Hydrogen-1 Nuclear Magnetic Resonance Evidence for Exchange Reactions in the Antimony(III)–Cysteine System and Synthesis of Antimony(III) Compounds of 3,3-Dimethylcysteine, Toluene-3,4-dithiolate, Dicyanoethylene-1,2-dithiolate, and 2,3-Bis(thiosemicarbazono)butane

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Exchange reactions in antimony(III)–cysteine and –3,3-dimethyl-D-cysteine (dmc) systems have been investigated. Exchange is rapid and independent of pH with antimony(III)–cysteine systems at pH 1—3 but is slow with potassium bis(tartrato)diantimonate(III)–cysteine. Antimony(III) compounds of dmc, toluene-3,4-dithiolate, dicyanoethylene-1,2-dithiolate, and 2,3-bis(thiosemicarbazono)butane have been synthesized and characterized.

ANTIMONY compounds have been the mainstay in the treatment of schistosomiasis and leishmaniasis for over 50 years despite their toxic side effects.[1] Research is needed to find new substitutes for the present drugs. There is considerable evidence that the toxicity of antimonals can be reduced by modification of the functional groups which bind Sb^{III}. Drugs containing antimony bound to sulphur are generally less toxic than those containing oxygen-bound antimony. In addition, it has recently been reported[2] that addition of penicillamine (3,3-dimethylcysteine,H_2dmc) to potassium bis(tartrato)-diantimonate(III) (tartar emetic,te) produces a dramatic decrease in toxicity with no loss in effectiveness. This

[1] E. A. H. Friedheim in 'Chemistry of Helminthiasis,' vol. 1, eds. R. Cavier and F. Hawkins, Pergamon Press, New York, 1973, ch. 2.

[2] (*a*) E. A. H. Friedheim, B.P. 1,093,445/1967; (*b*) M. T. Khayyal, N. I. Girgis, and E. McConnell, *Bull. World Health Org.*, 1967, **37**, 387; (*c*) N. Ercoli, *Proc. Soc. Expt. Biol. Med.*, 1968, **129**, 284; (*d*) K. Iyo and K. Kirita, *Bull. Pharm. Res.*, 1954, **7**, 1; (*e*) M. R. Pedrique, S. Barbera, and N. Ercoli, *Ann. Trop. Med. Parasitology*, 1971, **65**, 221.

paper reports the synthesis of an antimony(III)–penicillamine chelate and a study of the intermolecular ligand exchange in antimony(III)–cysteine systems.

Few dithiolate compounds of Group 5B have been reported.[3] Although air-unstable tetraethylammonium bis(dicyanoethylene-1,2-dithiolato)antimonate(III), $[Et_4N][Sb(ded)_2]$, and tris(toluene-3,4-dithiolato)diantimony(III), $[Sb_2(td)_3]$, have been reported,[3] earlier reports[3b] gave the impression that td could form only a bridged compound with Sb^{III}. The antimony compound formed with 2,3-bis(thiosemicarbazono)butane (H_2btb) has not been reported previously.

EXPERIMENTAL

General.—All chemicals were of reagent grade and were used without further purification. L-Cysteine, cysteine hydrochloride, potassium bis(tartrato)diantimonate(III), and trichloroantimony(III) were purchased from B.D.H., and D-penicillamine (gold label) was obtained from Aldrich Company. Sodium dicyanoethylene-1,2-dithiolate was prepared by the literature method.[4] 2,3-Bis(thiosemicarbazono)butane was obtained by condensing butane-2,3-dione with thiosemicarbazide in methanol. Recrystallization from methanol–water gave the pure compound. Molecular-weight determinations and elemental analyses were by either Dr. Franz Pascher, Mikroanalytisches Laboratorium Bonn, or Galbraith Laboratories, Inc., Knoxville, Tennessee.

Potassium Bis(3,3-dimethyl-D-cysteinato)antimonate(III), $K[Sb(dmc)_2]$.—Reaction of potassium bis(tartrato)diantimonate(III) (0.16 mol) with penicillamine (H_2dmc) (0.98 mol) in water at room temperature produced the colourless crystalline *compound* which was recrystallized from water (Found: C, 28.0; H, 4.80; N, 6.05; S, 13.04. Calc. for $C_{10}H_{18}KN_2O_4S_2Sb$: C, 26.4; H, 4.00; N, 6.15; S, 14.1%).

