Thiosemicarbazone complexes of copper(II): structural and biological studies

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ABBREVIATIONS*

HAcactsc	1-acetylacetone thiosemicarbazone
HAcPytsc	2-acetylpyridine thiosemicarbazone
HAcPyOtsc	2-acetylpyridine *N*-oxide thiosemicarbazone
HAntsc	*p*-anisaldehyde thiosemicarbazone
H_2ATS	diacetylglyoxalbis(thiosemicarbazone)
H_2BrSatsc	5-bromosalicylaldehyde thiosemicarbazone
HBzPytsc	2-benzoylpyridine thiosemicarbazone
HFoFutsc	2-formylfuran thiosemicarbazone
HFolQtsc	1-formylisoquinoline thiosemicarbazone
HFoPytsc	2-formylpyridine thiosemicarbazone
HFoPyOtsc	2-formylpyridine *N*-oxide thiosemicarbazone
H_2KTS	3-ethoxy-2-oxobutyraldehyde bis(thiosemicarbazone)
HMIstsc	*N*-(4-methylpiperidine)isatin thiosemicarbazone
HPictsc	3-hydroxy-5-hydroxymethyl-4-formyl-2-picoline thiosemicarbazone
HPiptsc	piperonaldehyde thiosemicarbazone
HPqtsc	9,10-phenanthroquinone thiosemicarbazone
H_2PTS	methylglyoxalbis(thiosemicarbazone)
H_2Pyrutsc	pyruvic acid thiosemicarbazone
H_2Pyrua(tsc4Me)$_2$	pyruvaldehyde bis(^{4}*N*-methylthiosemicarbazone)
H_2Satsc	salicylaldehyde thiosemicarbazone
HVatsc	vanillin thiosemicarbazone
RSV	Rous sarcoma virus

A. INTRODUCTION

(i) Biological importance of copper(II) complexes

Copper(II) is a biologically active, essential ion; its chelating ability and positive redox potential allow participation in biological transport reactions [1]. Also, copper(II) forms the active centers of more than a dozen metalloproteins [2–7]. Further, copper(II) complexes possess a wide range of biological activity and are among the most potent antiviral, antitumor and antiinflammatory agents. For example, a copper(II) complex of 2-formylpyridine thiosemicarbazone has been shown to inhibit the RNA-dependent DNA polymerases and the transforming ability of Rous sarcoma

* A symbol after tsc in an abbreviation indicates the substituent attached to or including ^{4}N of the thiosemicarbazone moiety. For example, 4Me = ^{4}*N*-methyl-4DMe = ^{4}*N*-dimethyl-, pip = piperidine includes ^{4}N.

virus (RSV) [8]. In addition, copper(II) complexes of 2-acetylpyridine thiosemicarbazones are active antimalarial agents [9]. They possess strong antineoplastic activity against a number of transplantable tumors, spontaneous murine tumors [10] and human tumors [11]. The mechanism of their antitumor action is considered to involve either inhibition of the enzyme, ribonucleotide reductase, an obligatory enzyme in DNA synthesis [12–14] or creation of lesions in DNA strands [15]. Synthetically prepared copper(II) complexes have been successful in treating inflammatory diseases such as rheumatoid arthritis [16–18]. These biological activities have provided an impetus to the study of transition metal ion complexes of thiosemicarbazones in general, and have prompted us to update [19–24] the structural-activity correlations of their copper(II) complexes. Throughout this work we concentrate on the relationship between the physical and biological properties of copper(II) thiosemicarbazone complexes of different stoichiometries.

(ii) Historical interest in copper(II) thiosemicarbazone complexes

Liebermeister [25] demonstrated that the presence of copper(II) ions enhances the antitubercular activity of *p*-acetamidobenzaldehyde thiosemicarbazone. Petering and co-workers [26] showed that the intermediate in the antitumor activity of 3-ethoxy-2-oxobutyraldehyde bis(thiosemicarbazone), H_2KTS, was the 4-coordinate chelate, [Cu(KTS)] (Fig. 1). Its crystal structure was reported shortly thereafter, confirming it as a CuN_2S_2 chromophore [27]. Electron spin resonance spectral studies [28] on this and related compounds have indicated the presence of both monomers and dimers with the latter having sulfur bridging to axial positions of two planar copper(II) centers to yield a centrosymmetric dimer. Binding of the anticancer agent Cu(FoPytsc), the copper(II) complex of 2-formylpyridine thiosemicarbazone, with Ehrlich ascites tumor cells has been described [29]. This complex was found to inhibit cellular DNA formation at low concentrations by binding via the thiol groups.

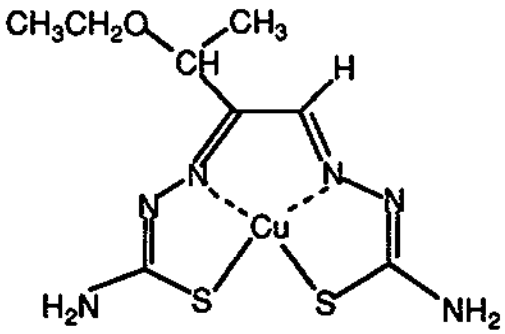

Fig. 1. [Cu(KTS)].

(iii) Synthesis

Synthetic methods for thiosemicarbazones have been well discussed by Klayman et al. [30,31], as well as in a more recent report by Scovill [32]. This latter method involves a trans-amination making use of ^4N-methyl-^4N-phenylthiosemicarbazide. Preparations of copper(II) complexes have been accomplished in a variety of solvents at different pH values and temperatures. These differing preparative methods and changes in the nature of the substituents attached to ^{1}N and ^{4}N (Fig. 2) have yielded cationic, neutral and anionic copper(II) complexes. Coordination sites in addition to those of the thiosemicarbazone moiety (e.g. phenol oxygen, pyridyl nitrogen, etc.) have yielded complexes in which the thiosemicarbazone is a tridentate or higher denticity ligand. The numbering of Fig. 2 is in accord with IUPAC convention and will be used throughout this review.

(iv) Bonding types

The thiosemicarbazone moiety (Fig. 2) without substituents attached to the thione sulfur coordinates as either a neutral or anionic NS bidentate ligand, depending on the method of complex preparation [33]; a third coordinating atom often gives ONS (e.g. 2-hydroxybenzaldehyde thiosemicarbazones) [34] or NNS (e.g. 2-acetylpyridine thiosemicarbazones, Fig. 3) tridentate ligands. A few examples of higher denticity involving one or more thiosemicarbazone moieties, as well as monodentate coordination, have been reported [35]. When an additional coordinating functionality is present in the proximity of the donating centers, the ligands bond in a tridentate manner. This occurs with either the neutral molecule [36], or the monobasic anion upon loss of a hydrogen from ^{2}N [35]. If the additional functionality

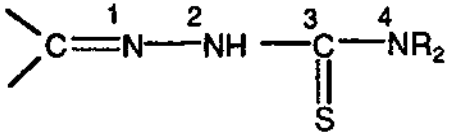

Fig. 2. Thiosemicarbazone moiety.

