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Oral Gold. Synthesis and Antiarthritic Properties of Some Large-Ring Gold Chelates

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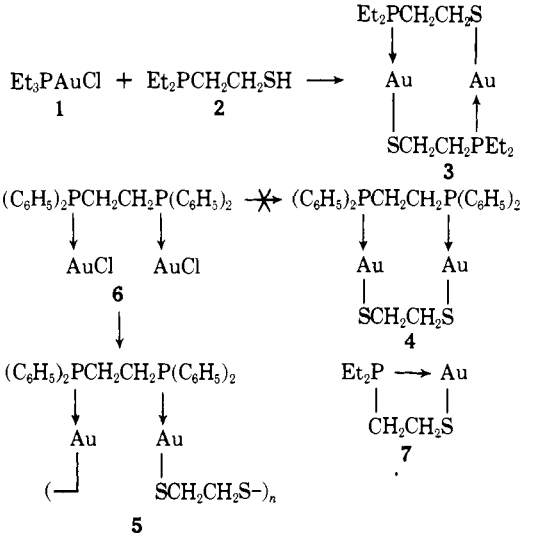
Received May 21, 1973

The antiadjuvant arthritic properties of several alkylphosphinegold coordination complexes were discussed in a previous report from this laboratory.[1] We now describe the antiarthritic properties of gold chelates.

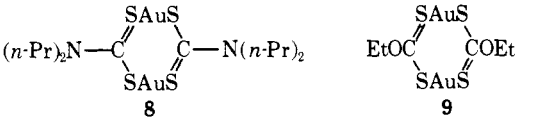
A typical orally active aurous complex, previously reported, was [(tetra-*O*-acetyl-β-D-glucopyranosyl)thio](triethylphosphine)gold which contains both phosphorus and sulfur ligands. Metabolism studies in animals‡ indicated that this complex extensively dissociated after absorption. This suggested that chelates of gold with the sulfur and phosphorus in one molecule, which should be chemically and possibly metabolically more stable, might have interesting biological profiles and led us to attempt preparation of a simple chelate **7**.

Chemistry. Treatment of AuCl with diethyl(2-thioethyl)phosphine (**2**)[2] in the presence of 1 mol of alkali did not result in the desired product. However, an exchange reaction, using the anion of **2** and chloro(triethylphosphine)-gold (**1**) gave a white solid in 77% yield whose elemental analysis indicated a one-to-one complex of the thiophosphine and gold. The mass spectrum and osmometric molecular weight clearly indicated that the compound was the dimer **3**.



In an attempt to prepare the similar dimer **4**, μ-[1,2-bis(diphenylphosphino)ethane]-bis(chlorogold) (**6**)[3] was treated with the dianion of 1,2-ethanedithiol. This reaction gave a high melting white solid in 68% yield which, in contrast to **3**, was quite insoluble in all of the common organic solvents. After washing with $CHCl_3$, the crude product gave an excellent analysis for **4** (or **5**), but in contrast to **3**, its mass spectrum did not show a molecular ion. These properties led us to assign the polymeric structure **5** to the product.

Dimer **3** is reminiscent of the di-μ-(*N*,*N*-dialkyldithiocarbamato)-digold complexes such as **8**[4] which have been studied by X-ray crystallographic analysis.[5] In **8** the S-Au-S bonds are linear, and the Au-Au bond distance (2.76 Å) is shorter than that found in the metal (2.88 Å), which was ascribed to Au-Au attraction.



Mass spectral fragmentation patterns of the compounds, reported here, suggested that chelated gold complexes were more stable structures than coordination complexes and that there was Au-Au interaction in the cylic structures. Thus, the spectrum of **1**, a nonchelate complex, shows a small molecular ion at *m/e* 350 and a major peak at *m/e* 315 corresponding to the loss of Cl to give Et_3PAu^+. Successive cleavage of C-P and C-C bonds occurs to give finally CH_2PHAu^+. However, the mass spectrum of **3** shows a strong M^+ peak at *m/e* 692 and less intense peaks at *m/e* 664, 637, 636, and 608, arising from successive losses of 2-carbon fragments leaving the large ring intact. Interestingly, several small peaks at *m/e* 547, 515, and 483 contain Au_2 moieties. Similarly, the mass spectra of **8** and **9** have molecular ion peaks and peaks probably containing the Au_2 moiety. However, the highest molecular weight peak seen in the mass spectrum of polymer **5** is *m/e* 462, corresponding to bis[1,2-(diphenylphosphino)ethane] disulfide. This probably came from thermal decomposition of the polymer.