Hydrogen Bis(toluene-3,4-dithiolato)antimonate(III) Hydrate, $H[Sb(td)_2]\cdot OH_2$.—Antimony trichloride (0.01 mol) dissolved in hot methanol (50 cm³) was treated with toluene-3,4-dithiolate (0.022 mol). Cooling the hot solution produced the deep yellow crystalline *product* which can be recrystallized from either methanol or chloroform (Found: C, 37.5; H, 2.70; S, 28.05. Calc. for $C_{14}H_{15}OS_4Sb$: C, 37.25; H, 3.35; S, 28.4%).

Chloro(toluene-3,4-dithiolato)antimony(III) Hydrate, $[Sb(td)Cl]\cdot OH_2$.—The dull yellow *compound* was obtained as above when $SbCl_3$ (0.01 mol) was treated with td (0.01 mol) in chloroform. Crystallization from methanol yielded the desired product (Found: C, 25.45; H, 1.75; S, 18.45. Calc. for $C_7H_8ClOS_2Sb$: C, 25.05; H, 2.40; S, 19.1%).

Tetra(n-butyl)ammonium Bis(dicyanoethylene-1,2-dithiolato)antimonate(III), $[Bu^n_4N][Sb(ded)_3]$.—Freshly prepared dicyanoethylene-1,2-dithiolate (0.025 mol) was dissolved in chloroform over a water-bath. To the hot solution was added $SbCl_3$ (0.01 mol). Addition of 0.1M-tetra(n-butyl)-ammonium hydroxide (20 cm³) in ethanol–toluene produced the air-stable deep-yellow crystalline *product* which was recrystallized from methanol (Found: C, 44.65; H, 5.40; N, 10.5; S, 19.45. Calc. for $C_{14}H_{36}S_4Sb$: C, 44.7; H, 5.65; N, 10.85; S, 19.9%).

[2,3-Bis(thiosemicarbazono)butane]chloroantimony(III), [Sb(btb)Cl].—2,3-Bis(thiosemicarbazono)butane (0.01 mol) in methanol was heated under reflux over a water-bath until all the solids had dissolved. Addition of $SbCl_3$ (0.01 mol) to the hot solution produced the desired light yellow *crystals* which were recrystallized from dimethyl sulphoxide (Found: C, 19.45; H, 3.40; N, 20.9; S, 16.25. Calc. for $C_6H_{10}ClN_6S_2Sb$: C, 18.6; H, 2.60; N, 21.7; S, 16.55%).

Physical Measurements.—^{1}H N.m.r. spectra were recorded on a Perkin-Elmer R 12B 60 MHz spectrometer with tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulphonate, Na(dss), as internal reference. The pH of the solutions was adjusted with NaOD solution. The kinetics of the exchange reactions in the antimony(III)–cysteine systems in D_2O were determined from the change in methylene proton chemical shift with concentration. Each dynamic process was treated as a simple two-site exchange between environments (A) and (B) which have identical populations and relaxation times. The rate constants for the exchange process were calculated from the equation of Gutowsky and Holm,[5] $\tau = 2^{\frac{1}{2}}[\pi(\nu_a - \nu_b)]^{-1}$. The chemical shift of the methylene protons in pure cysteine hydrochloride at 34 °C was taken as the frozen state of the systems.

TABLE 1

I.r. absorptions (cm^{-1}) for the antimony(III) complexes

K[Sb(dmc)]	3 290m, 3 240w, 3 100br, 2 950s, 2 900m, 2 455s, 2 420s, 1 710s, 1 620s, 1 590s, 1 380s, 1 330m, 1 310w, 1 278m, 1 135m, 1 092s, 1 080m, 1 040s, 892s, 860m, 820m, 755m, 685w, 670s
$H[Sb(tdc)_2]\cdot OH_2$	3 020w, 2 890w, 2 840w, 1 570w, 1 450s, 1 368m, 1 250m, 1 110m, 1 030m, 867m, 810s, 690m
$[Sb(td)Cl]\cdot OH_2$	2 890w, 2 838w, 1 570w, 1 445s, 1 365m, 1 252m, 1 145m, 1 110s, 1 035m, 1 000w, 948w, 860m, 810s, 690m
$[Bu^n_4N][Sb(ded)_2]$	2 935s, 2 910m, 2 850m, 2 203s, 2 195s, 2 183s, 1 475s, 1 470s, 1 460s, 1 450m, 1 443m, 1 370m, 1 365w, 1 177w, 1 138s, 1 100m, 1 050w, 1 032w, 997w, 880m, 850w, 800w, 696m
[Sb(btb)Cl] *	3 400s, 3 250s, 3 195s, 1 555s, 1 505s, 1 295s, 1 090s, 840s

* For a Nujol mull.