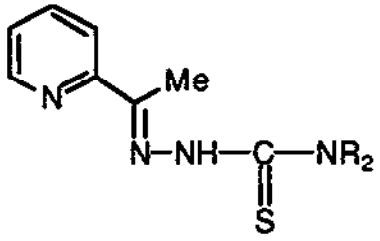

Fig. 3. 2-Acetylpyridine thiosemicarbazone, HAcPytsc.

can also lose a proton (e.g. phenolic group), anions of greater negative charge are formed. There are instances reported, however, where the heterocyclic atom and the azomethine nitrogen are involved in bidentate coordination [37], and the sulfur atom is considered not to be coordinated, weakly coordinated to the same metal center, or coordinated to an adjacent metal center [35].

B. CRYSTAL STRUCTURES OF COPPER(II) THIOSEMICARBAZONES

A number of crystal structures have been reported for thiosemicarbazone complexes, but most often the metal ion has been nickel(II) [38] rather than copper(II). One of the early structures solved was that of [Cu(butane-2-oxime-3-thiosemicarbazone)Cl] [39]. The copper(II) center has the thiosemicarbazone coordinating via the oxime nitrogen, azomethine nitrogen and thione (or thiol) sulfur with the chloro ligand completing the basal plane. A centrosymmetric dimer is formed by bridging sulfur atoms, with the Cu–S distances for the planar and axial sulfurs being 232 and 295 pm, respectively. Ferrari et al. [40] solved the crystal structure of 3-hydroxy-5-hydroxymethyl-4-formyl-2-picoline thiosemicarbazone, HPictsc (Fig. 4). HPictsc, when reacted with aqueous copper(II) chloride, yields [Cu(Pictsc)-H_2O]Cl·H_2O [41] and this green solid has the deprotonated Pictsc (from ^{2}N) coordinated via the pyridoxyl oxygen, axomethine nitrogen and thiol sulfur with an aqua ligand completing a nearly planar agreement about the copper(II) center. There is a weak interaction with the sulfur atom of a neighbouring site to form a centrosymmetric dimer.

Pyruvic acid thiosemicarbazone (Fig. 5), H_2Pyrutsc, forms copper(II) complexes of stoichiometry, [Cu(HPyrutsc)X]·nA (X = monobasic anion, n = 0, 1, 2 and A is the preparative solvent, e.g. methanol) [42]. More recently, crystal structures of the methyl ester of pyruvic acid thiosemicarbazone, HMePyrutsc, as well as its copper(II) complexes and that of the ethyl ester, HEtPyrutsc, were reported [43]. The uncoordinated HMePyrutsc was found to be 100% E-isomer (^{2}N trans to the more complex azomethine carbon substituent as in Fig. 4), as has been found for 2-formylpyridine thiosemicarbazone [44] and, more recently, for the lighter 2-acetylpyridine ^4N-

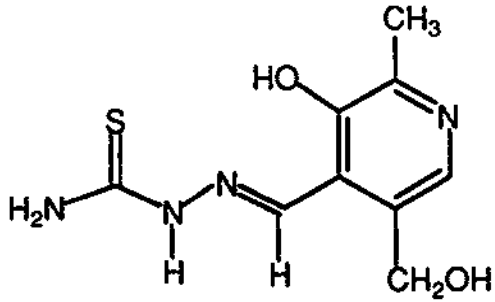

Fig. 4. 3-Hydroxy-5-hydroxymethyl-4-formyl-2-picoline thiosemicarbazone, HPictsc.

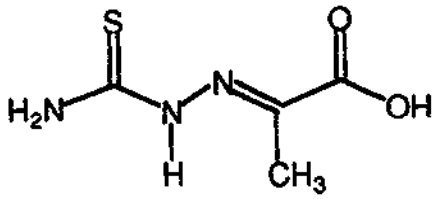

Fig. 5. Pyruvic acid thiosemicarbazone, HPyrutsc.

alkylthiosemicarbazones [45,46]. The green, dimeric complex, [{Cu(EtPyrutsc)Cl}$_2$], has a center of inversion between the five coordinate (4+1) square pyramidal copper(II) sites with a bridging chloro ligand occupying apical position(s) (Fig. 6) [43]. This compound was formed on reflux in ethanol when starting with the methyl ester. Also isolated from this same solution was a blue, polymeric complex, {[Cu(HPyrutsc)Cl]·2H$_2$O}$_n$ in which both thione sulfur and chlorine atoms are bridging to yield a zig-zag chain along the crystallographic *c* axis.

The structure of copper(II) pyruvaldehyde bis(^{4}*N*-methylthiosemicarbazone), [Cu{Pyrua(tsc4Me)$_2$}], has recently been shown to involve a Cu(SNNS) coordination sphere [47] similar to that shown in Fig. 1. The Cu–S bond lengths are 226 and 227 pm, while the Cu–N bond lengths are 197 and 198 pm with the coordination sphere approaching a square planar configuration. The copper atom interacts with a sulfur atom of an adjacent molecule and this bond length is 293 pm. This latter sulfur provides structural evidence for the vulnerability of the molecule to attack by sulfur at this coordination site. It is well documented that copper(II) bis(thiosemicarbazone) complexes are reductively decomposed by reaction with intracellular sulfhydryl groups [48]. Further, this compound is the most promising copper tracer studied

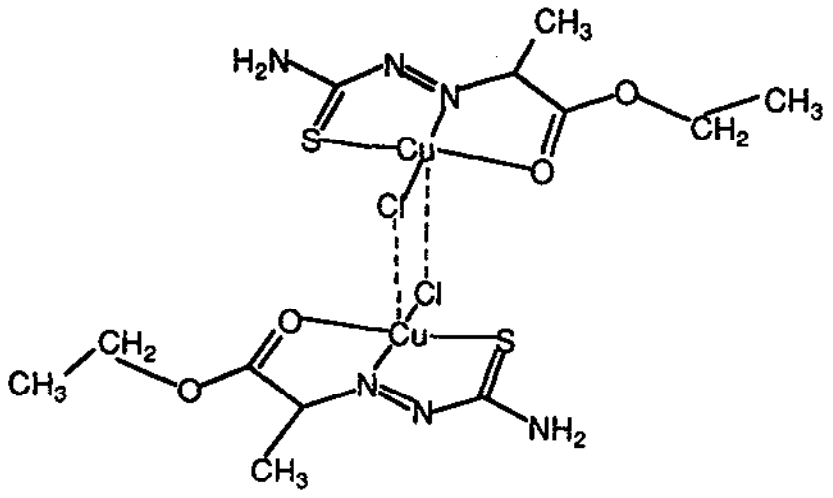

Fig. 6. [{Cu(EtPyrutsc)Cl}$_2$].