Formation of the dimeric chelate **3** rather than a monomeric chelate **7** is not surprising since gold forms linear complexes involving sp orbitals,[6] and the geometry of the PAuS array is such that P and S cannot be bridged by an ethylene group. However, two such arrays can be bridged by two ethylene groups. The formation of polymer **5** in preference to **4** can be rationalized in terms of intramolecular repulsive dipole interaction. In **4** similarly charged atoms would be adjacent while in **5** they could be at a distance. In **3** oppositely charged atoms are adjacent which contribute to the stability of the chelate.

Biology. Antiadjuvant arthritic properties of the Au compounds of this report were determined by previously described methods.[1,7] Chelate **3** was the only example which showed oral absorption properties. However, the magnitude of serum Au level attainment was less with **3** than with coordination complex **1** when the compounds were administered at doses equivalent in Au content. Compounds **5**, **8**, and **9** were ineffective when administered orally even though they exhibited markedly different solubility properties. The moderate Au levels obtained with **8** and **9** after intramuscular administration were ineffectual in preventing development of adjuvant arthritis in the rat. These data illustrate further that the nature of the Au complex markedly influences the biological fate of the antiarthritic species and suggest that a complex combination of physical and chemical factors is necessary for maximum biological efficacy. The increased stability per se of the chelates described in this paper related to **1** did not lead to higher serum gold levels (Table I).

Experimental Section

Melting points (uncorrected) were determined in a Thomas-Hoover capillary melting point apparatus. Mass spectra were obtained on a Hitachi Perkin-Elmer RMN-6E spectrometer. Nmr

†This article is dedicated to Professor Alfred Burger, our long-time friend and advisor.

‡B. Hwang, T. Flanagan, A. Intoccia, and S. Walkenstein, unpublished work, Smith Kline & French Laboratories.

Table I. Antiarthritic Activity and Plasma Au Concentration

Compd	Expt	Dose, mg/kg/day (calcd as Au)	Vehicle[a]	Hindleg vol, % redn from adj control[b]			Serum Au, μg/ml
				Injected leg		Uninjected leg,	
				Day 3	Day 16	Day 16	
1	1	18 po	T	24[f]	32[f]	52[f]	4.9
	5	15 im	B	16[f]	23[f]	19[e]	13.7
3	2	5 po	T	*c*	7[d]	*c*	1.2
	1	18 po	T	11[f]	14[e]	*c*	2.2
	2	20 po	T	*c*	*c*	*c*	2.3
	1	27 po	T	10[e]	*c*	*c*	3.5
	3	40 po	T	26[f]	25[f]	28[f]	4.8
	1	40 po	T	19[f]	14[e]	17[d]	4.0
	1	60 po	T	21[f]	37[e]	42[e]	6.7
5	4	20 po	T	*c*	*c*	*c*	0.0
8	4	20 po	T	*c*	*c*	*c*	0.0
	5	15 im	P	*c*	*c*	*c*	1.5
9	4	20 po	T	*c*	*c*	*c*	0.0
	5	11 im	P	*c*	*c*	*c*	3.1
10[g]	1	20 po	T	33[f]	40[f]	41[f]	
	2	20 po	T	26[f]	29[f]	41[f]	
	3	20 po	T	28[f]	33[f]	45[f]	
	4	20 po	T	30[f]	33[f]	34[f]	
	5	20 po	T	33[f]	41[f]	43[f]	

[a] T, tragacanth; B, benzyl alcohol; P, polyethylene glycol. [b] Per cent reduction from adjuvant control = (hindleg volume of untreated adjuvant control rat − hindleg volume of drug-treated rat)/hindleg volume of untreated adjuvant control rat. [c] No significant reduction in paw volume. [d] $0.01 < p < 0.05$. [e] $0.001 < p < 0.01$. [f] $p < 0.001$. [g] Prednisolone.

spectra were obtained on a Varian T-60 instrument (Me_4Si). Analyses are indicated by the symbols of the elements and were within 0.4% of the theoretical values. Diethyl(2-thioethyl)phosphine was obtained from Edward Lanpher, Orgmet, Inc., Haverhill, Mass.