I.r. spectra were obtained for KBr discs and Nujol mulls with a Pye Unicam SP 200 spectrophotometer. The major peaks of interest for the KBr discs are given in Table 1. Molar conductivities for 1mM solutions were measured with a Philips conductivity bridge PR 9501.* The pH measurements were made with a Pye Unicam model 292 MK2 pH meter using a Pye Unicam combination electrode.

RESULTS AND DISCUSSION

Intermolecular Ligand Exchange.—In an investigation of the possibility of intermolecular exchange between the Sb^{III}-bound and unbound cysteine, solutions of $SbCl_3$ and cysteine hydrochloride in D_2O were prepared and their ^{1}H n.m.r. spectra recorded. Each spectrum consisted of a doublet for the methylene protons, a triplet for the methyne proton, and a singlet for the exchanging SH, NH_2, and CO_2H protons [Figure 1(*a*)]. Figure 1 shows the change in chemical shift of the methylene protons as a function of the mol fraction. A plot of this variation was

* 1M = 1 mol dm^{-3}.

[3] (*a*) S. O. Wandiga, *Proc. 16th Internat. Conf. Co-ordination Chem.*, Dublin, 1974; (*b*) G. Hunter, *J.C.S. Dalton*, 1972, 1496; (*c*) E. Gagliardi and A. Durst, *Monatsh.*, 1972, **103**, 292.

[4] G. Bahr and G. Schleitzer, *Ber.*, 1955, **88**, 1771; 1957, **90**, 438.

[5] H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, 1956, **25**, 1228.

linear. Furthermore, the chemical shifts were independent of the pH in the range 1—3 up to the pH of crystallization (>3.0). This linear relation suggests that the

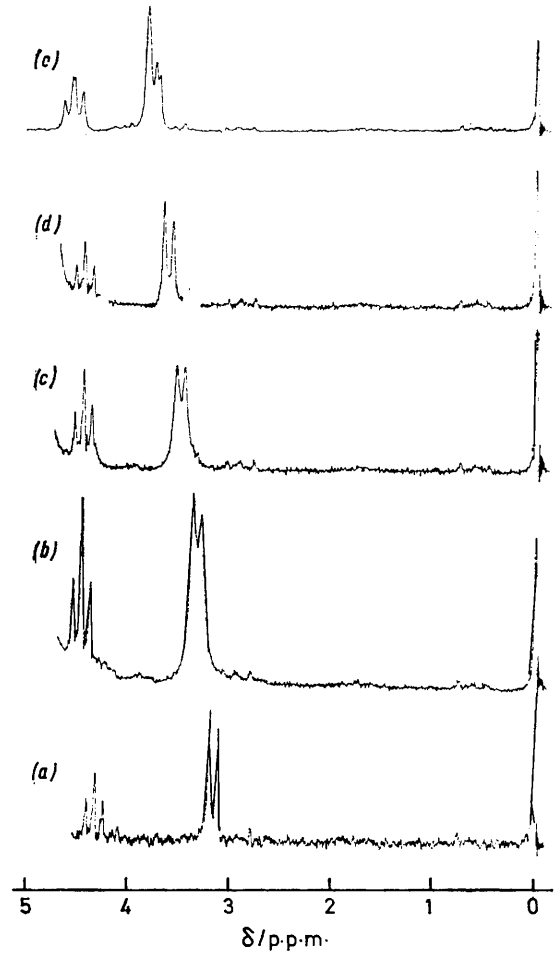

FIGURE 1 ^{1}H N.m.r. spectra of the antimony(III)–cysteine system at 34 °C in D_2O showing the methylene proton chemical shift as a function of mol ratio of cysteine: (*a*) 0.53M-Cys; (*b*) 1.03M-Cys + 0.17M-$SbCl_3$; (*c*) 0.52M-Cys + 0.13M-$SbCl_3$; (*d*) 0.39M-Cys + 0.16M-$SbCl_3$; (*e*) 0.32M-Cys + 0.20M-$SbCl_3$. The internal reference was Na(dss) and the HOD peak has been eliminated for clarity