to date; it shows excellent brain uptake and retention in animal model systems following i.v. injection and may be suitable for measurement of regional cerebral and myocardial blood flow [49]. A more recent study reports on the investigation of this compound, as well as the ^4N-dimethyl-, ^4N-ethyl- and unsubstituted thiosemicarbazone, as a radiopharmaceutical for evaluation of regional blood flow in the brain, heart and kidneys [50]. The ^4N-methyl and unsubstituted copper(II) complexes afford relatively high levels of radioactivity in these organs on intravenous injection, followed by prolonged tissue retention of the radiolabel.

The structure of the dimeric copper(II) complexes of the binucleating ligand 2,6-diformyl-4-methylphenol bis(*S*-methylisothiosemicarbazone) has been reported [51]. Each copper(II) center is coordinated by the azomethine nitrogen, ^{1}N, and the ^{4}N nitrogen with the phenolic oxygen serving as one of the bridging atoms, and the second bridging atom (group) being Cl, Br, OH, OCH_3, OC_2H_5 and O_2CCH_3. However, no biological studies of this type of thiosemicarbazone complex have been reported.

The structure of the dimeric copper(II) complex derived from 2-formylpyridine thiosemicarbazone, HFoPytsc, and copper(II) acetate has been reported by both Bell and Theocharis [52] and Muller and co-workers [53]. Both groups show the complex involves a tridentate (NNS), deprotonated thiosemicarbazone ligand the fourth basal position occupied by a strongly coordinated acetato oxygen (i.e. Cu–O, 195 pm). Figure 7 shows a representation of the centrosymmetric dimer, bridged by a more weakly coordinated, axial, acetato oxygen (i.e. Cu–O′, 242 pm).

The acetate dimer yields a second dimeric product when suspended in concentrated sulfuric acid [53]. The bridging of the sulfato ligands is unsymmetrical with respect to the two copper–oxygen bond distances (i.e. Cu–O, 192 pm; Cu–O′, 231 pm). The neutral 2-formylpyridine thiosemicarbazone coordinates via the pyridyl

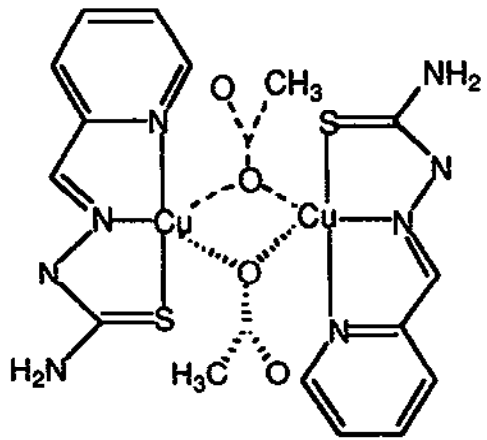

Fig. 7. $[\{Cu(HFoPytsc)CH_3CO_2\}_2]$.

nitrogen, azomethine nitrogen and thione sulfur. The Cu–S distance for the thione sulfur in this complex is 228 pm [53], while a value of 227 pm [52,53] is reported for the thiol sulfur in the acetato dimer. More recently, these authors reported an additional copper(II) complex of 2-formylpyridine thiosemicarbazone prepared from the trifluoroacetate salts [54]. The first 2-acetylpyridine ^{4}N-substituted thiosemicarbazone complex with copper(II) has been shown to be a planar arrangement of the NNS anionic thiosemicarbazone with a chloro ligand completing the coordination of the copper(II) center [55].

2-Formylpyridine *N*-oxide thiosemicarbazone forms a dimeric complex with copper(II), $[Cu_2(HFoPyOtsc)_2(H_2O)_2]$, which features *N*-oxide bridges [56]. Variable temperature magnetic studies have been reported for this complex [57], but no biological studies have been reported.

C. MAGNETIC STUDIES

(i) Magnetic moments

The majority of the magnetic moments of copper(II) thiosemicarbazone complexes have been measured at room temperature. Many are at, or above, the spin-only value of 1.73 B.M. even though weak interactions (Cu–Cu distances of more than 350 pm) occur between adjacent copper(II) sites. An example of this is 3-hydroxy-5-hydroxymethyl-4-formyl-2-picoline thiosemicarbazone (Fig. 3), H_2Pictsc, which, when reacted with aqueous copper(II) chloride, yields dark green [Cu(HPictsc)H_2O]Cl·H_2O [27]. This compound has a magnetic moment of 1.81 B.M., and the ligand is coordinated via the phenolic oxygen, azomethine nitrogen and thiol sulfur with an aqua ligand completing the nearly planar arrangement about the copper(II) center. There is a weak interaction with a sulfur of a neighboring site to form a centrosymmetric dimer.

We concentrate our discussion on those copper(II) complexes that have magnetic moments significantly less than 1.73 B.M. A 1:1 $CuCl_2$ to 2-hydroxynaphthaldehyde thiosemicarbazone, H_2Naptsc, mixture refluxed in DMF formed [Cu(HNaptsc)Cl] [15]. Although its electronic and ESR spectra were not recorded, the compound has a magnetic moment of 1.54 B.M. suggesting axial interactions of the copper(II) centers; sulfur is the probable bridging atom, based on recent structural studies discussed earlier. The above-mentioned dimers, $[Cu(FoPytsc)OAc]_2$ [47,48] and $[Cu(HFoPytsc)SO_4]_2$ [48] possess normal magnetic moments, indicating weak copper(II)–copper(II) interaction (the Cu···Cu distance is >340 pm). A chloro complex of 2-formylpyridine thiosemicarbazone, $[Cu(HFoPytsc)Cl_2]$ does have a magnetic moment of 1.51 B.M. [58]. $[Cu(HAcPytsc4Me)_2])BF_4)_2$, [Cu(AcPytsc4Me)Cl], and $[Cu(HAcPytsc4Me)Br_2]$ prepared from 2-acetylpyridine ^{4}*N*-methylthiosemicarbazone all have magnetic moments in the range 1.3–1.4 B.M. [59], but the crystal structures have not yet been reported for any of these compounds. In contrast,

