Mono and Dinuclear Gold(I) Complexes with Neutral and Deprotonated 1,4-Benzodiazepin-2-ones. Crystal and Molecular Structure of (L-H)Au(PPh_3)·Et_2O, where L = 1,3-Dihydro-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one, NITRAZEPAM

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Abstract

The preparation of a series of neutral (L)AuCl (**1a**–**3a**) and cationic [(L)Au(PPh_3)][BF_4] (**1b**–**5b**) gold(I) complexes is described (L = DIAZEPAM, **1**; PRAZEPAM, **2**; NITRAZEPAM, **3**; LORAZEPAM, **4**; NIMETAZEPAM, **5**).

In the presence of alkali, (PPh_3)AuCl reacts with 1-unsubstituted 1,4-benzodiazepin-2-ones such as NITRAZEPAM (**3**) and LORAZEPAM (**4**) to give neutral gold(I) species (L-H)Au(PPh_3) (**3c** and **4c**). The benzodiazepine anion is bonded to Au via the N(1) atom, as shown, in the case of **3c**, by X-ray analysis: (L-H)Au(PPh_3)·Et_2O, $C_{33}H_{25}AuN_3O_3P$·$C_4H_{10}O$, monoclinic, space group $P2_1/c$, a = 12.717(9), b = 19.270(7), c = 14.696(3) Å, β = 107.85(3)°, Z = 4. Au–P = 2.238(1), Au–N = 2.071(3) Å. The crystal structure was determined by standard methods and refined to R = 0.028 and R_w = 0.035 on the basis of 4456 unique reflections.

The complex **3c** reacts with [(Ph_3P)Au(S)][BF_4], as obtained from (PPh_3)AuCl and $AgBF_4$ in methanol, to give the dinuclear cationic species [(Ph_3P)Au{μ-(L-H)}Au(PPh_3)][BF_4] (**3d**) where the deprotonated NITRAZEPAM bridges two (Ph_3P)Au groups through the N(1) and N(4) atoms. All the new derivatives were characterized by elemental analyses and spectroscopic methods (IR; ^1H, ^{31}P NMR).

Introduction

Following our previous reports on the reactivity of gold(III) [1] and palladium(II) [2] ions with some 1,4-benzodiazepin-2-ones [3], in the current work we set out to synthesize a series of gold(I) derivatives with the same type of ligands. Our aim was to investigate the coordination modes of these molecules, which have great therapeutic importance, with a metal ion known to exert biological activity in its own right, and to get further information on the effect of coordination on the properties and structure of benzodiazepines.

In recent years, a few complexes of 1,4-benzodiazepin-2-ones have been studied by X-ray diffraction methods. In the adducts $(L)_2CuCl_2$ [4] (L = DIAZEPAM, **1**), (L)$AuCl_3$ [1] and *trans*$(L)_2PdCl_2$ [2] (L = PRAZEPAM, **2**) the ligand binds the metal through the N(4) atom, and is only slightly affected by coordination.

In a mercury(II) adduct, (L)$HgCl_2$ [5] (L = TEMAZEPAM: 7-chloro-3-hydroxy-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one), besides the 4-nitrogen atom, the keto oxygen and the 3-hydroxy group were found to interact with a dimeric $HgCl_2$ unit, to give a polymeric structure. In the adducts of some benzodiazepines having a 5-pyridyl substituent, chelation through N(4) and the pyridine-nitrogen was observed [6].

Besides the adducts, in the chemistry of palladium(II) with molecules such as DIAZEPAM (**1**) and PRAZEPAM (**2**) which have a 5-phenyl substituent, even complexes of the deprotonated ligands were obtained, e.g. $[(L\text{-}H)PdCl]_2$ and [(L-H)(Ph_3P)PdCl] [2]. The latter were shown to be organopalladium species: the ligand is coordinated via N(4) and the *ortho*-carbon atom of the 5-phenyl substituent [2, 7].

On the whole it seems that the N(4) atom is the preferred donor site. A N(4)–metal bond was found in all the complexes which have been investigated so far by X-ray methods.

Other coordination modes have been claimed [8], including coordination of the neutral ligands via N(1): however, none of them has been ascertained.

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Here we report three sets of complexes of gold(I):

(a) neutral (L)AuCl (**1a–3a**) and cationic $[(L)Au(PPh_3)]^+$ (**1b–5b**) species, where, according to spectroscopic evidences, the ligands are likely to be bonded via N(4);

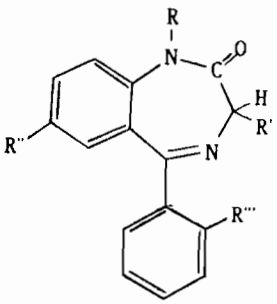
(b) neutral complexes of 1-unsubstituted benzodiazepines such as NITRAZEPAM (**3**) and LORAZEPAM (**4**) where the ligand acts as an anion through the N(1) atom, giving (imido)gold triphenylphosphine complexes $(L\text{-}H)Au(PPh_3)$ (**3c** and **4c**). The structure of **3c** was solved by X-ray diffraction;

(c) binuclear gold(I) complexes obtained by reaction of the imido species **3c** with $[(Ph_3P)Au(S)][BF_4]$ (S = solvent). In the resulting $[(L\text{-}H)\{Au(PPh_3)\}_2][BF_4]$ complex (**3d**), the deprotonated ligand bridges two $(Ph_3P)Au$ moieties through N(1) and N(4).

In the complexes (a)–(c) the 1,4-benzodiazepin-2-ones, (L), display different behaviour. Of these, (b) and (c) are unprecedented in the coordination chemistry of 1,4-benzodiazepin-2-ones. A preliminary report of this work has been given [9].

Results and Discussion

All the 1,4-benzodiazepin-2-ones which were used (**1–5**) contain a 5-phenyl substituent: two of them, namely **3** and **4**, NITRAZEPAM and LORAZEPAM respectively, are N-1 unsubstituted.