TABLE 2

N.m.r. data and results of exchange in antimony(III)–cysteine in D_2O at 34 °C

[$SbCl_3$]/M	[Cys]/M	x_{Cys}	δ(CH_2)/p.p.m.	Δ/Hz	τ_A/s
0.17	1.03	0.86	3.34	12.00	0.037
0.13	0.92	0.88	3.33	11.40	0.039
0.15	0.72	0.83	3.39	15.00	0.030
0.16	0.62	0.79	3.48	20.40	0.022
0.13	0.52	0.80	3.50	21.60	0.021
0.14	0.40	0.74	3.58	26.40	0.017
0.16	0.39	0.71	3.63	29.40	0.015
0.20	0.32	0.62	3.78	38.40	0.012
0.00	0.12	1.00	3.14	0.00	

magnetic equivalence of the cysteine protons in the two environments is due to exchange, since equivalence of the protons for other reasons would not give, in general, such a linear function. The insolubility of the antimony–cysteine compound in water and many organic solvents and the ready hydrolysis of $SbCl_3$ at higher pH prevented investigation of ligand exchange above pH 3. However, when tartar emetic (te) was used instead of $SbCl_3$ it was found that no exchange occurred in solution containing cysteine hydrochloride in mol fractions below 0.50. Insoluble crystals were formed above this mol fraction.

The mean lifetimes, τ_A, of the cysteine groups (as a function of the methylene protons) before exchange were calculated from the data of Table 2 and are presented in the last column of the Table. A plot of log τ_A as a function of log [Cys] was linear over the range of concentrations investigated and gave an overall kinetic order of 1.09. Since a change in pH does not affect the chemical shift of the methylene protons, it is reasonable to conclude that, under conditions where soluble antimony–cysteine complexes are formed, cysteine will weakly bind antimony and can be replaced by other functional groups.

An investigation of the tartar emetic–D-penicillamine system was made to ascertain the nature of the chelate formed. The 3,3-dimethyl protons in penicillamine (dmc) showed the same chemical shifts for all the solutions studied. The methyne proton chemical shift showed slight initial broadening in going from a neat dmc solution to one containing 0.22M-dmc plus 0.34M-te. This broadening could result from a change in viscosity of the solutions. Solutions with dmc mol fractions $\geqslant$0.80 formed glasses on standing.

Molecular models indicate that dmc cannot bind antimony through the sulphur atom on C^3 and hydroxyl oxygen on C^1 without serious steric interaction between the 3,3-dimethyl and NH_2 protons. However, binding can occur either through the sulphur and nitrogen atoms or through the hydroxyl oxygen and nitrogen. In addition, dmc can act as a tridentate ligand without much steric interference as has been demonstrated for Pb^{2+}.[6] However, this mode of bonding is not very likely for Sb^{III}.[7] Spectrum (*e*) of Figure 1 indicates that sulphur does bind antimony since this is the only way the chiral nature of the methylene protons could be exhibited. Furthermore, the change in chemical shifts of the methylene protons results from some interaction between sulphur and antimony. On the other hand, the bonding mode for dmc cannot be determined from n.m.r. data alone. The KBr-disc i.r. spectrum of K[Sb(dmc)$_2$] did not show a normal carboxylic acid spectrum, but exhibited a broad peak between 3 160 and 3 090 cm^{-1} and two peaks at 2 455 and 2 420 cm^{-1} The bands occurring in the range 2 476—2 420 cm^{-1} have been assigned to chelated S–H in monothio-β-keto-esters.[8] It is possible that the peaks observed at 2 455 and 2 420 cm^{-1} indicate sulphur bonding either to antimony or to the hydrogens of the amine in the solid state.

1,2-*Dithiolato- and Penicillamine Compounds.*—Chemo-

[6] H. C. Freeman, G. N. Stevens, and I. F. Taylor, jun., *J.C.S. Chem. Comm.*, 1974, 366.

[7] T. N. Polynova and M. A. Porai-Koshits, *J. Struct. Chem.*, 1966, **7**, 147.