copper(II) complexes of 2-acetylpyridine ^4N-alkylthiosemicarbazones, $[Cu(HL)X_2]$, with larger alkyl groups generally have normal magnetic moments [46,60,61]. Exceptions are $[Cu(HAcPytsc4Et)_2](BF_4)_2$ and $[Cu(HAcPytsc4CH)_2](BF_4)_2$, where HAcPytsc4Et and HAcPytsc4CH represent 2-acetylpyridine ^4N-ethyl- [46] and ^4N-cyclohexylthiosemicarbazones [60], respectively. Similary, the majority of the copper(II) complexes prepared from 2-acetylpyridine ^4N-dialkylthiosemicarbazones [62,63], as well as 2-acetylpyridine 3-azacyclothiosemicarbazones [64–67] with copper(II) halides have normal magnetic moments. However, complexes having the general formula $[Cu(HL)L]BF_4$ often have moments in the 1.4–1.6 B.M. range [63,66]. It is interesting to note that, when a simple bridging anion such as chloride, acetate, or sulfate is not present, those complexes having magnetic moments less than the spin-only value often have one or more neutral thiosemicarbazone ligands present. This may be indicative of bonding to a second metal center by the thione sulfur. Recently, a report [68] on metal complexes of 2-benzoylpyridine thiosemicarbazone, HBzPytsc, included the black copper(II) complex, [Cu(BzPytsc)Cl], with $\mu = 1.65$ B.M. and considerable activity against *E. coli* 10536.

The magnetic moments of $[Cu(HAcPyOtsc)Cl_2]$ and $[Cu(HAcPyOtsc)Br_2]$, where HAcPyOtsc is 2-acetylpyridine *N*-oxide thiosemicarbazone, are 1.3 and 1.2 B.M., respectively [69]. This suggests considerable interaction between copper(II) centers, presumably via the thione sulfur atom although numerous examples of copper(II) complexes exist with the *N*-oxide oxygen acting as the bridge [70]. Lending credibility to this suggestion is the more recent finding that the bulkier complexes formed with HAcPyOtsc4Et, $[Cu(HAcPyOtsc4Et)Cl_2]$ and $[Cu(HAcPyOtsc4Et)Br_2]$ have magnetic moments of 1.8 and 1.9 B.M., respectively [71].

Complexes of 2-formylfuran ^4N-phenylthiosemicarbazone, HFoFutsc4Ph, having the general formula $[Cu(FoFutsc4Ph)X]_2.2H_2O$, where X = Cl and Br, have magnetic moments in the 0.7–0.8 B.M. range, leading the authors to propose dimeric structures with halo bridges [72]. No crystal structures have yet been reported for these complexes. To date, few copper(II) complexes, which have had their crystal structure solved, have been studied for their biological activity. The structure of the nickel(II) complex of 2-acetylpyridine 3-azabicyclo[3.2.2]-nonylselenocarbazone has been shown to be planar [73]. This thiosemicarbazone and its nickel(II) and copper(II) complexes all show considerable growth inhibitory activity against *Paecilomyces variotii* [74].

(ii) Electron spin resonance spectra

(a) Bis(thiosemicarbazones), Cu(SNNS)

The ESR spectrum [75] of the active antitumor agent [26] [Cu(KTS)] (Fig. 1) was measured in *N,N*-dimethylformamide at 1.4 K. The spectrum showed nine lines imposed on the $g_{\|}$ position and was interpreted as being consistent with superhyperfine interaction with four nitrogens. However, studies [76] of copper(II) complexes

of closely related bis(thiosemicarbazone) ligands have shown that the spectrum should be interpreted as superhyperfine coupling to two nitrogens (i.e. other coordination sites are occupied by the thiol sulfurs). The extra lines are due to hyperfine interactions with ^{63}Cu and ^{65}Cu (this was indicated in a footnote in the earlier paper) [75]. The spectrum of the copper(II) complex hosted by its nickel(II) complex using ^{63}Cu confirms this interpretation [77]. Other bis(thiosemicarbazones) have yielded copper(II) complexes (i.e. CuN_2S_2 chromophores) with essentially the same ESR parameters: $g_{\|}=2.12$ and $A_{\|}=192.5$ G and five superhyperfine lines due to two nitrogens with $A(N)=15$ G [78]. More recently, an ESR study of the copper(II) complex of 3-ethoxy-2-oxobutyraldehyde bis(^4N-dimethylthiosemicarbazone), [Cu(KTS4DMe)], in frozen DMSO solution has been reported [79]. The ESR spectrum of this CuSNNS center (i.e. $g_{\|}=2.14$) is very similar to the antitumor agent, [Cu(KTS)]. [Cu(KTS)] readily undergoes reduction in the presence of Ehrlich cells, but [Cu(KTS4DMe)] is stable with its ESR signal unchanged. Report of an ESR spectral study of the copper(II) complexes of diacetyl- and methylglyoxalbis(thiosemicarbazones), H_2ATS and H_2PTS, show similar ESR parameters (e.g. [Cu(ATS)]: $g_{\|}=2.118$, $A_{\|}=189$ G and [Cu(PTS)]: $g_{\|}=2.130$ and $A_{\|}=185$ G) [80].

(b) Tridentate thiosemicarbazones, Cu(ONS)

ESR studies of copper(II) complexes containing chelating ONS thiosemicarbazones such as those derived from salicylaldehyde, [Cu(Saltsc)], have been reported [81]. There is little variation in the spectra with changes on the ligand's aromatic ring and typical ESR parameters are $g_{\|}=2.190$, $A_{\|}=190$ G for these complexes in frozen DMF. Another series of copper(II) complexes containing an ONS chelating thiosemicarbazone were prepared from 2-acetylpyridine *N*-oxide 3-azabicyclo[3.2.2.]-nonylthiosemicarbazone, HAcPyOtscbcn, and ESR parameters for [Cu(AcPyOtscbcn)Cl] are $g_{\|}=2.211$ and $g_{\perp}=2.050$ [35]. More recently, there have been studies of copper(II) complexes prepared from ^4N-alkyl- [71,82] and ^4N-dialkylthiosemicarbazones [71,83] derived from 2-acetylpyridine *N*-oxide. Also, copper(II) complexes of 2-acetylpyridine *N*-oxide thiosemicarbazone [68] and 3-pyrrolidinylthiosemicarbazone (HAcPyOtscpo) [74] have now been studied. Complexes of stoichiometry $[Cu(HL)Cl_2]$ are often formed by the ^4N-alkyl- and smaller 3-azacyclic derivatives, but the ^4N-dialkyl- and larger 3-azacyclic compounds form [Cu(L)Cl] complexes. The former have $g_{\|}=2.190$–2.210, but $g_{\|}$ values for the latter complexes are in the 2.130–2.150 range [71]. These copper(II) complexes of 2-acetylpyridine *N*-oxide thiosemicarbazones showed no growth inhibitory activity against *Aspergillus niger*, but $[Cu(HAcPyOtscpo)X_2]$ (X = Cl and Br) shows modest activity against *Paecilomyces variotii*, though not as great as the copper(II) complexes of the analogous 2-acetylpyridine thiosemicarbazone [84].