1, DIAZEPAM (D): R = CH_3; R′ = H; R″ = Cl; R‴ = H

2, PRAZEPAM (P): R = $CH_2\text{–}\overline{CH\text{–}CH_2\text{–}CH_2}$; R′ = H; R″ = Cl; R‴ = H

3, NITRAZEPAM (N): R = H; R′ = H; R″ = NO_2; R‴ = H

4, LORAZEPAM (LOR): R = H; R′ = OH; R″ = Cl; R‴ = Cl

5, NIMETAZEPAM (NIM): R = CH_3; R′ = H; R″ = NO_2; R‴ = H

The synthesis of the neutral complexes (L)AuCl (**1a–3a**) according to reaction (1) is not straightforward: yields are often low and variable amounts

$$\{(CH_3)_2S\}AuCl + L \longrightarrow (L)AuCl + (CH_3)_2S \qquad (1)$$

of unreacted starting material are recovered. The complexes **1a–3a**, which are white when freshly prepared, rapidly become violet on exposure to light.

In dichloromethane solution they are non-electrolytes: in agreement, all of them show, in the IR spectrum (nujol mull) a strong absorption in the range 353–347 cm^{-1}, i.e. in the range expected for the stretch of a gold(I)–Cl bond *trans* to a nitrogen ligand [10]. In contrast, ionization is observed for all the adducts in acetone solution.

In the ^1H NMR spectra ($CDCl_3$ solution, room temperature (r.t.)) no free ligand is detected: a resonance with an AB pattern is easily assigned to the protons of the CH_2 group. As previously observed [1, 2], the value of the geminal H–H coupling constant increases upon coordination. For complex **3a**, (L)AuCl, (L = NITRAZEPAM), at room temperature, a singlet is observed, as in the free molecule. In the assumption of a boat conformation of the ring, the fast exchange between the CH_2 protons is likely to be related to an easy inversion of the seven-membered cycle.

No reaction occurs between $(Ph_3P)AuCl$ and the ligands, even in the presence of a non-coordinating anion such as BF_4^-. The synthesis of the cationic species **1b–5b** requires previous removal of the chloride ligand by means of a silver salt (eqn. (2))

$$(Ph_3P)AuCl + AgBF_4 \xrightarrow{S = CH_3OH} [(Ph_3P)Au(S)][BF_4] + AgCl$$

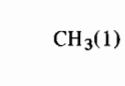
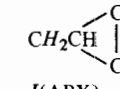
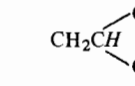
$$[(Ph_3P)Au(S)][BF_4] + L \longrightarrow [(Ph_3P)Au(L)][BF_4] \qquad (2)$$

The white complexes are air and moisture stable in the solid state: in acetone solution they behave as 1:1 electrolytes. In the IR spectrum (nujol mull and $CHCl_3$ solution) they show strong absorptions in the regions 1715–1680 and 1620–1590 cm^{-1}. The two sets of 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 adducts having the ligand coordinated through the N(4) atom [1, 2].

In the ^1H NMR spectra (Table 1), the AB system due to the CH_2 protons is shifted to lower field with respect to the free ligands. For $[(Ph_3P)Au(L)]^+$ (**3b**) (L = NITRAZEPAM) the AB pattern is observed only at low temperature: at r.t. a sharp singlet appears at **4**.59 δ, 0.23 ppm downfield from the free ligand (4.36 δ). For comparison, the CH_2 protons resonate at 4.80 δ in the protonated ligand (BF_4 salt).

In the ^{31}P NMR spectra (Table 2) two signals are observed with integral ratios function of temperature and concentration. The most intense signal, in the range 28.7–29.7 ppm, is assigned to the

TABLE 1. ^{1}H NMR data (δ)

Compound	Aromatic	CH_2(3) J(AB)	CHOH(3) J(AB)	CH_3(1)	 J(ABX)			NH
DIAZEPAM (1)	7.70–7.30	4.80, 3.74 (10.8)		3.34				
PRAZEPAM (2)	7.86–7.08	4.64, 3.95 (10.25)			4.15, 3.40 (14.22)	0.96	0.24	
NITRAZEPAM (3)[a]	8.59–7.47	4.71, 4.04 (10.5)						10.55
LORAZEPAM (4)	7.70–7.06		5.07, 4.81 (9.0)					9.71
NIMETAZEPAM (5)	8.59–7.42	4.86, 4.04 (10.4)		3.46				
[NH][BF_4]	8.82–7.63	4.80						11.0
D–Au–Cl (1a)	7.80–7.30	4.72, 3.92 (12.2)		3.39				
P–Au–Cl (2a)	7.85–7.08	5.01, 4.17 (11.63)			4.19, 3.65 (14.50)	0.99	0.35	
N–Au–Cl (3a)	8.84–7.57	4.80						11.06
[D–Au–PPh_3][BF_4] (1b)	7.98–7.17	4.98; 4.32 (12.5)		3.53				
[P–Au–PPh_3][BF_4] (2b)	8.0–7.0	4.94, 4.31 (12.27)			4.24, 3.72 (14.4)	1.0	0.35	
[N–Au–PPh_3][BF_4] (3b)[b]	8.36–7.08	4.94, 4.24 (11)						10.33
[Lor–Au–PPh_3][BF_4] (4b)[c]	8.36–7.07		6.11, 5.15 (7.3) 6.56, 5.50 (5.1)					10.88
[Nim–Au–PPh_3][BF_4] (5b)	8.54–7.15	5.0, 4.35 (12.6)		3.59				
(N-H)–Au–PPh_3 (3c)[d]	8.3–7.24	4.96, 3.70 (9.8)						
(Lor-H)–Au–PPh_3 (4c)	7.70–7.0	5.19, 4.87 (8.57)						
[(N-H)($AuPPh_3$)$_2$][BF_4] (3d)[e]	8.47–7.00	5.09, 4.11 (11.3)						

[a] $t = -50$ °C; at room temperature, $\delta(CH_2)$ 4.36s. [b] $t = -50$ °C; at room temperature, $\delta(CH_2)$ 4.59s (sharp); δ(NH) 10. [c] $t = -50$ °C; the signal at δ 5.15 is further split into a doublet which is likely to be due to a long range coupling with ^{31}P ($^4J(^1H-^{31}P)$ 3.0 Hz). [d] $t = -50$ °C; at room temperature, $\delta(CH_2)$ 4.34s (sharp). [e] $t = -50$ °C; at room temperature, $\delta(CH_2)$ 4.58, broad.

TABLE 2. ^{31}P NMR data

Compound	$\delta(PPh_3)$	Integral ratio
$[(Ph_3P)_2Au][BF_4]$	44.98	
$[D-Au-PPh_3][BF_4]$ (**1b**)	45.03; 28.80	1:4
$[P-Au-PPh_3][BF_4]$ (**2b**)	45.01; 28.90	1:13
$[N-Au-PPh_3][BF_4]$ (**3b**)	45.0; 30.92; 28.78	1.5:1:3
$[Lor-Au-PPh_3][BF_4]$ (**4b**)	45.0; 31.0; 29.65	1:1:4
$[Nim-Au-PPh_3][BF_4]$ (**5b**)	45.04; 28.73	1:5
$(N\text{-}H)-Au-PPh_3$ (**3c**)	31.31	
$(Lor\text{-}H)-Au-PPh_3$ (**4c**)	31.58	
$[(N\text{-}H)(AuPPh_3)_2][BF_4]$ (**3d**)	30.96; 28.75	1:1

cationic complex. The resonance at *c.* 45 ppm, observed in most cases and independent of the ligand (L), can be assigned to the $[(Ph_3P)_2Au]^+$ species, by comparison with the spectrum of an authentic sample obtained from $[(Ph_3P)Au(S)]^+$ and Ph_3P (molar ratio 1:1). In addition, for the complexes **3b** and **4b**, i.e. with the 1-unsubstituted ligands, a third signal at *c.* 31 ppm is observed and is likely to be due to the $(Ph_3P)Au(L\text{-}H)$ species (see later). According to preliminary data, the $[(Ph_3P)_2Au]^+$ cation is formed even in vapour phase as shown by MS experiments carried out under FAB conditions.

In the presence of alkali (reaction (3)), in methanol solution, the ligands **3** and **4** react with (Ph_3P)-AuCl to give complexes of the deprotonated benzodiazepines, **3c** and **4c**, respectively.

$$(Ph_3P)AuCl + L + KOH \xrightarrow{CH_3OH} (Ph_3P)Au(L\text{-}H) + KCl + H_2O \quad (3)$$

Metallation of the ligands through the C(3) atom is ruled out by the ^1H NMR spectra. The broad signal observed at room temperature for the CH_2 protons in complex **3c**, separates into a well resolved AB system at low temperature (−50 °C). On the other hand, no N–H resonance is observed, suggesting coordination of the anionic ligand through the N(1) atom.

In agreement, the resonances at 31.31 (**3c**) and 31.58 (**4c**) ppm, observed in the ^{31}P NMR spectra, are comparable with the resonance at 32.7 ppm reported for $(Ph_3P)Au$(phtalimido) [11], i.e. for a molecule having a phosphorus *trans* to a nitrogen atom. However the lack in the IR spectrum of the

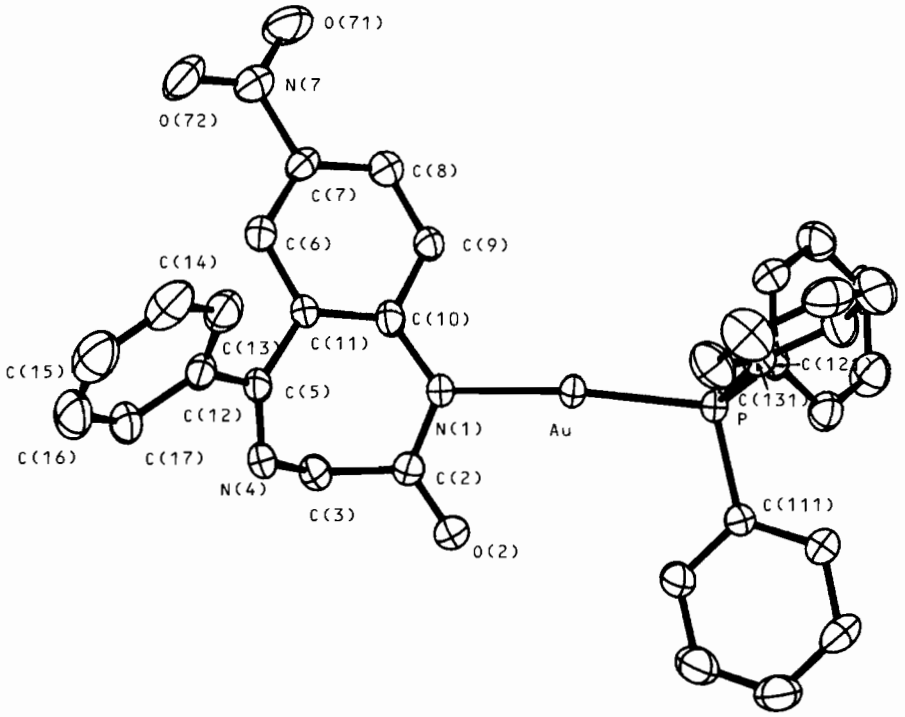


Fig. 1. ORTEP drawing of complex **3c**. Thermal ellipsoids are drawn at 30% probability.