[8] F. Duus and S. O. Lawesson, *Arkiv. Kemi*, 1968, **29**, 127; A. R. Hendrickson and R. L. Martin, *Austral. J. Chem.*, 1972, **25**, 257.

therapeutic and toxicological evaluations of the antimony tartrate–penicillamine system were made [2c] with compounds obtained by treating potassium bis(tartrato)-diantimonate(III) (te) (1 mol) with DL-penicillamine (3.4 and 4.5 mol). This was followed by freeze-dry work-up to isolate the crystalline product. There are two basic reasons why such preparations are not good for biological evaluations: (*i*) te has been shown [9] to be dimeric both in the solid and liquid states, dmc may displace one or all the tartrates co-ordinated to Sb^{III}, and the clinical results observed may be due to the chemical and structural nature of the new compound; (*ii*) L-penicillamine is more toxic and is absorbed by the human body more than the D form.[10]

Reactions of te with dmc in mol ratios less than 1:3 did not produce crystalline products. However, mixtures with mol ratios greater than 1:3 produced white crystalline products within 5 min of mixing. The ^1H n.m.r. spectrum of this compound has been discussed. The chemical-shift and i.r. data are given in Tables 3 and 1,

TABLE 3

N.m.r. data for the antimony(III) compounds at 34 °C

	δ/p.p.m.		
Compound	CH	CH_3	SH, OH, CO_2H, NH_2
$K[Sb(dmc)_2]$ [a]	3.74	1.50, 1.57	4.60
te [a]	4.68		4.61
$H[Sb(td)_2]\cdot OH_2$ [b]	6.63, 6.75, 7.12, 7.22	2.22	1.56
$[Sb(td)Cl]\cdot OH_2$ [c]	6.70, 6.85, 7.20, 7.75	2.30	
[Sb(btb)] [d]		3.20	2.15

[a] In D_2O with Na(dss) as internal reference. [b] In $CDCl_3$ with $SiMe_4$ as internal reference. [c] In CCl_4 with $SiMe_4$ as internal reference. [d] In $(D_3C)_2SO$ with $SiMe_4$ as internal reference.

respectively. Apart from the i.r. peaks discussed in the previous section, other prominent peaks in the spectrum occurred at 1 580 (CO stretch) and 1 515 cm^{-1} (NH_2 bend).

The ^1H n.m.r. spectra of $[Sb(td)Cl]\cdot OH_2$ and $H[Sb(td)_2]\cdot OH_2$ in CCl_4 and $CDCl_3$, respectively, are shown in Figure 2. The observation of a single resonance for the methyl protons (δ 2.22 p.p.m.) and a set of resonances for the benzene protons (δ 6.63, 6.75, 7.12, and 7.22 p.p.m.) for $H[Sb(td)_2]\cdot OH_2$ and a single methyl peak (δ 2.30 p.p.m.) and a set of benzene resonances (δ 6.70, 6.85, 7.20, and 7.75 p.p.m.) for $[Sb(td)Cl]\cdot OH_2$ confirms the equivalence of the magnetic environments of the protons in the two chelates. The i.r. spectra for the two compounds were similar except for more peaks for $[Sb(td)Cl]\cdot OH_2$ (Table 1).

The measured conductances of 1mM solutions of $H[Sb(td)_2]\cdot OH_2$ in chloroform and $[Sb(td)Cl]\cdot OH_2$ in methanol were 0.0 and 6.5 S cm^2 mol^{-1}, respectively. These values imply little ionization in the two solvents in which the compounds are most soluble. However, the insolubility or decomposition of these two compounds in water or other organic solvents prevented accurate determination of their conductance. The molecular weights for the two compounds in chloroform are 660 and 780, respectively. The value for the latter compound in glycol monomethyl ether is 275 (Calc.: 347). These values are consistent with a dimeric structure for the two compounds in chloroform solution and an unassociated structure for the latter compound in glycol monomethyl ether solution. The combined ^1H n.mr., i.r., analysis, molecular-weight, and conductance data are consistent with formation of a four-co-ordinate structure for $H[Sb(td)_2]\cdot OH_2$ and a three-co-ordinate structure for $[Sb(td)Cl]\cdot OH_2$.