A thiosemicarbazone of a Mannich base of isatin with 4-methylpiperidine, HMIstsc, was reported to be an effective antifungal agent [85]. Four copper(II) complexes were isolated and their ESR spectra were recorded as powders and as

DMF solutions. [Cu(Mlstsc)Cl] and [Cu(Mlstsc)Br] have isotropic signals in both media, $g_{iso}=2.105$ and 2.114, respectively, but [Cu(Mlstsc)OAc] and [Cu(HMlstsc)SO_4] have rhombic signals with $g_1=2.226$, $g_2=2.106$ and $g_3=2.048$ and $g_1=2.209$, $g_2=2.110$ and $g_3=2.052$, respectively. [Cu(Pqtsc)Cl]·2DMF, where HPqtsc is 9,10-phenanthroquinone thiosemicarbazone, also yielded a rhombic ESR spectrum, but the g values, 2.129, 2.072 and 2.018, are vastly different [86].

(c) Tridentate thiosemicarbazones, Cu(NNS)

The majority of the ESR studies have concentrated on copper(II) complexes of heterocyclic thiosemicarbazones, and in particular those derived from 2-formyl- and 2-acetylpyridine. The powder ESR spectrum of {[Cu(Fotsc)OAc]$_2$} is rhombic with g values of 2.20, 2.06 and 2.04 [53]. In frozen DMSO, the dimer remains intact, but in aqueous solution it converts to [Cu(Fotsc)(H_2O)]$^+$. The olive green [Cu(HFotsc)Cl_2], as well as [Cu(Fotsc)Cl], which has the anionic form of the ligand on loss of the ^{2}N proton, have similar g values [58], but anisotropic spectra.

Two copper(II) complexes of 2-acetylpyridine thiosemicarbazone, HAcPytsc, were included in this study [58]; [Cu(AcPytsc)OAc] and [Cu(HAcPytsc)Cl_2] both have $d_{x^2-y^2}$ ground state ESR spectra with $g_{\|}=2.16$ and 2.18, respectively. A much larger number of copper(II) complexes of ^{4}N-substituted 2-acetylpyridine thiosemicarbazones have ESR data reported [32,35,46,60–63,65,66,74,82,84] than those of 2-formylpyridine thiosemicarbazones. Fungal growth inhibitory studies of these copper(II) complexes have been included in some of the recent reports [63,73,84]. With increasing bulkiness of the ^{4}N-substituent(s), there is a trend to lower $g_{\|}$ values and higher $A_{\|}$ values. This increase in size parallels the ability of these complexes to inhibit the growth of *Aspergillus niger* [63], *Penicillium rubrum* [84] and *Aspergillus terreus* [84]. However, a fourth fungus, *Paecilomyces variotii*, against which these complexes show their greatest inhibitory activity, is most affected by copper(II) complexes of thiosemicarbazones having medium to small substituents attached at ^{4}N [63,84]. Further, copper(II) complexes of 2-acetyl-pyridine thiosemicarbazones ^4N-dialkyl- and 3-azacyclic substituents, in contrast to ^4N-alkyl- substituents [74], have considerably more activity against all four fungi [63,73]. Similar trends in size of ^{4}N-substituent, $g_{\|}$ and inhibition of fungal growth have been observed for 2-acetylpyrazine ^{4}N-substituted thiosemicarbazones [87]. A biological study of some of these complexes, as well as the uncoordinated thiosemicarbazones and their thiosemicarbazides, has shown that there is no inhibition of chitin biosynthesis [88]. This indicates that the toxicity of these compounds to fungi is not the result of destruction of the cell wall.

A green, monomeric complex of 2-aminoacetophenone ^4N-phenylthiosemicarbazone, [Cu(NNS)OAc]·3H_2O has been isolated along with this ligand's complexes with other metal centers [89]. The antimicrobial data of this complex was not reported, but the nickel(II), cobalt(II) and zinc(II) complexes all possess greater

activity than the uncomplexed ligand with the zinc complex having the greatest activity against each of the organisms tested.

(d) Pentadentate thiosemicarbazones, Cu(SNNNS)

It has been reported [90] that 2,6-diacetylpyridine bis(thiosemicarbazone) does not possess significant activity in a P388 lymphocytic leukemia screen. This ligand coordinates via the pyridyl nitrogen, both azomethine nitrogens and both thione sulfurs based on infrared studies (vide infra). Its copper(II) complex, as well as the other metal complexes, are somewhat more active than the uncoordinated bis(thiosemicarbazone), but are toxic at higher concentrations. The zinc(II) complex was the most active in the leukemia screen. This same laboratory [91] prepared metal complexes of a variety of bis(thiosemicarbazones) of 2,6-diacetylpyridine with both ^{4}N atoms involved in a cyclic ring. The copper(II) complexes of these bis(3-azacyclothiosemicarbazones) again have the stoichiometry [Cu(SNNNS)] and their ESR spectral parameters were reported. The signal at $g \approx 2.020$ indicates a d_{z^2} ground state and the signal is non-axial with the other two g values at ca. 2.117 and 2.244, indicating considerable distortion from trigonal bipyramidal symmetry. Even though most of the thiosemicarbazones and their complexes do not show significant activity against P388 lymphocytic leukemia test system in mice, the copper(II) complex of 2,6-diacetylpyridine bis{3-(3,5-piperidinyl)thiosemicarbazone} was the most active.