TABLE 3. Selected bond distances (Å) and angles (°) with e.s.d.s in parentheses

Au–N(1)	2.071(3)	Au–P	2.238(1)
N(1)–C(10)	1.385(5)	N(1)–C(2)	1.352(5)
C(2)–C(3)	1.518(6)	C(3)–N(4)	1.449(6)
N(4)–C(5)	1.272(5)	C(5)–C(11)	1.491(6)
C(11)–C(10)	1.414(6)	C(11)–C(6)	1.382(6)
C(6)–C(7)	1.388(6)	C(7)–C(8)	1.379(6)
C(8)–C(9)	1.362(6)	C(9)–C(10)	1.417(6)
C(7)–N(7)	1.473(6)	C(5)–C(12)	1.501(7)
N(7)–O(71)	1.213(6)	N(7)–O(72)	1.212(6)
C(12)–C(13)	1.410(7)	C(13)–C(14)	1.410(8)
C(14)–C(15)	1.348(10)	C(15)–C(16)	1.357(10)
C(16)–C(17)	1.396(8)	C(17)–C(12)	1.396(6)
C(2)–O(2)	1.216(5)	P–C(111)	1.818(5)
P–C(121)	1.814(5)	P–C(131)	1.820(5)
N(1)–Au–P	174.1(1)	Au–N(1)–C(10)	124.9(3)
Au–N(1)–C(2)	112.3(3)	C(2)–N(1)–C(10)	122.2(4)
N(1)–C(10)–C(11)	125.6(4)	C(10)–C(11)–C(5)	121.1(4)
C(11)–C(5)–N(4)	124.1(4)	C(5)–N(4)–C(3)	117.2(4)
N(4)–C(3)–C(2)	108.3(4)	C(3)–C(2)–N(1)	116.5(4)
C(3)–C(2)–O(2)	120.8(4)	N(1)–C(2)–O(2)	122.7(4)
N(4)–C(5)–C(12)	117.3(4)	C(11)–C(5)–C(12)	118.6(4)
C(6)–C(11)–C(10)	121.4(4)	C(11)–C(6)–C(7)	118.4(4)
C(6)–C(7)–C(8)	122.6(4)	C(7)–C(8)–C(9)	118.7(4)
C(8)–C(9)–C(10)	122.0(4)	C(9)–C(10)–C(11)	116.8(4)
C(6)–C(7)–N(7)	117.8(4)	C(8)–C(7)–N(7)	119.6(4)
C(7)–N(7)–O(71)	118.7(5)	C(7)–N(7)–O(72)	118.2(5)
O(71)–N(7)–O(72)	123.0(5)	N(1)–C(10)–C(9)	117.4(4)
C(5)–C(11)–C(6)	117.4(4)		

typical absorption in the range 1720–1680 cm^{-1}, assigned in the free ligand to the prevailing contribution of ν(CO) and observed in all the adducts, made questionable the coordination mode of the ligand. Attack of the (Ph_3P)Au moiety to the oxygen atom of the tautomeric form $-N(1)=C(OH)-CH_2-$, although unlikely, could not be completely excluded.

The X-ray structure analysis of complex **3c** removed any doubts as to the structure, showing coordination through the N(1) atom. A perspective drawing of complex **3c** is shown in Fig. 1. Selected bond distances and angles are listed in Table 3.

Crystals of compound **3c** consist of (L-H)Au-(Ph_3P) (L = NITRAZEPAM) discrete molecules and clathrated diethyl ether molecules, packed with normal van der Waals interactions. The coordination around the gold atom is approximately linear: the deviation from linearity, as shown by the P–Au–N(1) angle, 174.1(1)°, is larger than in (Ph_3P)Au-(adeninate) (**6**) 177.6(1)° [12] or (Ph_3P)Au (1-methylthyminato-N(3)) (**7**) 178.7(4)° [13], but comparable with that observed in (Ph_3P)Au(6-methylpyridonato-N) (**8**) 173.4(3)° [14]. The large variety of values observed for the P–Au–N angle is related to packing effects.

The Au–P and Au–N distances, 2.238(1) and 2.071(3) Å, respectively, are in the range of values found in related species, e.g. 2.240(1) and 2.038(4) Å in **6**, 2.236(3) and 2.077(9) Å in **8**, 2.233(5) and 2.022(12) Å in 1,3-bis(triphenylphosphinegold)-5,5-diethylbarbituric acid [15] and 2.238(6) and 2.05(2) Å in (Et_3P)Au(phthalimido) [11].

The geometry of the coordinated benzodiazepine is very similar to that of the free molecule: most of the bond distances and angles are statistically coincident within three e.s.d.s [16]. A good agreement is also observed for the conformational parameters. The seven-membered ring is in the boat-type conformation with the C(5)–C(11)–C(10)–N(1) and the C(5)–N(4)–C(2)–N(1) moieties planar. The dihedral angle between these planes is 145.7° and that between the C(5)–N(4)–C(2)–N(1) and N(4)–C(3)–C(2) planes is 62.0°. The plane through the nitro group makes an angle of 7.8° with the C(6)–C(11) phenyl plane (6.6° in NITRAZEPAM). The torsion angle C(11)–C(5)–C(12)–C(13) is 35.1° (34.5° in NITRAZEPAM).

The conformational parameters seem to be almost invariant, as can be inferred from the structural data of various benzodiazepin-2-ones [17] as well as of their metal complexes [1, 2, 4]. They are likely to be determined by intramolecular contacts rather than by intermolecular packing effects. In spite of the remarkable differences, observed in the 1720–1590 cm^{-1} region of the IR spectrum,

between the free ligand and the $(Ph_3P)Au$-containing molecule, no significant difference is found for the N(1)–C(2), 1.352(5) Å, and C(2)–O(2), 1.216(5) Å, distances (1.362(4) and 1.225(5) Å, respectively, in the free ligand). A difference, however, is found in the value of the C(2)–N(1)–C(10) angle: 122.2(4)° in complex **3c** and 126.1(3)° in the free molecule. The same trend is found on going from 1-unsubstituted benzodiazepin-2-ones such as NITRAZEPAM, to a N(1)-alkyl substituted molecule, e.g. DIAZEPAM, (R = CH_3), where the C(2)–N(1)–C(10) angle is 123.1(2)°.