The ^1H n.m.r. spectrum of [Sb(btb)Cl] in $(D_3C)_2SO$ showed a single peak for the exchanging amine and imine

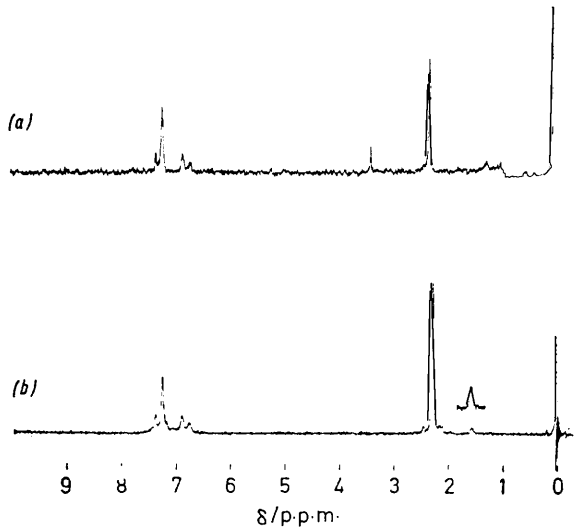

FIGURE 2 ^1H N.m.r. spectra of $[Sb(td)Cl]\cdot OH_2$ in CCl_4 (*a*) and $H[Sb(td)_2]\cdot OH_2$ in $CDCl_3$ (*b*) at 34 °C with $SiMe_4$ as internal reference

protons (δ 2.15 p.p.m.) and a single resonance for the methyl protons (δ 3.20 p.p.m.), similar to the spectrum of the ligand alone in this solvent [δ 3.22 (CH_3), 2.18 p.p.m. (NH and NH_2)] except for the peak ratios which approach 2:3 in the former and 1:1 in the latter. The Nujol-mull i.r. spectrum of [Sb(btb)Cl] (Table 1) exhibited a peak at 3 400s cm^{-1}, assigned to unco-ordinated amine, and three peaks at 3 250s, 3 195s, and 3 150s cm^{-1}, assigned to the co-ordinated imine stretches. The other i.r. peaks indicate reduced C=N and C=S strengths. The measured molar conductance of a 1mM solution of this compound in dimethyl sulphoxide was 2.5 S cm^2 mol^{-1}. These data, together with the elemental analyses, indicate that the charged Sb^{III} is neutralized by the ligand which completely encapsulates the cation in either a trigonal-bipyramidal or pseudo-trigonal-bipyramidal structure.

Earlier reports [3b] indicated that $[Et_4N][Sb(ded)_2]$ was unstable to air oxidation. We found that replacement of the cation by $[Bu^n_4N]^+$ results in very stable crystals which can be left open to the air indefinitely. The i.r

[9] R. E. Tapscott, R. L. Belford, and I. C. Paul, *Co-ordination Chem. Rev.*, 1969, **4**, 323; A. Zalkin, D. H. Templeton, and T. Ueki, *Inorg. Chem.*, 1973, **12**, 1641; G. Anderegg and S. Malik, *Helv. Chim. Acta*, 1970, **53**, 577; *Chimia*, 1967, **27**, 541.

[10] B. Sarkar, *Proc. 16th Internat. Conf. Co-ordination Chem.*, Dublin, 1974.

spectra of ded chelates are characterized by three bands, namely the perturbed C=C stretching mode, ν_1, the perturbed C=S stretching mode, ν_2, and the RC(S)C stretching mode, ν_3. In most square-planar transition-metal complexes these bands appear as singlets. However, in square-pyramidal or less-symmetric chelates [11] these frequency modes may be split. I.r. spectra for KBr discs and Nujol mulls were recorded for $[Bu^n_4N][Sb(ded)_2]$. The KBr spectrum (Table 1) showed multiple peaks for the C≡N, C=C, and C=S regions. This may be due to the less-symmetric structure of this compound. The molar conductance of a 1mM methanol solution of $[Bu^n_4N][Sb(ded)_2]$ was 66.25 S cm^2 mol^{-1} and indicates a 1:1 electrolyte. These data alone cannot determine unambiguously the structure of $[Sb(ded)_2]^-$, but the postulate of a square-pyramidal or pseudo-trigonal-bipyramidal structure would not be inconsistent. Detailed studies of the biological activity, and redox and hydrolysis properties, of these compounds are in progress.

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[11] A. L. Blach, *J. Amer. Chem. Soc.*, 1969, **91**, 6962; J. A. McCleverty, J. Locke, and E. J. Wharton, *J. Chem. Soc.* (*A*), 1968, 816.