Although a number of biological studies of copper(II) thiosemicarbazone complexes, as well as other metal complexes, have recently appeared, few have included ESR data. A recent report on five copper(II) complexes, CuL_2, of phenylazo-3-methoxysalicylidene thiosemicarbazone and some of its ^{4}N-substituted derivatives has both ESR information and antitumor activity [92]. The bonding is considered to be via the deprotonated phenolic oxygen and azomethine nitrogen, but not the thione sulfur. The unsubstituted thiosemicarbazone complex of copper(II) has $g_{\|} = 2.125$, surprisingly low for the absence of sulfur coordination, and shows promising growth inhibition in vitro and in vivo against P388 lymphocytic leukemia cells.

D. SPECTRAL STUDIES

(i) Infrared spectra

Earlier reviews [19–21,23,24] have detailed assignment of the important bands of thiosemicarbazide and a number of thiosemicarbazones. Thiosemicarbazone coordination often occurs with loss of the ^{2}N proton and involves bonding via the azomethine nitrogen, ^{1}N, and thiol sulfur. Decreases by 10–30 cm^{-1} of ν(C=N) (ca. 1590 cm^{-1}) accompanied by the appearance of a band in the 420–480 cm^{-1} region assignable to ν(CuN) have been used to establish nitrogen coordination. Deprotonation results in double bond formation beteen ^{2}N and ^{3}C and a band at ca. 1600 cm^{-1} has caused some authors to suggest an increase in energy of the azomethine bond.

Decreases of ca. 100 cm^{-1} to 700–730 cm^{-1} for ν(CS) and ν(CuS) in the 330–380 cm^{-1} region are consistent with thiol coordination. Some authors have reversed the energies for ν(CuS) and ν(CuN) with the latter proposed to be of lower energy. Nevertheless, there is considerable agreement that loss of the ^{2}N proton promotes binding of the azomethine nitrogen and thiol sulfur of the thiosemicarbazone moiety. This bonding can be accompanied by coordination of another atom such as a phenolic oxygen in salicylaldehyde thiosemicarbazones or a pyridine nitrogen of 2-formyl- or 2-acetylpyridine pyridine thiosemicarbazones, as indicated earlier.

There is less certainty concerning the bonding of neutral thiosemicarbazone moieties. Bonding of the azomethine nitrogen, ^{1}N, is generally considered to occur, but coordination of the thione sulfur may, or may not, occur. The thioamide IV band, which has considerable ν(CS) character, shifts to lower energy by 10–30 cm^{-1} on coordination, and the spectra are very complicated in this spectral region. This is particularly true for thiosemicarbazones having additional coordinating sites. Heterocyclic thiosemicarbazones have provided complexes of stoichiometry [Cu(HL)(L)]X (where HL = neutral thiosemicarbazone, L = anionic thiosemicarbazone bound as NNS or ONS tridentate ligand and $X = ClO_4^-$ or BF_4^-). It is suggested, based on an unshifted ν(CS), that coordination does not occur via the thione sulfur, but interaction with an adjacent copper(II) center may occur [35,59]. As indicated in Sect. B of this review, too few X-ray crystallographic studies of this type of thiosemicarbazone complex have been completed to establish whether the thione sulfur of a neutral thiosemicarbazone moiety is *always* coordinated as a part of a chelating agent to the same metal ion.

A monomeric copper(II) complex of *p*-anisaldehyde thiosemicarbazone, $[Cu(HAntsc)SO_4]\cdot H_2O$, was shown to have less antifungal activity against three fungi than the uncomplexed thiosemicarbazone [93]. Bonding of HAntsc, based on infrared studies, is via the azomethine nitrogen and thione sulfur, and coordination of these functions was indicated as the reason for the reduced activity of the complexes [93]. A later report of the inhibition of fungal growth by metal complexes (i.e. Mn(II), Fe(II), Co(II), and Ni(II)) of HAntsc showed them to be superior to the free thiosemicarbazone [94].

(ii) Electronic spectra

This technique is less valuable than others discussed for studying this group of complexes. All thiosemicarbazones have a strong band due to a $n\rightarrow\pi^*$ transition at ca. 30 000 cm^{-1} and some have a second $n\rightarrow\pi^*$ band at ca. 25 000 cm^{-1}, both of which tail into the visible region [63]. Heterocyclic, as well as thiosemicarbazones with another coordinating function, often possess additional bands in the near UV region [87]. For the complexes, particularly on coordination of either the thiol or thione function, charge transfer bands occur at energies as low as 22 000 cm^{-1}

(20 000 cm^{-1} if Br is coordinated). Therefore, assignment of d–d bands is often based on resolution of shoulders on the more intense, higher energy bands. A copper complex of 1-formylisoquinoline thiosemicarbazone, [Cu(HFolQtsc)Cl_2], shows d–d bands at 9260 and 12 500(sh) cm^{-1} in its reflectance spectrum [95]. This led to assignment of approximately trigonal bipyramidal symmetry, and this complex showed some activity in the P388 lymphocytic leukemia screen, though not as much as [Ni(HFolQtsc)Cl_2]. A complex of the same stoichiometry prepared with 4-methyl-5-amino-1-formylisoquinoline had d–d bands at 10 200 and 13 510 cm^{-1} and showed less activity [96] in the screen than [Cu(HFolQtsc)Cl_2]. Similarly, the copper(II) complex of 4-(*m*-aminophenyl)-2-formylpyridine thiosemicarbazone had bands at 10 300 and 13 500 cm^{-1} and was toxic to the mice [97]. The uncomplexed thiosemicarbazone showed good antitumor activity in vivo against sarcoma 180 ascites cells in earlier tests [98]. Vanillin thiosemicarbazone forms [Cu(HVatsc)Cl_2], which is considered a $CuNSCl_2$ center, and has a d–d band at 15 400 cm^{-1} [99]. This complex was the most effective against three different pathogenic fungi compared to seven complexes of other metals and the free ligand.

The red-brown copper(II) complexes of salicylaldehyde and 5-bromosalicylaldehyde thiosemicarbazones, Cu(Satsc) and Cu(BrSatsc), respectively, have magnetic moments considerably less than 1.73 B.M. with the former being diagmagnetic [100]. Normal magnetic moments were found for the 1 : 1 heterocyclic base adducts which are green; [Cu(Satsc)py] has a d–d band at 16 950 cm^{-1}. The copper(II) complexes and the heterocyclic base adducts have similar growth inhibition activity against the fungi *Alternaria alternata*, *Fusarium moniliforme* and *Drechslera oryzae*. Both are considerably more active than the nickel(II) complexes and the uncomplexed thiosemicarbazones [100]. 1-Benzoin ^4N-phenylthiosemicarbazone, H_2Bztsc4Ph, forms a green 1 : 1 complex with $\mu = 1.27$ B.M. on loss of two hydrogens [101]. Cu(Bztsc4Ph) has a d–d composite band maximum at 17 240 cm^{-1} and is active against the two fungi, *Aspergillus niger* and *Candida tropicalis*, and two bacteria, *Staphylococcus aureus* and *Escherichia coli*. The copper(II) complex of 1-acetylacetone ^4N-ethylthiosemicarbazone, [Cu(HAcactsc4Et)$(OAc)_2$], has a composite d–d band maximum of 17 860 cm^{-1}, and possesses inhibitory activity against these same fungi and bacteria [102].