In conclusion it seems that, besides the striking difference due to the existence of intermolecular N(1)–H···O hydrogen bonds in NITRAZEPAM [16], substitution at N(1) of the isolobal but bulkier $(Ph_3P)Au$ unit, only slightly affects the structure of the ligand. The minor differences observed between the two structures are comparable with those induced by replacement of H at N(1) with an alkyl group.

The imido-gold complex **3c** reacts with various acidic reagents HX (X = Cl, BF_4, $S(C_6H_4CH_3p)$ with displacement of NITRAZEPAM (L) (eqns. (4)–(6)).

$$(L\text{-}H)Au(PPh_3) + HCl \longrightarrow (Ph_3P)AuCl + L \quad (4)$$

$$(L\text{-}H)Au(PPh_3) + HBF_4 \longrightarrow [\{(Ph_3P)Au\}_3O][BF_4] + L \quad (5)$$

$$(L\text{-}H)Au(PPh_3) + HSR \longrightarrow (Ph_3P)AuSR + L \quad (6)$$

With tetrafluoboric acid (eqn. (5)), no simple solvato species is obtained: work up of the reaction mixture (see 'Experimental') affords the well known polynuclear complex $[\{(Ph_3P)Au\}_3O][BF_4]$ [18], which is likely to form in presence of traces of water.

The cleavage of the nitrogen–gold bond is easily attained even by reaction with a weak acid. Thus, as expected in view of the soft character of gold(I), reaction with a thiol, RSH, gives, in good yields, the complex $(Ph_3P)Au$–SR. In the ^{31}P NMR spectrum, one signal appears at 38.75 ppm, i.e. at position typical for a P–Au–S arrangement (P = PPh_3) [19].

In the imido complexes, **3c** and **4c**, the (triphenylphosphino)gold moiety is bonded to the N(1) atom: the N(4) atom is not involved in coordination. Since the latter atom is the preferred site of coordination for the benzodiazepin-2-ones, attempts were made to employ the gold derivatives (e.g. **3c**) as ligands through N(4). So far, only the dinuclear gold(I) derivative **3d** has been obtained, according to reactions (7) and (8).

$$(Ph_3P)AuCl + AgBF_4 \xrightarrow{CH_3OH = S} [(Ph_3P)Au(S)][BF_4] \quad (7)$$

$$[(Ph_3P)Au(S)][BF_4] + (L\text{-}H)Au(PPh_3) \longrightarrow [(Ph_3P)Au\{\mu\text{-}(L\text{-}H)\}Au(PPh_3)][BF_4] \quad (8)$$

The dinuclear complex **3d** behaves as a 1:1 electrolyte in acetone solution. The pattern of the IR spectrum (nujol), in the region 1720–1590 cm^{-1}, reminds us that of the parent complex (L-H)Au-(PPh_3). The absence of the absorption around 1700 cm^{-1} seems to be typical of the N(1)–metal substituted benzodiazepines. In the ^1H NMR spectrum, the CH_2 protons give a broad signal at δ 4.58, which split into the usual **AB** resonance at low temperature. In the $^{31}P\{^1H\}$ spectrum, two well separated signals (1/1) at 30.96 and 28.75 ppm can be assigned, by comparison with the spectra of **3c** and **3b**, to the phosphorous atoms *trans* to N(1) and N(4), respectively. Both the signals are rather broad at room temperature and become sharp at *c.* 0 °C.

Attempts to build up heterodinuclear systems (e.g. gold–palladium), were unsuccessful: so far, only mixture of products, probably arising from scrambling of the ligands, were obtained.

In conclusion it seems that an extensive series of gold(I) derivatives of 1,4-benzodiazepin-2-ones can be synthesized. Among these, the imido gold(I) complexes appear to be quite similar to the organic molecules as for the structure as well as for the reactivity. Of the full set of the possible molecules, H–N(1)N(4), $(Ph_3P)Au$–N(1)N(4), [H–N(1)N(4)-H]$^+$, [H–N(1)N(4)-Au(PPh_3)]$^+$, [(Ph_3P)Au–N(1)-N(4)-Au(PPh_3)]$^+$, [(Ph_3P)Au–N(1)N(4)-H]$^+$, where the hydrogen atom and the $(Ph_3P)Au$ unit are vicarious, only the last species has not been obtained, owing to the easy cleavage of the gold(I)–N(1) bond brought about by acids.

Experimental

The ligands **1**, **3**, **4** and **5** were provided by Roche and ligand **2** by Parke-Davis. They were used without further purification; $(CH_3)_2SAuCl$ and Ph_3PAuCl were prepared according to known procedures.

Elemental analyses were performed on a Perkin-Elmer 240B Elemental Analyzer (Sassari) and by Mikroanalytisches Labor Pascher (Remagen, F.R.G.). The ^1H and $^{31}P\{^1H\}$ NMR data are reported in Tables 1 and 2 respectively. The spectra were recorded with a Bruker WP 80 instrument. Infrared spectra were recorded with Perkin-Elmer 1310 and 983 spectrophotometers.

*Synthesis of the adducts (L)AuCl (**1a**; **2a**; **3a**) (L = DIAZEPAM, 1; PRAZEPAM, 2; NITRAZEPAM, 3)*

An acetone solution of L (e.g. 284.7 mg of **1**, 1 mmol) and $(CH_3)_2SAuCl$ (294.5 mg, 1 mmol) was stirred for 10–20 h at room temperature. A small amount of metallic gold was formed. After

filtration, the solution was concentrated and unreacted {$(CH_3)_2S$}AuCl was filtered off. The solution was concentrated to small volume and diethyl ether added to give a pale yellow precipitate which was crystallized from $CHCl_3$/diethyl ether to give the analytical sample.

