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Gold(III) Complexes of some 1,4-Benzodiazepin-2-ones

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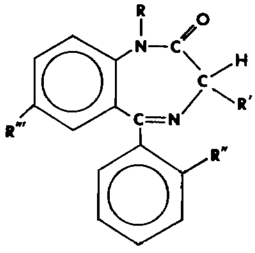
Derivatives of 1,4-benzodiazepin are now widely and successfully employed in medicine as tranquillizing and sedative–hypnotic agents [1]. In the belief that metal complexes of ligands having biological activity may be more active than the free ligands, the interaction of these molecules with transition metal ions is a subject to which some attention has been paid in the last years. Indeed, complexes of several metals (*e.g.* Cu(II), Zn, Cd, Co(II), Ni(II), Pd(II), Pt(II) [2–5]) have been synthesized and characterized, mainly through spectroscopic investigations (IR and electronic spectra): on this basis, different coordination modes have been suggested, including monodentate and bridging behaviour. In only one case, however, was the coordination ascertained through an X-ray structure [2].

Following our interest in the chemistry of gold [6, 7], an element which is relevant *per se* in the pharmaceutical field [8, 9], we report here the synthesis of some 1,4-benzo-diazepin-2-ones derivatives of gold(III), as well as the preliminary data of the X-ray structure of one of them.

Results and Discussion

The gold(III) complexes which are described here belong to the series L → $AuCl_3$, where L is one of the following 1,4-benzodiazepin-2-ones (trade name in parenthesis).



(*I*) (DIAZEPAM): R = CH_3, R′ = R″ = H, R‴ = Cl

(*II*) (PRAZEPAM): R = $CH_2(\overline{CHCH_2CH_2})$, R′ = R″ = H, R‴ = Cl

(*III*) (NIMETAZEPAM): R = CH_3, R′ = R″ = H, R‴ = NO_2

(*IV*) LORAZEPAM): R = H, R′ = OH, R″ = R‴ = Cl

(*V*) (NITRAZEPAM): R = R′ = R″ = H, R‴ = NO_2

The complexes were obtained directly from $AuCl_3$ and the ligand in chloroform solution: in any case only the 1:1 adducts were isolated, even when excess ligand was employed. The orange-yellow compounds are stable in the solid state and in chlorinated solvents, where they are only sparingly soluble; in donor solvents (*e.g.* acetone) a certain degree of ionization is observed as a function of the nature of the substituents R–R‴.

In the IR spectrum (nujol) of the ligands, in the range 1600–1700 cm^{-1}, two strong absorptions are attributed to the prevailing contribution of ν(C=N) and ν(C=O), respectively, (*e.g.* NIMETAZEPAM ν(C=N) 1610, ν(C=O) 1675 cm^{-1}). In the adducts, the two bands are shifted to higher (ν(C=O)) and lower (ν(C=N)) wavenumber ((NIMETAZEPAM)-AuC3, ν(C=O) 1705, ν(C=N) 1590 cm^{-1}), suggesting coordination to the metal through the imino nitrogen atom. It is well known, however, that the assignment of these bands is not easy: it is likely that the C=O and C=N vibrations conjugate each other so that any suggestion on the coordination mode on the basis of the IR data should be considered tentative.

To settle this point, an attempt was made to grow crystals suitable for an X-ray structure determination. Small flat red crystals of the complex (PRAZEPAM)-$AuCl_3$ were obtained by slow evaporation of a *ca.* 1:1 $CHCl_3/Et_2O$ solution. The structure of the complex, together with some relevant bond lengths and angles, is shown in Fig. 1.

The gold(III) ion is, as usual, in a square planar environment and the ligand is coordinated via the imino nitrogen. The small difference between the Au–Cl(1) and Au–Cl(2) or Au–Cl(3) bond lengths is consistent with a weak *trans*-influence of the nitrogen ligand, comparable with that of the chloride ion. The ligand as a whole does not seem to be markedly affected by the complexation to the gold atom [10].

It is noteworthy that in both cases which were investigated by X-ray, the gold(III) complex reported here and the copper(II) complex $Cu(L)_2Cl_2$ [2] (L = DIAZEPAM), the coordination mode of the ligand is the same, *i.e.* through the nitrogen of the $>$C=N$<$group.

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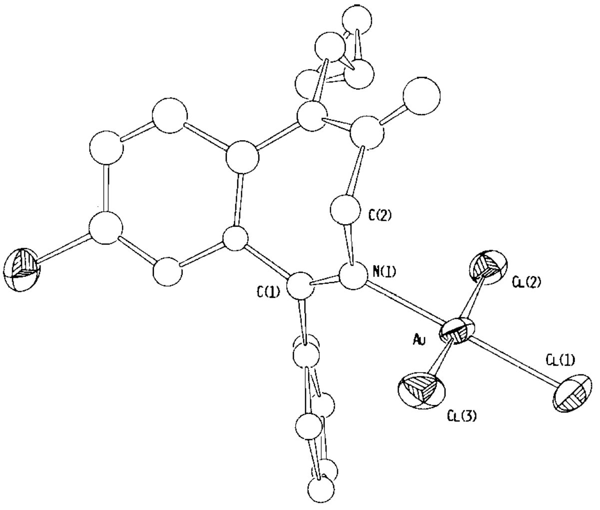

Fig. 1. ORTEP view of (PRAZEPAM)$AuCl_3$. Relevant bond parameters are: Au–Cl(1) 2.259(7), Au–Cl(2) 2.275(8), Au–Cl(3) 2.277(8), Au–N(1) 2.031(17), N(1)–C(1) 1.25(2), N(1)–C(2) 1.52(2) Å, Cl(1)–Au–Cl(2) 91.4(3), Cl(1)–Au–Cl(3) 91.3(3), Cl(2)–Au–N(1) 89.5(5), Cl(3)–Au–N(1) 87.8(5)°.

The refinement of the structure and other data relative to the behaviour of these gold derivatives in solution (NMR data) will be reported elsewhere.

Experimental

The ligands were supplied by Roche and were used without further purification.

The adducts L → $AuCl_3$, (L = *I–V*), were prepared by mixing at room temperature a chloroform solution of $AuCl_3$ (*ca.* 300 mg) with a solution of the ligand in the same solvent (molar ratio 1:1). After 24 hours, the solutions were concentrated to small volume and diethyl ether was added to precipitate the crude products. The analytical samples, orange-yellow, were obtained by crystallization from the same solvents. All the complexes gave satisfactory C, H, N analyses.

Crystal data: L → $AuCl_3$ (L = *II*, PRAZEPAM), $C_{19}H_{17}AuCl_4N_2O$, M.W. 628.1, monoclinic, space group $P2_1/n$, $a = 12.542(4)$, $b = 9.269(4)$, $c = 19.574(6)$ Å, $\beta = 102.67(2)°$, $U = 2220.1$ Å^3, $Z = 4$, μ(Mo–Kα) = 73.5 cm^{-1}. Intensity data were collected on an ENRAF-Nonius CAD-4 diffractometer with graphite-mono-chromated Mo(Kα) radiation, in the 2θ range 3–48°. The structure was solved by conventional Patterson and Fourier methods, on the basis of 1380 independent, decay-and absorption-corrected reflections, having $I \geqslant 3\sigma(I)$. Full-matrix least-squares refinements, with anisotropic thermal parameters for Au and Cl atoms, led to a current R-value of 0.059.

Acknowledgements

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