)
Z	2	4
D_{calc} (g cm^{-3})	1.524	1.547
μ(Mo Kα) (cm^{-1})	9.39	9.18
Min. transmission factor	0.96	0.73
Scan mode	ω	ω
ω-scan width (°)	1.2 + 0.35 tan θ	1.2 + 0.35 tan θ
θ-range (°)	3–25	3–24
Octants of reciprocal space explored	$\pm h + k + l$	$\pm h + k + l$
Measured reflections	3681	5180
Unique observed reflections having $I \geq 3\sigma(I)$	2403	1919
Final R [a] and R_w [b] indices	0.032, 0.042	0.076, 0.090
No. variables	254	234
e.s.d.[c]	1.119	2.031

[a] $R = \Sigma(F_o - k\|F_c\|)/\Sigma F_o$. [b] $R_w = [\Sigma w(F_o - k\|F_c\|)^2/\Sigma w F_o^2]^{1/2}$. [c] e.s.d. $= [\Sigma w(F_o - k\|F_c\|)^2/(N_O - N_V)]^{1/2}$.

filtered off and crystallized twice from chloroform/diethyl ether. *Anal.* L = Diazepam, Found: C, 53.99; H, 4.17; N, 7.94. Calc. for [(L–H)(L)PdCl]; C, 53.98; H, 3.65; N, 7.87. L = Prazepam, Found: C, 56.96; H, 4.20; N, 6.91. Calc. for [(L–H)(L)PdCl]: C, 57.61; H, 4.29; N, 7.07%.

Reaction of 2 and 6 with Triphenylphosphine: Compounds 3 and 7

A solution of triphenylphosphine (60 mg) in chloroform was added to a suspension of compound **2** (or **6**) (90 mg) in the same solvent. The mixture was stirred at room temperature until a clear solution was obtained (*ca.* 1 h). The solution was concentrated to small volume and diethyl ether was added: the pale yellow precipitate was filtered off and crystallized from chloroform/diethyl ether. Yields *ca.* 90%.

Reaction of 2 and 6 with Thallium(I)acetylacetonate: Compounds 4 and 8

Compound **2** (150 mg) (or **6**) and Tl(acac) (100 mg) were suspended in chloroform (*ca.* 50 ml) and the mixture was stirred at room temperature (*ca.* 2 h). After removal of thallium(I)chloride, the orange solution was concentrated to small volume and hexane was added to give an orange precipitate. Yields 85%.

X-ray Structure of Compound 5

The two crystalline modifications of compound **5** were obtained in a form suitable for X-ray structure examination by slow evaporation of a $CHCl_3/Et_2O$ solution (**5a**) and CH_2Cl_2/Et_2O solution (**5b**).

The crystal data for compounds **5a** and **5b** are summarized in Table IX, together with some experimental details. The diffracted intensities were collected at room temperature on a CAD-4 diffractometer with Mo Kα radiation ($\lambda = 0.71073$) and reduced to F_o values corrected for absorption by the empirical method described in ref. 13. Both structures were solved by Patterson and Fourier methods, and refined by full-matrix least-squares, the minimized function being $\Sigma w(F_o - k|F_c|)^2$. Weights assigned to individual observations were $w = 1/\sigma^2(F_o)$, where $\sigma(F_o) = [\sigma^2(I) + (AI)^2]^{1/2}/2F_oL_p$ and $A = 0.05$ and 0.04 for **5a** and **5b**, respectively. The Enraf-Nonius SDP package of crystallographic programs was used, with the physical constants tabulated therein [14]. The real and imaginary components of the anomalous dispersion were taken from ref. 15. The hydrogen atoms were placed in calculated positions (C–H distance 0.95 Å). The atomic coordinates for non-hydrogen atoms of both compounds are reported in Tables IV and V.

Supplementary Material

Thermal parameters for non-hydrogen atoms for compounds **5a** and **5b**; and fractional atomic coordinates of hydrogen atoms for compound **5a** are available from the authors on request.

Acknowledgements

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