D–Au–Cl, **1a**; yield 35%, melting point (m.p.) 144–146 °C. *Anal.* Found: C, 36.78; H, 3.18; N, 5.05. Calc. for $C_{16}H_{13}AuCl_2N_2O$: C, 37.12; H, 2.51; N, 5.41%. IR (nujol; cm^{-1}): 1690vs; 1600m; 348 cm^{-1}, ν(Au–Cl). Λ_M (5×10^{-4} M) CH_2Cl_2: 5.5; $(CH_3)_2CO$: 88 ohm^{-1} cm^2 mol^{-1}.

P–Au–Cl, **2a**; yield 35%, m.p. 139–140 °C. *Anal.* Found: C, 40.72; H, 3.08; N, 4.92. Calc. for $C_{19}H_{17}AuCl_2N_2O$: C, 40.91; H, 3.05; N, 5.02%. IR (nujol; cm^{-1}): 1665vs; 1580s; 353 cm^{-1}, ν(Au–Cl). Λ_M (5×10^{-4} M) CH_2Cl_2: 3.8; $(CH_3)_2CO$: 38 ohm^{-1} cm^2 mol^{-1}.

N–Au–Cl, **3a**; yield 50%, m.p. 242–244 °C. *Anal.* Found: C, 34.51; H, 2.44; N, 7.76. Calc. for $C_{15}H_{11}AuClN_3O_3$: C, 35.04; H, 2.14; N, 8.17%. IR (nujol; cm^{-1}): 1710vs; 1590s; 347 cm^{-1}, ν(Au–Cl). Λ_M (5×10^{-4} M) CH_2Cl_2: not observed; $(CH_3)_2CO$: 115 ohm^{-1} cm^2 mol^{-1}.

Synthesis of the adducts [(L)Au(PPh$_3$)][BF$_4$] (1b; 2b; 3b; 4b; 5b) (L = DIAZEPAM, 1; PRAZEPAM, 2; NITRAZEPAM, 3; LORAZEPAM, 4; NIMETAZEPAM, 5)

A methanolic solution of $AgBF_4$ (97.3 mg, 0.5 mmol) was added to a solution of Ph_3PAuCl in the same solvent (247.2 mg, 0.5 mmol). After removal of AgCl, a methanolic solution of L (e.g. 142.3 mg of **1**, 0.5 mmol) was added. The resulting solution was stirred for 2–3 h at room temperature and then evaporated to dryness. The residue was dissolved in $CHCl_3$, filtered and concentrated to small volume: addition of diethyl ether gave a white precipitate, which was crystallized from $CHCl_3$/diethyl ether to give the analytical sample.

[D–Au–PPh_3][BF_4], **1b**; yield 65–70%, m.p. 220–221 °C. *Anal.* Found: C, 49.59; H, 3.47; N, 3.09. Calc. for $C_{34}H_{28}AuBClF_4N_2OP$: C, 49.12; H, 3.37; N, 3.37%. IR (nujol; cm^{-1}): 1680vs; 1595s; 1050vs (broad), ν(BF_4). Λ_M (5×10^{-4} M) $(CH_3)_2CO$: 149 ohm^{-1} cm^2 mol^{-1}.

[P–Au–PPh_3][BF_4], **2b**; yield 65–70%, m.p. 115–116 °C. *Anal.* Found: C, 50.65; H, 3.95; Au, 23.0; N, 3.16. Calc. for $C_{37}H_{32}AuBClF_4N_2OP$: C, 51.0; H, 3.67; Au, 22.6; N, 3.21%. IR (nujol; cm^{-1}): 1680vs; 1590s; 1060vs (broad), ν(BF_4). Λ_M (5×10^{-4} M); $(CH_3)_2CO$: 138 ohm^{-1} cm^2 mol^{-1}.

[N–Au–PPh_3][BF_4], **3b**; yield 65–70%, m.p. 232–233 °C. *Anal.* Found: C, 47.44; H, 3.38; N, 4.80. Calc. for $C_{33}H_{26}AuBF_4N_3O_3P$: C, 47.88; H, 3.14; N, 5.07%. IR (nujol; cm^{-1}): 1715vs; 1600s; 1060vs (broad), ν(BF_4). Λ_M (5×10^{-4} M) $(CH_3)_2CO$: 128 ohm^{-1} cm^2 mol^{-1}.

[Lor–Au–PPh_3][BF_4], **4b**; yield 65–70%, m.p. 169–170 °C. *Anal.* Found: C, 47.64; H, 3.18; N, 2.47. Calc. for $C_{33}H_{25}AuBCl_2F_4N_2O_2P \cdot Et_2O$: C, 47.18; H, 3.72; N, 2.97%. IR (nujol; cm^{-1}): 1710vs; 1620s; 1590s; 1055vs (broad), ν(BF_4). Λ_M (5×10^{-4} M) $(CH_3)_2CO$: 112 ohm^{-1} cm^2 mol^{-1}.

[Nim–Au–PPh_3][BF_4], **5b**; yield 65–70%, m.p. 216–217 °C. *Anal.* Found: C, 48.86; H, 3.55; N, 4.88. Calc. for $C_{34}H_{28}AuBF_4N_3O_3P$: C, 48.51; H, 3.33; N, 4.99%. IR (nujol; cm^{-1}): 1700vs; 1605s; 1590s; 1050vs (broad), ν(BF_4). Λ_M (5×10^{-4} M) $(CH_3)_2CO$: 140 ohm^{-1} cm^2 mol^{-1}.

Synthesis of the metallated derivatives (L-H)Au(PPh$_3$) (3c; 4c) (L = NITRAZEPAM, 3; LORAZEPAM, 4)

Addition of methanolic 0.5 M KOH (1 ml) to a methanolic solution of L (e.g. 140 mg of **3**, 0.5 mmol) gave an intense yellow solution. To the solution, Ph_3PAuCl (247.2 mg, 0.5 mmol) dissolved in methanol was added: the mixture was stirred for 3–4 h at room temperature and then evaporated to dryness. The residue was dissolved in $CHCl_3$, filtered to remove KCl, and concentrated to small volume; addition of diethyl ether gave a white precipitate which was crystallized from $CHCl_3$/diethyl ether to give the analytical sample.