Di-μ-(diethylphosphinoethylthio)-digold (3). To a solution of 8.50 g (0.0565 mol) of diethyl(2-thioethyl)phosphine[2] in 40 ml of EtOH was added a solution of 2.26 g (0.0565 mol) of NaOH in 40 ml of 50% H_2O–EtOH, followed by a solution of 19.8 g (0.056 mol) of chloro(triethylphosphine)gold in 60 ml of a $CHCl_3$–EtOH (2:1) solution. After stirring for 1 hr, the filtered solution was evaporated to dryness and the residue extracted with about 200 ml of $CHCl_3$. The dried $CHCl_3$ was concentrated under vacuum to give a yellow oil which crystallized on cooling. The solid was washed with Et_2O and then recrystallized from MeOH to give 15.2 g (77.0%) of white crystals: mp 136–138°; mass spectrum, molecular ion at *m/e* 692 containing two atoms of sulfur; osmometric molecular weight ($CHCl_3$) calcd 692.4, found 723.7; nmr ($CDCl_3$) δ 1.20 (complex multiplet, 12 H, CH_3), 2.10 (complex multiplet, 12 H, CH_2P), 3.37 (doublet of triplets, 4 H, J = 21, 6 Hz, CH_2S). *Anal.* ($C_{12}H_{28}Au_2P_2S_2$) C, H, P.

Poly-μ-[1,2-bis(diphenylphosphinoethane)]-μ-(1,2-ethanedithio)-digold (5). A solution of 2.16 g (2.5 mmol) of μ-[1,2-bis(diphenylphosphine)ethane]-bis(chlorogold)[3] in 25 ml of CH_2Cl_2 was added in two portions to a solution of 0.24 g (2.5 mmol) of 1,2-ethanedithiol in 30 ml of H_2O–EtOH (2:1) containing 0.20 g (5 mmol) of NaOH. A white solid formed after all the reagents were added. The mixture was stirred under N_2 for 45 min and filtered, and the white solid was washed with $CHCl_3$. Drying gave 1.50 g (68%) of a solid, mp 219–221°, which was practically insoluble in all the common solvents tried for recrystallization: mass spectrum, ion of highest mol wt, *m/e* 462, containing two atoms of sulfur by isotope measurements. *Anal.* ($C_{28}H_{28}Au_2P_2S_2$) C, H, P.

Di-μ-(*N,N*-di-*n*-propyldithiocarbamato)-digold (8). The literature[4] procedure gave **8**, mp 219–220°, in 64% yield: mass spectrum, molecular ion at *m/e* 746. *Anal.* ($C_{14}H_{28}Au_2N_2S_4$) C, H, N.

Di-μ-(ethyl xanthate)-digold (9). AuCl was prepared by adding 1.22 g (0.01 mol) of thiodiglycol in 20 ml of H_2O to a solution of 1.97 g (0.005 mol) of $HAuCl_4$ in 50 ml of saturated aqueous NaCl. Potassium ethyl xanthate (0.80 g, 0.005 mol), dissolved in 20 ml of MeOH, was added to give a yellow solid which was collected by filtration and washed with H_2O and MeOH. Soxhlet extraction with CS_2 gave 0.75 g (47%) of a yellow solid: mp 168–170°; mass spectrum, molecular ion at *m/e* 636. *Anal.* ($C_6H_{10}Au_2O_2S_4$) C, H, S.

Acknowledgments. We are indebted to our Analytical and Physical Chemistry Section personnel for analytical and physical data, Miss Edith Reich for elemental analyses, and Dr. Edward White and Mr. Gerald Roberts for mass spectra.

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Synthesis and Biological Properties of [2-L-β-(Pyrazolyl-3)alanine]-Luteinizing Hormone-Releasing Hormone

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The replacement of the imidazole moiety by the isosteric pyrazole ring system in peptides that contain histidine has become a useful means of evaluating the role played by that amino acid in determining biological activity. Thus, β-(pyrazolyl-3)alanine has been substituted for histidine in the RNase S peptide[1] resulting in a material which binds competitively and strongly with the S protein to give a complex which is, however, devoid of enzymatic activity. Substitution of the amino acid for the histidine residues in angiotensin II,[2] β-corticotropin,[3,4] and thyrotropin-releasing hormone[5] gave compounds which retained appreciable hormonal activity.

In view of the apparent importance of the histidine residue of LH-RH in maintaining high levels of biological po-

† This note is dedicated to Alfred Burger in recognition of his many significant contributions to medicinal chemistry.