The 2-acetylpyridine thiosemicarbazones that form complexes with loss of the ^{2}N proton, [Cu(L)X], have their ν(d–d) composite bands in the 16 500–18 000 cm^{-1} range and often have a discernible shoulder at ca. 14 000 cm^{-1} [63]. These complexes show considerable growth inhibitory activity against various fungi. Complexes of stoichiometry [Cu(HL)X_2] show little or no activity against these same fungi [74,82]. These latter complexes have a composite ν(d–d) band in the 14 000–15 000 cm^{-1} range.

Formation of a series of copper(II) complexes of bis(thiosemicarbazones) was confirmed by their absorption at 20 400 cm^{-1} and molar absorptivity at this wavelength of $2–3 \times 10^3$ [103]. These complexes were being evaluated for use in binding

radioisotopes of copper to antibodies and it was demonstrated that the shorter-chain analogues of the thiosemicarbazone chelates derived from 1,2-diketones give the highest radiolabeling yields.

E. THERMAL STUDIES

There have been few thermal studies and no report of the detailed kinetic study on the thermal decomposition of thiosemicarbazones or their metal complexes [104]. Recently, Laly and Parameswaran [105] have studied the thermal decomposition of copper(II) complexes of the thiosemicarbazones of salicylaldehyde, 5-bromosalicylaldehyde, 2-hydroxy-1-naphthaldehyde, and vanillin. All four complexes have $\mu = 1.1$–1.2 B.M. and are considered dimers, $[Cu(L)Cl]_2$. They thermally decomposed in two stages with the first stage ending by 350°C (except for the heavier 2-hydroxy-1-naphthaldehyde thiosemicarbazone complex which required 500°C), and the second stage ending in the 700–750°C range. Loss of the chloro ligand and a thiosemicarbazide molecule occurs in the first stage and the hydroxyaldehyde portion of the ligand in the second stage, leaving a copper oxide residue.

Two copper(II) complexes of 3,4-dihydroxybenzaldehyde thiosemicarbazone, $[Cu(LH)Cl]\cdot H_2O$ and $[CuL_2]\cdot 2H_2O$, were shown by thermal analyses to have hydrate water molecules [106]. Both of these complexes are superior to the uncoordinated ligand in their ability to scavenge superoxide ion.

A copper(II) complex of piperonaldehyde thiosemicarbazone, [Cu(Piptsc)Cl], was found to have a weak endothermic peak at 250°C followed immediately by a strong exothermic peak at 265°C [107]. On further heating, a medium exothermic peak was observed at 480°C, but no interpretation or TGA information other than temperatures were reported.

A DSC/TGA study of heterocyclic thiosemicarbazones, $HAcPytsc4Me_2$, $HAcPytsc4Et_2$ and $HAcPytsc4Pr_2$ (Fig. 3), showed loss of the ^4N secondary amine (e.g. Me_2NH) as their initial endothermic decomposition step [73]. More recent studies with more sophisticated instrumentation indicates that the thiosemicarbazones melt with heats of fusion in the range 20–35 kJ mol^{-1} prior to their initial decomposition step starting at 220°C or higher [108]. The copper(II) complexes of these thiosemicarbazones, $[Cu(AcPytsc4Me_2)Cl]$, etc. start decomposition above 250°C with enthalpy values of 45–55 kJ mol^{-1}, and this endothermic peak is often closely followed (ca. 10°C higher) by a medium to strong exothermic peak. This latter peak is indicative of dimerization or polymerization with increasing coordination numbers of the copper(II) centers. It is of interest that the analogous nickel(II) complexes do not show this exothermic transition. Preliminary results [108] indicate that 2-cyanopyridine may be the first fragment lost in the decomposition of the copper(II) complexes, but the decomposition for many of the complexes studied to date are continuous to ca. 1000°C.

F. ELECTROCHEMICAL STUDIES

Few electrochemical results have been reported to date for either thiosemicarbazones or their metal complexes, although their biological properties may be related to their redox properties. Polarographic reduction of thiosemicarbazones and semicarbazones prepared from aliphatic, aromatic and heterocyclic aldehydes and ketones in aqueous solution have produced contradictory results. Some workers suggest that reduction in acidic solution is a two-electron process [109], but others indicate a four-electron process [110].

Fleet and Zuman [111], in the course of their study of substituent effects in polarographic behavior, conclusively showed that reduction of the cations of thiosemicarbazones of saturated aldehydes occurs predominantly by a four-electron process to form a primary amine and thiourea. Results indicating less than a four-electron process may be due to (a) too high a pH, (b) partial formation of thiosemicarbazides and (c) the limiting current was not reached. Kitaev and Skrebkova [112] carried out polarographic studies of thiosemicarbazones in *N,N*-dimethylformamide with a supporting electrolyte of tetraethylammonium bromide. Of the two waves that were observed, the first was a well-defined one with electron transfer at −1.00 to −1.80 V to form an anion radical. The second wave lies at a more negative potential, −2.00 to −2.30 V, which is less defined and sometimes merges into the decomposition region of the medium.

The electrochemical properties of metal complexes with sulfur donor atoms have been determined primarily when the ligands have two sulfur donor atoms, such as dithiolenes, xanthates and dithiocarbamates [113]. Leovac et al. [114] have reported the voltammetric characterization of some iron(III) and nickel(II) complexes of aromatic *S*-methylthiosemicarbazones with various substituents on the aromatic ring. Recently, with an aim at modelling of active sites of molybdoenzymes, electrochemical behavior of molybdenum(VI), (V) and (IV) oxo complexes with salicylaldehyde thiosemicarbazone and its ^4N-phenyl derivative have been studied [115].

Cyclic voltammetry studies of copper(II) complexes of 2-acetylpyridine ^4N-dimethyl, ^4N-diethyl and ^4N-dipropylthiosemicarbazones, [Cu(L)X] (X = Cl, Br) have revealed that the copper(II)/copper(I) couples are ca. −0.44 V and ca. −0.39 V for the chloro and bromo complexes, respectively [116]. The reduction of the conjugated portion of the coordinated thiosemicarbazone ligand ranges from −1.15 to −1.30 V, with higher potentials being required for the larger dialkyl substituents. This parallels the growth inhibitory activity of these complexes for *Paecilomyces variotti*, suggesting that ease of reduction of the thiosemicarbazone ligand is important to its antifungal activity. The growth inhibition of *Aspergillus niger*, *Penicillium rubrum* and *Aspergillus terreus* by these complexes, however, appears to be less dependent on size, or to increase with increasing size of the dialkyl function [61]. Further studies of the copper(II) complexes of 2-acetylpyridine ^4N-diethylthiosemicarbazone, 2HAcPytsc4-DEt, show that they possess a broad spectrum of antifungal activity against all four

types of fungi (i.e. dermatophytes, subcutaneous and systemic, candidiasis and opportunistic pathogens) [117]. The bromo complex, [Cu(AcPytsc4DEt)Br], is generally more active than the corresponding chloro complex. Additional cyclic voltammetry studies [118] of copper(II) complexes of 2-acetylpyridine thiosemicarbazones with 3-azacyclic substituents have shown that copper(II)/copper(I) couples average less than −0.44 V. The lowest value of −0.40 V occurs for the planar complex, [Cu(AcPytscbcn)Cl], where AcPytscbcn is the anion of 2-acetylpyridine 3-azabicyclo[3.2.2]-nonylthiosemicarbazone, and is the bulkiest ligand studied to date. Reduced bulkiness of the ligand causes an increase in the potential to −0.45 V for [Cu(AcPytscpo)Cl], where AcPytscpo is 2-acetylpyridine 3-pyrrolidinylthiosemicarbazone, and it was suggested that solvent molecules are more likely to coordinate to this complex, making the conversion to a copper(I) coordination sphere more difficult. The thiosemicarbazone moiety is also more easily reduced with the presence of a bulkier 3-azacyclic group. The antifungal activity of these complexes increases with size of the azacyclo group for *Aspergillus niger*, *Penicillium rubrum* and *Aspergillus terreus*, but, again, not for *Paecilomyces variotti* [118].

G. RECENT BIOLOGICAL STUDIES OF THIOSEMICARBAZONES

This section deals with recent biological studies of thiosemicarbazones where the metal complexes have not been prepared and evaluated.

Thiosemicarbazones of 4-formylpyridazine, 3-formylpyridazine, 4-acetylpyridazine, 3-acetylpyridazine and 3-propionylpyridazine have been prepared [119,120] and their cytotoxic and antiherpetic potentials evaluated [120]. The thiosemicarbazones of 3-formyl-β-carboline and 3-acetyl-β-carboline were found to effectively inhibit the in vitro growth of the promastigote form of *Leishmania donovani*. 2-Formylpyridine thiosemicarbazone was considerably less active, while the thiosemicarbazone of ethyl-5-formyl-6-azaindole-2-carboxylate was inactive [119]. 3-Formyl-β-carboline thiosemicarbazone was observed preferentially to block DNA rather than RNA synthesis, but for 3-acetyl-β-carboline thiosemicarbazone, the reverse was true. 3-Acetyl-β-carboline thiosemicarbazone was the most active compound studied, and thus, may act (at least partly) via a novel, though as yet unelucidated, mechanism [121].

2-Acetylpyridine ^{4}N-(2-acetoxyethoxymethyl)thiosemicarbazone was shown [122] to have, among a fairly large number of thiosemicarbazones, the highest inhibitory activity against the growth of the following microorganisms: *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans* and *Aspergillus niger*. It also has activity against resistant strains of *W-2 Indochina Plasmodium falciparum* and *D-6 African Plasmodium falciparum*. This thiosemicarbazone containing the 2-acetoxyethoxy moiety, which could conceivably take up a conformation analogous to that of the ribosyl group, while the thiosemicarbazone portion of the molecule, in the presence of a suitable enzymatic site, could mimic the triazine group

found in a number of antifolates [123]. When evaluated for its antifolate activity against bovine liver dihydrofolate reductase, this thiosemicarbazone is a fully uncompetitive inhibitor of the enzyme, and it enhances the activity of methotrexate, which could make it useful for therapeutic purposes. Thiosemicarbazones derived from 2-acetylpyridine have been evaluated for their antifilarial activity [124], and the most promising was found to be 2-acetylpyridine ^{4}N-(2-aminophenyl)thiosemicarbazone. Its lack of water solubility and instability of the soluble dichloride salt on dissolution hinder its usefulness at present. It and 2-acetylpyridine 3-hexamethyleneiminylthiosemicarbazone do show promising results from in vitro testing against *Onchocerca gutturosa* and *Onchocerca volvulus* adult worms.

A number of thiosemicarbazones derived from acetophenone and derivatives of acetophenone, as well as 4-phenyl-3-buten-2-one and its derivatives, have been tested for their anticonvulsant activities [125]. The structure of 4-(4-methylphenyl)-3-buten-2-one thiosemicarbazone was found to be E with respect to both the olefinic and azomethine double bonds and it showed good activity. Acetophenone thiosemicarbazones were found to be a mixture of E and Z isomers with respect to the azomethine double bonds: the isomer ratio depends on the size of the groups attached to the azomethine carbon.

Isatin-β-thiosemicarbazones and methylisatin-β-thiosemicarbazones prevent the production of small pox virus and the latter have also been used in the clinical treatment of small pox [126].

A recent report on some gallium(III) complexes of selected-2-acetylpyridine thiosemicarbazones indicates that they are being tested for anti-HIV activity at NCI [127]. This article contains some useful NMR spectral data on the thiosemicarbazones, as well as the gallium complexes, while other recent reports deal with ^{1}H- and ^{13}C-NMR assignments of thiosemicarbazones and their platinum(II) [128], nickel(II) [129] and cobalt(III) [130] complexes.

H. CONCLUSION

Cationic, neutral and anionic copper(II) complexes of thiosemicarbazones, coordinated as both neutral and anionic ligands and as monodentate through pentadentate ligands, are represented in this review. Coordination numbers of four through six as well as monomeric and dimeric copper(II) centers have been identified. Biological screening against a number of organisms has been carried out on many of these compounds and their uncoordinated thiosemicarbazones. There is a definite pattern in the biological activity and the size of the substituents attached to the thiosemicarbazone moiety among particular classes of thiosemicarbazones. Further, those complexes having thiol, rather than thione sulfur coordination, appear to be more active. Lower $g_{\|}$ values, higher ν(d–d) band maxima and lower reduction potentials seem to relate to increased biological activity.

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