(N-H)–Au–PPh_3, **3c**; yield 84%, m.p. 209–211 °C. *Anal.* Found: C, 53.49; H, 3.68; Au, 26.7; N, 5.48. Calc. for $C_{33}H_{25}AuN_3O_3P$: C, 53.56; H, 3.38; Au, 26.6; N, 5.68%. IR (nujol; cm^{-1}): 1615vs, 1590vs, ν(C=O) + ν(C=N), 1550s. Λ_M (5×10^{-4} M) $(CH_3)_2CO$: 4.4 ohm^{-1} cm^2 mol^{-1}.

(Lor-H)–Au–PPh_3, **4c**; yield 70%, m.p. 135–136 °C. *Anal.* Found: C, 50.64; H, 3.05; N, 3.23. Calc. for $C_{33}H_{24}AuCl_2N_2O_2P$: C, 50.82; H, 3.08; N, 3.59%. IR (nujol; cm^{-1}): 1615vs (broad), ν(C=O) + ν(C=N). Λ_M (5×10^{-4} M) $(CH_3)_2CO$: 3.4 ohm^{-1} cm^2 mol^{-1}.

Reaction of (N-H)Au(PPh$_3$) (3c) with HCl

Addition of 0.1 M HCl (2 ml, 0.2 mmol) to a methanolic solution of compound **3c** (148 mg, 0.2 mmol) gave a white precipitate which was filtered off and identified as Ph_3PAuCl. The mother solution was concentrated to small volume: a precipitate was filtered and identified as NITRAZEPAM (**3**).

Reaction of (N-H)Au(PPh$_3$) (3c) with HBF$_4$

Addition of $HBF_4 \cdot Et_2O$ (0.1 ml, 0.63 mmol) to a chloroform solution of compound **3c** (140 mg, 0.19 mmol) gave a white precipitate which was filtered off, washed with $CHCl_3$ and diethyl ether and then crystallized from $(CH_3)_2CO$/diethyl ether to give the tetrafluoroborate salt, [NH][BF_4]; m.p. 271–272 °C. *Anal.* Found: C, 47.62; H, 3.18; N, 10.82. Calc. for $C_{15}H_{12}BF_4N_3O_3$: C, 48.78; H, 3.25; N, 11.38%. IR (nujol; cm^{-1}): 3580s; 3510s; 3270s;

1715s; 1640m; 1050s (broad), $\nu(BF_4)$. Λ_M (5×10^{-4} M) $(CH_3)_2CO$: 111 ohm^{-1} cm^2 mol^{-1}.

A second product, obtained by concentration of the chloroform mother solution and addition of diethyl ether, was identified as $[\{(Ph_3P)Au\}_3O][BF_4]$: m.p. 220–221 °C (literature [18]: 220–221 °C). *Anal.* Found: C, 42.42; H, 3.25. Calc. for $C_{54}H_{45}Au_3BF_4OP_3$: C, 43.78; H, 3.04. IR (nujol; cm^{-1}): 1050s (broad), $\nu(BF_4)$.

Reaction of (N-H)Au(PPh$_3$) (3c) with HSR (R = p-CH$_3$C$_6$H$_4$)

A solution containing RSH (59 mg, 0.47 mmol) and compound **3c** (300.5 mg, 0.4 mmol) in methanol (30 ml) was stirred for 1 h at room temperature and then evaporated to dryness. The residue was taken up with diethyl ether to give a white product which was filtered off and identified as NITRAZEPAM (**3**) (m.p. and IR criterion). The diethyl ether solution was evaporated to dryness: to the residue, dissolved in $CHCl_3$, n-hexane was added to give a white product.

$(Ph_3P)Au(SR)$: yield 86%; m.p. 152–153 °C. *Anal.* Found: C, 51.79; H, 3.93. Calc. for $C_{25}H_{22}AuPS$: C, 51.54; H, 3.78. Λ_M (5×10^{-4} M) CH_2Cl_2: not observed. $^{31}P\{^1H\}$ NMR: 38.75 ppm ($CDCl_3$).

Synthesis of [(L-H)(AuPPh$_3$)$_2$][BF$_4$] (3d) (L = NITRAZEPAM, 3)

A methanolic solution of $AgBF_4$ (65 mg, 0.33 mmol) was added to a solution of Ph_3PAuCl in the same solvent (164.8 mg, 0.33 mmol). After removal of AgCl, a methanolic solution of (N-H)$AuPPh_3$ (**3c**) (246.4 mg, 0.33 mmol) was added. The resulting solution was stirred for 1 h at room temperature and then evaporated to dryness; the residue was dissolved in $CHCl_3$, filtered, and concentrated to small volume. Addition of diethyl ether gave a white precipitate, which was crystallized from $CHCl_3$/diethyl ether to give the analytical sample.

$[(L\text{-}H)(AuPPh_3)_2][BF_4]$, **3d**; yield 80%; m.p. 180–181 °C. *Anal.* Found: C, 47.56; H, 3.16; N, 3.25. Calc. for $C_{51}H_{40}Au_2BF_4N_3O_3P_2$: C, 47.62; H, 3.11; N, 3.26%. Λ_M (5×10^{-4} M) $(CH_3)_2CO$: 108 ohm^{-1} cm^2 mol^{-1}. IR (nujol; cm^{-1}): 1620s; 1590s; 1570s; 1050vs, $\nu(BF_4)$.

