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REFERENCES

- [1] N.J. BIRCH in H. SIGEL (ed.), «Metal Ions in Biological Systems», vol. 14, M. Dekker, New York, 1982, pp. 257-313.
- [2] N.J. BIRCH, I.P.L. COLEMAN, A.R. KARIM, *Brit. J. Pharmacol.*, **80**, 443P (1983).
- [3] N.J. BIRCH, I.P.L. COLEMAN, H.E. HILBURN, A.R. KARIM, *Brit. J. Pharmacol.*, **81**, 168P (1984).
- [4] A.R. KARIM, I.P.L. COLEMAN, N.J. BIRCH, *Gastroenterol. Clin. et Biol.*, **8**(11), 867-868 (1984).
- [5] B.E. EHRLICH, J.M. DIAMOND, *Lancet*, **1**, 306 (1983).
- [6] N.J. BIRCH *et al.*, *Biochem. Soc. Trans.*, **13**, 250 (1985).
- [7] F. LAUTERBACH, *Arch. Pharmacol.*, **297**, 201-212 (1977).
- [8] N.J. BIRCH, D. ROBINSON, R.A. INIE, R.P. HULLIN, *J. Pharm. Pharmacol.*, **30**, 683-685 (1978).
- [9] D.J. BENOS, *Am. J. Physiol.*, **242**, C131-C145 (1982).
- [10] J.L. MADARA, *J. Cell Biol.*, **97**, 125-136 (1983).



PS6.14 — MO

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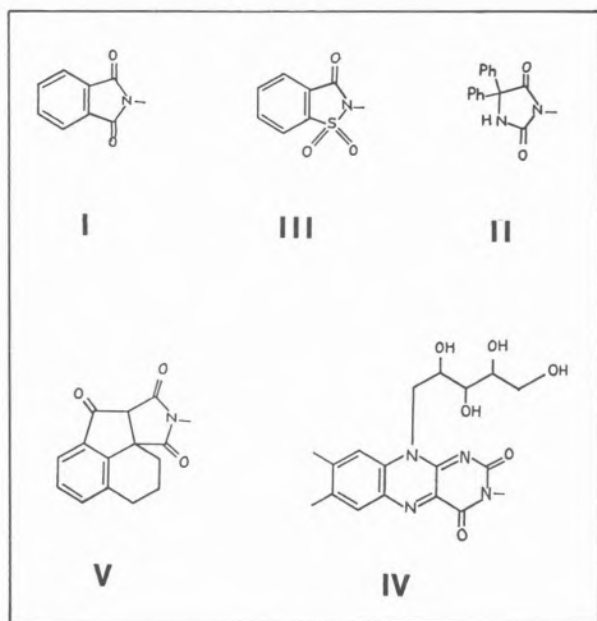
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PREPARATION, CHARACTERIZATION AND ANTI-INFLAMMATORY ACTIVITY OF IMIDO GOLD(I) TRIETHYLPHOSPHINE COMPLEXES

The orally-administered gold(I) compound auranofin ("Ridaura", Smith Kline and French Laboratories) [(2,3,4,6-tetra-*O*-acetyl-1-thio- β -D-glucopyranosato-S)(triethylphosphine)gold] exhibits anti-inflammatory activity in animal models and is currently undergoing Phase IV clinical testing [1]. Structure-activity correlations with the series of complexes $R_3P-Au-SR'$ (where SR' is a sugar thiolate) have shown optimum activity when the phosphine is PEt_3 [2]. We report here the preparation, characterization and biological testing of a series of new imido complexes of triethylphosphine gold(I).

There have been very few previous reports of Au(I) complexes with nitrogen ligands. Gold(I)-N bonds are usually considered to be relatively weak. Five complexes of general formula $Et_3PAu(imide)$ containing the imido ligands shown in the Figure were prepared in good yield and gave satisfactory elemental analyses. The structure of one of them $Et_3P-Au-(phthalimide)$ was determined by X-ray crystallography and



Figure

Structure of the imido ligands in complexes of general formula $\text{Et}_3\text{PAuN}(\text{imide})$

shown to contain linear P-Au-N bonds (P-Au 2.24 Å, Au-N 2.05 Å) [3]. The X-ray absorption spectra of the Au L_{III} edges suggested that the gold coordination was similar in all of these new complexes [4]. All have a distinctive spike in the near-edge region attributable to an electronic transition involving vacant π -acceptor orbitals on the imide ligand.

The structures of these complexes in solution were investigated by the use of ^{31}P and ^{15}N NMR spectroscopy. Two-bond ^{15}N - ^{31}P spin-spin couplings were observed from solutions of $\text{Et}_3\text{P-Au-(}^{15}\text{N)}$ phthalimide confirming the existence of P-Au-N bonding in solution.

The phthalimide complex was tested first in the oxazolone-induced contact sensitivity assay in mice and was found to produce activity (66% stimulation) at a dose of 1 mg gold/kg, *i.v.*, comparable to that of Et_3PAuCl (72% stimulation). All of the complexes were tested in the carrageenan-induced rat paw edema assay [5], and the results are shown in the Table. When administered orally all complexes were effective in inhibiting the edema volume of the hind paw.