X-ray Data Collection and Structure Determination

Crystal data and other experimental details are summarized in Table 4. The diffraction experiment was carried out on an Enraf-Nonius CAD-4 diffractometer at room temperature using Mo Kα radiation ($\lambda = 0.71073$ Å). The calculations were performed on a PDP11/73 computer using the SDP-Plus Structure Determination Package [20]. The diffracted intensities were corrected for Lorentz, polarization and absorption (empirical correction) [21], but not for extinction. Scattering factors and anomalous

TABLE 4. Crystallographic data

Formula	$C_{33}H_{25}AuN_3O_3P \cdot C_4H_{10}O$
Formula weight (amu)	813.65
Crystal system	monoclinic
Space group	$P2_1/c$
a (Å)	12.717(9)
b (Å)	19.270(7)
c (Å)	14.696(3)
β (°)	107.85(3)
U (Å^3)	3428(7)
Z	4
D_{calc} (g cm^{-3})	1.576
μ (Mo Kα) (cm^{-1})	43.70
Minimum transmission factor	0.72
Crystal dimensions (mm)	0.20 × 0.10 × 0.08
Scan mode	ω
ω scan width (°)	1.1 + 0.35 tan θ
θ range (°)	3–25
Octants of reciprocal space explored	$\pm h, +k, +l$
Measured reflections	6422
Unique observed reflections with $I > 3\sigma(I)$	4456
Final R and R_w indices[a]	0.028, 0.035
No. of variables	415
e.s.d.[b]	1.282

[a] $R = [\Sigma(F_o - k|F_c|)/\Sigma F_o]$; $R_w = [\Sigma w(F_o - k|F_c|)^2/\Sigma w F_o^2]^{1/2}$; $w = 1/(\sigma(F_o))^2$; $\sigma(F_o) = [\sigma^2(I) + (0.04I)^2]^{1/2}/2F_o$Lp. [b] e.s.d. = $[\Sigma w(F_o - k|F_c|)^2/(N_{observations} - N_{variables})]^{1/2}$.

TABLE 5. Positional parameters and their e.s.d.s

Atom	x	y	z
Au	0.19016(1)	−0.00536(1)	−0.07284(1)
P	0.2233(1)	0.03890(6)	−0.20217(8)
O(2)	0.1619(3)	−0.1542(2)	−0.0419(2)
O(71)	0.0520(4)	0.1447(2)	0.3372(3)
O(72)	0.1442(5)	0.0680(3)	0.4339(3)
N(1)	0.1635(3)	−0.0563(2)	0.0422(2)
N(4)	0.2036(3)	−0.1739(2)	0.1851(3)
N(7)	0.1029(5)	0.0906(2)	0.3539(3)
C(2)	0.1475(4)	−0.1253(2)	0.0269(3)
C(3)	0.1098(4)	−0.1655(2)	0.1000(3)
C(5)	0.2353(4)	−0.1206(2)	0.2375(3)
C(6)	0.1687(4)	−0.0131(2)	0.2911(3)
C(7)	0.1200(4)	0.0520(3)	0.2730(3)
C(8)	0.0872(4)	0.0807(2)	0.1827(4)
C(9)	0.1033(4)	0.0437(2)	0.1090(3)
C(10)	0.1492(4)	−0.0239(2)	0.1216(3)
C(11)	0.1826(4)	−0.0509(2)	0.2157(3)
C(12)	0.3320(4)	−0.1292(3)	0.3260(3)
C(13)	0.4101(5)	−0.0760(3)	0.3592(4)
C(14)	0.5036(5)	−0.0893(4)	0.4384(4)
C(15)	0.5184(5)	−0.1514(4)	0.4828(4)
C(16)	0.4424(6)	−0.2026(3)	0.4522(4)
C(17)	0.3489(5)	−0.1930(3)	0.3733(4)
C(111)	0.2454(4)	−0.0316(2)	−0.2764(3)
C(112)	0.2864(5)	−0.0182(3)	−0.3525(4)

(continued)

TABLE 5. *(continued)*

Atom	x	y	z
C(113)	0.3036(5)	−0.0731(3)	−0.4073(4)
C(114)	0.2805(5)	−0.1396(3)	−0.3880(4)
C(115)	0.2389(6)	−0.1522(3)	−0.3136(4)
C(116)	0.2208(5)	−0.0992(2)	−0.2581(4)
C(121)	0.1143(4)	0.0935(2)	−0.2765(3)
C(122)	0.0583(4)	0.0769(3)	−0.3708(4)
C(123)	−0.0238(5)	0.1213(3)	−0.4246(4)
C(124)	−0.0484(5)	0.1816(3)	−0.3849(4)
C(125)	0.0062(5)	0.1973(3)	−0.2917(4)
C(126)	0.0868(4)	0.1541(3)	−0.2376(4)
C(131)	0.3489(4)	0.0905(2)	−0.1755(3)
C(132)	0.4381(5)	0.0697(3)	−0.1030(5)
C(133)	0.5376(5)	0.1048(3)	−0.0840(5)
C(134)	0.5470(5)	0.1607(3)	−0.1346(4)
C(135)	0.4574(5)	0.1827(3)	−0.2072(5)
C(136)	0.3582(5)	0.1472(3)	−0.2277(4)
O(900)	0.3243(6)	0.1807(3)	0.1254(5)
C(901)	0.2694(8)	0.1985(5)	0.0347(7)
C(902)	0.1930(8)	0.2523(5)	0.0279(8)
C(903)	0.409(1)	0.1234(5)	0.141(1)
C(904)	0.425(1)	0.0941(6)	0.221(1)

dispersions corrections for scattering factors of non-hydrogen atoms were taken from ref. 22. The structure was solved by Patterson and Fourier methods and refined by full-matrix least-squares, minimizing the function $\Sigma w(F_o - k|F_c|)^2$.

Weights assigned to individual observations were $w = 1/[\sigma(F_o)]^2$, where $\sigma(F_o) = [\sigma^2(I) + (0.041)^2]^{1/2}/2F_o\,Lp$.

Anisotropic thermal factors were refined for all the non-hydrogen atoms. Although all the hydrogen atoms were located from a difference Fourier map, their positions were not refined but calculated with C–H = 0.95 Å. The final difference Fourier synthesis showed maxima residuals of 0.4 e/Å^3. The atomic coordinates of the structure model are listed in Table 5.

Supplementary Material

A list of calculated and observed structure factors amplitudes is available from the authors.

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