Thus it would appear that the presence of a thiolate, as in auranofin, is not essential for oral anti-inflammatory activity in animal models. How-

Table
Anti-inflammatory activity of triethylphosphine gold(I) imide complexes [3]

Imide	Dose ^{a)}	% Inhibition ^{b)c)}
I Phthalimide	15	42**
II Diphenylhydantoin	10	36*
III Saccharin	20	38**
IV Riboflavin	20	65**
V Tetrahydrosuccinimido-acenaphthenone	20	50**
Auranofin	5	17*
	10	24**
	20	56**

a) mg Au/kg.

b) % inhibition of paw volume in the rat carrageenan assay.

c) *, $P < 0.05$, **, $P < 0.01$ as significant differences from control using Student's *t* test.

ver, the *in vivo* displacement of the imido ligand by a naturally-occurring thiolate such as glutathione would be expected to be a very favourable reaction. This was confirmed by *in vitro* reactions.

The most active complex was that of riboflavin (vitamin B_2 , ligand IV). The variations in the activities observed may be partly related to the extent of oral absorption. The imides II, III, IV, and V are all biologically-active ligands in their own right as anticonvulsants (II and V), sweetener (III) and vitamin (IV). The anti-inflammatory activities of the imides alone were not determined.

This work demonstrates that stable Au(I) phosphine imide complexes can be readily prepared and exhibit anti-inflammatory activity. Further interest in the stability of P-Au-N bonds arises from the reported anticancer activity of auranofin in P388 leukaemia [6]. Using the ^{15}N - ^{31}P NMR methods described here it may be possible to map out possible Et_3PAu^+ binding sites on nucleic acid bases and DNA [7].

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REFERENCES

- [1] Articles in, *J. Rheumatol.* (1982), Suppl. 8.
 [2] B.M. SUTTON, E. MCGUSTY, D.T. WALZ, M.J. DiMARTINO, *J. Med. Chem.*, **15**, 1095 (1972).
 [3] S.J. BERNERS PRICE, M.A. MAZID, P.J. SADLER, R. KURODA, M.J. DiMARTINO, D.T. HILL, *Inorg. Chem.*, submitted for publication.
 [4] S.J. BERNERS PRICE, I.M. ISMAIL, M.A. MAZID, M.T. RAZI, P.J. SADLER, G.N. GREAVES, «Proceedings of Conf. on Biological Systems: Structure and Analysis», March 1984, Daresbury, U.K., in press.
 [5] D.T. WALZ, M.J. DiMARTINO, C.L. GRIFFIN, A. MISHER, *Arch. Int. Pharmacodyn.*, **185**, 337 (1970).
 [6] T.M. SIMON, D.H. KUNISHIMA, G.J. VIBERT, A. LORBER, *Cancer*, **44**, 1965 (1979).
 [7] C.E. BLANK, J.C. DABROWIAK, *J. Inorg. Biochem.*, **21**, 21 (1984).



PS6.15 — TU

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PLATINUM(II) AND PALLADIUM(II) HALIDE COMPLEXES WITH DITHIOCARBAMIC DERIVATIVES AND THEIR CYTOSTATIC ACTIVITY

The elevated toxicity is a severe dose-limiting factor in cisplatin antitumor therapy. Nephrotoxicity is one of the most important effects and it seems due to some metabolic pathways of the drug. It can be prevented by the contemporary administration of diuretics [1]. Protection by sulfur containing compounds could be an alternate mean of

preventing toxicity [2]. So far sodium diethyldithiocarbamate (DDTC) is the most promising one. Moreover DDTC exhibits a protective effect against chemical induced tumors. Its immunostimulating properties have been recently evidenced also [3]. The efficacy of cisplatin-DDTC combination is dose and time dependent in *in vivo* experiments.

Owing to the importance of DDTC metabolites and their possible interaction with cisplatin, we prepared and studied Pt(II) and Pd(II) complexes with dithiocarbamic esters. A number of them showed *in vitro* cytotoxicity (Table I), but the generally low solubility prevented to carry out a study in solution [4].

Table I
 "In vitro" Cytostatic Activity against KB cells

			Complexes	ID ₅₀ (μg/ml) *
$\begin{array}{c} R \\ \diagdown \\ N-C \begin{array}{l} \nearrow S \\ \searrow SR' \end{array} \end{array}$	R = R' = Me	TMDT	Pd(DMDTE)Cl ₂	**
	R = R' = Et	TEDT	Pd(DMDTE)Br ₂	3.6
	R = Me, R' = Et	DMDTE	Pd(TEDT)Cl ₂	0.17
	R = Et, R' = Me	DEDTM	Pd(TMDT) ₂ Cl ₂	1.02
			Pd(DMDTE) ₂ Br ₂	0.98
			Pt(TEDT) ₂ I ₂	3.8
			Pt(TMDT) ₂ Br ₂	2.8
			Pt(DMDTE) ₂ Br ₂	0.4

* The results of the cytostatic activity are expressed as dose at which the cells showed a 50% growth inhibition (ID₅₀). ID₅₀ value for cisplatin is 0.11 μg/ml.

** The complex is active but the value was not determined since dose-response relationship was not observed.

The following anions and some related esters have been synthesized:

