APPLIED ORGANOMETALLIC CHEMISTRY, VOL. 5, 45–50 (1991)

Antifungicidal, antibacterial and antifertility activities of biologically active heterocyclic thiosemicarbazones and their coordination complexes with the dimethylsilicon moiety

D Singh,* R B Goyal† and R V Singh*‡
* Department of Chemistry, and † Zoology Department, University of Rajasthan, Jaipur 302004, India

Synthetic, structural and biological aspects of trigonal-bipyramidal, $Me_2Si(NS)Cl$ and octahedral, $Me_2Si(NS)_2$ types of organosilicon(IV) complexes of heterocyclic thiosemicarbazones (N—SH) have been described. The complexes were characterized by elemental analysis, molecular weight determination, conductance measurements and electronic, infrared, ^1H and ^{13}C NMR spectral studies. Some ligands and their corresponding dimethylsilicon(IV) complexes have been tested for their effects on several pathogenic fungi and bacteria. Two representative complexes have also been found to act as sterilizing agents by reducing the production of sperm in male mice.

Keywords: Heterocyclic thiosemicarbazones, Dimethylsilicon complexes, antifungicidal activity, antibacterial activity, antifertility activity, ^1H NMR spectra, ^{13}C NMR spectra

INTRODUCTION

Extensive research work on thio-Schiff base derivatives of transition elements has been reported in the literature[1–4] and at present such derivatives of non-transition elements[5–7] are also receiving attention. A general survey of the literature reveals that in the Main Group IV, much attention has been paid to studies of the Schiff base derivatives of tin(IV) and lead(IV). Comparatively fewer references on the silicon(IV) complexes are so far available. Due to the limited work reported on the silicon–thio-Schiff base derivatives, and their possible applications in diverse areas including biochemical and medicinal aspects, it was considered worthwhile to undertake synthetic and biochemical studies of organosilicon derivatives with sulphur donor ligands having the donor set (N—SH).

EXPERIMENTAL

All the chemicals used were dried and distilled before use. Moisture was excluded from the glass apparatus using calcium chloride drying tubes.

Preparation of ligands

The ligands were prepared by the condensation of 2-acetylfuran, 2-acetylthiophene, 2-acetylpyridine and 2-acetylnaphthalene in 1:1 stoichiometric proportions with thiosemicarbazide ($NH_2NHCSNH_2$) in absolute alcohol. These were purified by recrystallization from the same solvent and analysed before use (Table 1).

Preparation of complexes

To a weighed amount of dimethyldichlorosilane in approx. 30 cm^3 of dry methanol in a 100 cm^3 round-bottom flask was added the calculated amount of the sodium salt of the ligands in 1:1 and 1:2 molar ratios. The contents were refluxed for 10–12 h and the precipitate of sodium chloride so formed was filtered off. The excess of the solvent was removed under reduced pressure and the products were dried for 2–3 h. The analysis of these new complexes (Table 2) for silicon, carbon, hydrogen, sulphur, chlorine and nitrogen agreed with the theoretical values within the limits of experimental error.

---

‡ Author to whom all correspondence should be addressed.

0268-2605/91/010045-06$05.00

Received 10 November 1990
Accepted 5 August 1990

Table 1 Ligands

Ligand	Colour of solid	M.P. (°C)
2-Acetylfuran thiosemicarbazone (AcFur.TsczH)	Brown	168
2-Acetylthiophene thiosemicarbazone (AcThiop.TsczH)	Yellow	130
2-Acetylpyridine thiosemicarbazone (AcPyd.TsczH)	Brown	158
2-Acetylnaphthalene thiosemicarbazone (AcNaph.TsczH)	White	155

Analytical methods and physical measurements

Carbon and hydrogen analyses were performed at the Microanalytical Laboratory of this Department. Nitrogen and sulphur were estimated by Kjeldahl's and Messenger's methods, respectively. Silicon was estimated gravimetrically as SiO_2. Conductivity was measured at 32 ± 1°C with a conductivity bridge (type 305 Systronics model) and molecular weights were determined by the Rast camphor method. Infrared spectra were recorded on a Perkin–Elmer 577 grating spectrophotometer in KBr pellets. The electronic spectra of the ligand and its silicon complexes were obtained on a Pye–Unicam SP-8-100 spectrophotometer in dry methanol. ^1H and ^{13}C NMR spectra were recorded on a JEOL FX 90Q spectrometer at 89.5 and 22.49 MHz, respectively.

RESULTS AND DISCUSSION

The reactions of dimethyldichlorosilane with the sodium salts of monobasic bidentate thio-Schiff bases in different stoichiometric proportions resulted in the isolation of $Me_2Si(NS)Cl$ and $Me_2Si(NS)_2$ complexes. These are soluble in common organic solvents and have sharp melting points. The low values of molar conductance ($10–12\ \Omega^{-1}\,cm^2\,mol^{-1}$) show them to be non-electrolytes. The monomeric nature of these complexes was confirmed by molecular weight determinations.

Electronic spectra

The electronic spectra of 2-acetylpyridine thiosemicarbazone and its silicon complexes have been recorded. A band due to the $>C{=}N$ chromophore[8,9] in the spectra of the ligand at 380 nm shifts to a lower wavelength in the silicon complexes and appears at 365 nm and 342 nm in

Table 2 Physical properties and analytical data of silicon complexes

			Elemental analysis (%)						
Product and Colour	Yield (%)	M.p. (°C)	C Found (Calcd)	H Found (Calcd)	N Found (Calcd)	S Found (Calcd)	Cl Found (Calcd)	Si Found (Calcd)	Mol. wt Found (Calcd)
$Me_2Si(AcFur.Tscz)Cl$	66	206	39.01	4.91	15.00	11.83	13.08	10.39	288.73
Greenish brown			(39.19)	(5.12)	(15.23)	(11.62)	(12.85)	(10.18)	(275.84)
$Me_2Si(AcFur.Tscz)_2$f17	73	151	45.29	5.03	19.63	15.39	—	6.81	433.89
Yellow			(45.47)	(5.25)	(19.89)	(15.17)		(6.65)	(422.61)
$Me_2Si(AcThiop.Tscz)Cl$	65	185	36.81	4.58	14.19	22.21	12.41	9.87	277.89
Yellow			(37.08)	(4.83)	(14.40)	(21.97)	(12.15)	(9.62)	(291.90)
$Me_2Si(AcThiop.Tscz)_2$	63	158	42.01	4.69	18.21	28.43	—	6.00	468.79
Brownish yellow			(42.26)	(4.88)	(18.48)	(28.20)		(6.18)	(454.74)
$Me_2Si(AcPyd.Tscz)Cl$	68	258	41.63	5.03	19.30	11.37	12.63	10.00	299.81
Greenish yellow			(41.87)	(5.27)	(19.53)	(11.18)	(12.36)	(9.79)	(286.86)
$Me_2Si(AcPyd.Tscz)_2$	71	241	48.38	5.26	25.02	14.67	—	6.68	463.48
Yellow			(48.62	(5.44)	(25.20)	(14.42)		(6.32)	(444.66)
$Me_2Si(AcNaph.Tscz)Cl$	63	190	53.42	5.22	12.73	9.71	10.78	8.61	351.18
Light brown			(53.63)	(5.40)	(12.91)	(9.54)	(10.55)	(8.36)	(355.94)
$Me_2Si(AcNaph.Tscz)_2$	68	162	61.73	5.31	15.26	12.03	—	5.44	551.89
Dark brown			(61.96)	(5.57)	(15.48)	(11.81)		(5.17)	(542.81)

the 1:1 and 1:2 products, respectively. This clearly indicates the coordination of azomethine nitrogen to the silicon atom. Further, two bands at 283 nm and 302 nm remain approximately at the same positions in the spectra of the silicon complexes.

IR spectra

The IR spectra of thiosemicarbazones do not show a νSH frequency at 2570 cm^{-1}, indicating that in the solid state the thione form is present. The medium-intensity bands exhibited in the region 3300–3100 cm^{-1} can be assigned to the νNH frequency of the free ligands, which disappear in the silicon complexes suggesting the possible loss of a proton of the α-nitrogen on complexation of the silicon atom. In the case of thiosemicarbazones, the bands observed at ~3440 and ~3360 cm^{-1} are due to the symmetric and asymmetric modes of the amino (NH_2) group. These bands are observed at almost the same position in the spectra of silicon complexes suggesting the non-involvement of this amino group in chelation.[10] The >C═N frequency of free azomethine observed in the region 1600–1650 cm^{-1} is shifted to the lower-frequency region in the case of complexes. This lowering of the ν(C═N) on complexation may be attributred to a lowering of the >C═N bond order as a result of Si←N bond formation. In the literature, a shift of this frequency to the higher-[11] as well as lower-[12] wavenumber side has been noted and in some cases even no change has been reported.[13] Further, in the case of thiosemicarbazones, a strong band at ~1060 cm^{-1} is indicative of νC═S). The lowering of this band in the form of νC—S) can be attributed to the coordination of the ligand through the thiolo sulphur atom.[10,14]

Several new bands in the complexes at 770–740, 580–555 and 540–530 cm^{-1} are due to ν(Si—C),[15] ν(Si—N)[15] and ν(Si—S),[5] respectively, which are absent in the spectra of ligands. It is known that the *cis* form of such types of complexes give rise to two ν(M—N) bands, whereas the *trans* complexes give rise to only one IR-active ν(M—N) band. The presence of only one ν(Si—N) band, in the present case, suggests that the complexes exist in the *trans* form.

Finally, in the case of $Me_2Si(NS)Cl$ type of complexes, a band of medium intensity at around 450 cm^{-1} is due to ν(Si—Cl) vibration.[17]

^{1}H NMR spectra

The proton magnetic resonance spectra of all the ligands and their corresponding silicon complexes have been recorded in DMSO-d_6 using TMS as the internal standard. The chemical shifts values (δ, ppm) of the different protons have been recorded in Table 3. For the sake of convenience the spectra of AcPyd.TsczH and its 1:1 and 1:2 silicon complexes Me_2Si(AcPyd.Tscz)Cl and Me_2Si(AcPyd.Tscz)$_2$, respectively have been discussed in detail. The broad signal exhibited by the ligand due to the NH proton at δ10.64 ppm disappears in the silicon derivatives indicating the coordination of nitrogen with simultaneous covalent bond formation by the sulphur with the silicon due to the tautomerization of the ligand in the thiolo form.[9,10] In the spectra of the complexes, a downfield shift in the positions of —CH_3 and

Table 3 ^{1}H NMR spectral data (δ, ppm)[a] of ligands and their corresponding silicon(IV) complexes

Compound	Aromatic(m)	NH(bs)	NH_2(bs)	CH_3(s)	Si—CH_3(s)
AcFur.TsczH	7.80–6.60	9.90	2.83	1.8	—
Me_2Si(AcFur.Tscz)Cl	8.12–6.72	—	2.85	2.10	1.23
Me_2Si(AcFur.Tscz)$_2$	8.24–6.81	—	2.86	2.12	1.19
AcThiop.TsczH	8.68–7.16	10.68	2.81	1.68	—
Me_2Si(AcThiop.Tscz)Cl	8.91–7.25	—	2.83	1.85	1.28
Me_2Si(AcThiop.Tscz)$_2$	9.10–7.31	—	2.85	1.88	1.25
AcPyd.TsczH	8.92–7.48	10.64	2.84	1.80	—
Me_2Si(AcPyd.Tscz)Cl	9.18–7.53	—	2.88	2.15	1.72
Me_2Si(AcPyd.Tscz)$_2$	9.24–7.55	—	2.90	2.18	1.63
AcNaph.TsczH	8.92–7.56	10.65	2.90	1.91	—
Me_2Si(AcNaph.Tscz)Cl	9.18–7.65	—	2.92	2.10	1.33
Me_2Si(AcNaph.Tscz)$_2$	9.22–7.73	—	2.90	2.15	1.28

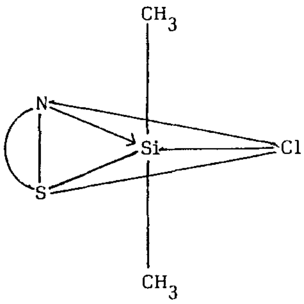
[a] m, Complex multiplet; bs, broad singlet; s, singlet.

aromatic protons indicates deshielding[18] as well as the coordination of azomethine nitrogen to the silicon atom. This is probably due to the donation of the lone pair of electrons by the nitrogen to the central silicon atom resulting in the formation of a coordinate linkage (Si←N). The appearance of signals due to NH_2 protons at the same positions in the ligand and its complexes shows the non-involvement of this group in coordination. Further, new signals at $\delta 1.72$ ppm and $\delta 1.63$ ppm in 1:1 and 1:2 complexes, respectively, are due to the methyl protons of Me_2Si group.

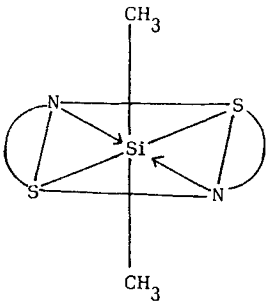
^{13}C NMR spectra

The ^{13}C NMR spectra of 2-acetylpyridine thiosemicarbazone and its corresponding silicon complexes have also been recorded. A considerable shift (Table 4) in the positions of carbons attached to the different participating groups clearly indicates the bonding of azomethine nitrogen and thiolic sulphur to the silicon atom.

On the basis of the above spectral studies, trigonal-bipyramidal[19] and octahedral[9] geometries have been suggested for $Me_2Si(NS)Cl$ and $Me_2Si(NS)_2$ types of complexes, respectively (illustrated below).



(1:1 complex)



(1:2 complex)

BIOLOGICAL STUDIES

Antibacterial activity

The bactericidal activity of 2-acetylthiophene thiosemicarbazone and its corresponding silicon complexes has been tested against *Escherichia coli* (−), *Staphylococcus aureus* (+), *streptococci* (+) and *Bacillus subtilis* (+) by the paper disc plate method at 1000 ppm concentration in methanol. The discs having a diameter of 5 mm were soaked in these solutions. These discs were placed on the appropriate medium previously seeded with organisms in Petri dishes and stored in an incubator at 30 ± 1°C. The inhibition zone around each disc was measured after 24 h and the results of these studies have been recorded in Table 5.

Antifungal activity

The above-mentioned compounds were also screened for their antifungal activity on *Rhizopus oryzae*, *Helminthosporium graminium*, *Aspergillus flavus* and *Alternaria solani*. The compounds were directly mixed with the medium (potato, dextrose, agar and distilled water) in different concentrations and the linear growth of the fungus was obtained by measuring the fungal colony diameter after five days (Table 6). The amount of growth inhibition in all the replicates was recorded and calculated by the equation:

$$\text{Percentage inhibition} = \frac{(C-T)\times 100}{C}$$

where C = diameter of fungal colony in control plate and

T = diameter of fungal colony in test plate.

The results reported in Tables 5 and 6 reveal that the silicon complexes of thiosemicarbazones are

Table 4 ^{13}C NMR spectral data (δ, ppm) of 2-acetylpyridine thiosemicarbazone and its corresponding silicon complexes

Compound	1	2	3	4	5	6	7	8	Si—CH_3
AcPyd.TsczH[a]	156.20	147.52	123.04	119.89	135.50	146.88	11.33	179.19	—
Me_2Si(AcPyd.Tscz)Cl	151.04	144.28	124.81	119.97	134.73	146.27	13.33	171.59	14.28
$Me_2Si(AcPyd.Tscz)_2$	148.28	143.17	125.03	120.48	134.92	145.91	14.04	169.01	13.47

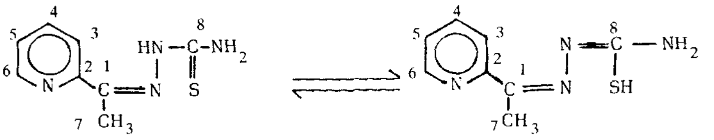


Table 5 Antibacterial activity of 2-acetylthiophene thiosemicarbazone and its silicon(IV) complexes[a]

Bacteria	Diameter of inhibition zone (mm) AcThiop.TsczH	$Me_2Si(AcThiop.Tscz)Cl$	$Me_2Si(AcThiop.Tscz)_2$
E. coli	11	15	17
Staph. aureus	13	19	20
Streptococci	16	23	22
B. subtilis	15	24	22

[a] 1000 ppm in methanol.

more active for all the test organisms than the corresponding semicarbazone complexes reported in our earlier publication,[20] and this also indicates that sulphur is more affective than oxygen as suggested by Tweedy.[21] The compounds containing a halogen atom attached directly to the silicon atom also showed moderate activity. Almost all the compounds were found to be more active against all the organisms used than the ligand itself. The mode of action of these compounds may involve the formation of a hydrogen bond through the $—N{=}\overset{|}{C}—S$ group with the active centres of the cell constituents, resulting in an interference with the normal cell processes. Therefore it might be inferred, from the above studies, that the introduction of sulphur and silicon in the organic moiety leads to increased antibactericidal and fungicidal activities, and the preliminary results achieved have led us to conclude that this type of compounds should be studied in detail for their applications in diverse areas.

Antifertility activity

The salts of transition metals have long been reported to possess antitesticular activity and metal complexes of heterocycles such as furan, benzofuran and pyridine have been shown to exhibit antioestrogenic and antitesticular activties.[22] A large number of silicon complexes[23] have been shown to cause atropy of testis, prostate and epididymis in male mice and, keeping these facts in view, studies on the antifertility activity of the ligand AcFur.TsczH and its silicon complexes in male mice have been undertaken.

Twenty adult male mice (body weight 40–50 g) were divided into four groups of five animals each. The animals were kept in plastic cages 10 in × 8 in × 8 in; 25 cm × 20 cm × 20 cm and three animals were housed in each case. The animals were fed mouse-feed pellets and tap water was provided *ad libitum*. Of four groups, one was used as a control group and the animals of this group received 0.2 cm^3 olive oil day^{-1} per animal, orally. The ligand and its complexes were suspended in olive oil separately and given to animals at a dose level of 20 mg kg body weight day^{-1} orally by gavage tube for 20 days. Twenty-four hours after the last administration of the compound, the animals were autopsied and the reproductive tract was dissected out. The motility and the sperm count were measured. It was observed that the motility and the sperm count decreased after the administration of the organic moiety and its silicon complexes. A significant decrease ($P<0.01$) in motility from 79.33 ± 2.02 to 34.66 ± 2.60% was observed in the animals treated with ligand and the sperm count also

Table 6 Antifungal activity of 2-acetylthiophene thiosemicarbazone and its silicon(IV) complexes

	Average percentage inhibition after 96 h							
	Helminthosporium graminium		*Rhizopus oryzae*		*Aspergillus flavus*		*Alternaria solani*	
Compound	0.01%	0.1%	0.01%	0.1%	0.01%	0.1%	0.01%	0.1%
AcThiop.TsczH	39	41	37	42	41	52	31	35
$Me_2Si(AcThiop.Tscz)Cl$	55	56	58	59	52	55	47	49
$Me_2Si(AcThiop.Tscz)_2$	56	59	60	61	53	56	48	51

Table 7 Antifertility activity of 2-acetylfuran thiosemicarbazone and its silicon(IV) complexes

Compound	Sperm motility (%)	Sperm count in cauda epididymis
Vehicle alone (olive oil)	79.33 ± 2.02	28.66 ± 0.66
AcFur.TsczH	34.66 ± 2.60^a	14.00 ± 1.52^a
$Me_2Si(AcFur.Tscz)Cl$	27.66 ± 4.17^a	14.33 ± 2.18^b
$Me_2Si(AcFur.Tscz)_2$	24.33 ± 2.33^a	10.00 ± 2.08^b

[a] $P<0.001$. [b] $P<0.01$.

decreased ($P<0.001$) from $28.66(\pm 0.66) \times 10^6$ to $14.00 \pm 1.562 \times 10^6\ cm^{-3}$. A highly significant ($P<0.001$) decline in the motility of sperm was observed in the case of silicon complexes. The sperm count was also found to decrease significantly in the treated animals. The data recorded in Table 7 indicate that the ligand and its complexes affect the motility as well as the sperm count in male mice. Further, it is also observed that the ligand itself is able to inhibit fertility, but due to the added synergistic effects of silicon complexes its activity is enhanced. Thus, it can be postulated that further intensive studies in this direction will lead to quite interesting results.

Acknowledgement Financial support from the CSIR, New Delhi, is gratefully acknowledged. The authors are also thankful to Professor J P Tandon, ex-Chairman of the Department, for his kind suggestions.

REFERENCES

1. Ali, M A and Livingstone, S E *Coord. Chem. Rev.*, 1974, 13: 101
2. Kanoongo, N, Singh, R V and Tandon, J P *Transition Metal Chem.*, 1987, 12: 271
3. Kanoongo, N, Singh, R V and Tandon, J P *Bull. Chem. Soc. Jpn*, 1989, 62: 1385
4. Mookerjee, M N, Singh R V and Tandon, J P *Acta Chim. Acad. Sci. Hung.*, 1984, 117: 89
5. Singh, K, Singh, R V and Tandon, J P *Inorg. Chim. Acta*, 1988, 151: 179
6. Singh, K, Singh, R V and Tandon, J P *Synth. React. Inorg. Met.-Org. Chem.*, 1986, 16: 1341
7. Saxena, A K and Huber, F *Coord. Chem. Rev.*, 1989, 95: 109
8. Garg, A and Tandon, J P *Transition Met. Chem.*, 1987, 12: 212
9. Singh, K, Singh R V and Tandon, J P *Polyhedron*, 1988, 7: 151
10. Mookerjee, M N, Singh, R V and Tandon, J P *Synth. React. Inorg. Met.-Org. Chem.*, 1985, 15: 13
11. Aminabhavi, T M, Biradar, N S, Patel, S B, Roddabasanagoudar V L and Rudzinski, W E *Inorg. Chim. Acta*, 1985, 107: 231
12. Saxena, A, Tandon, J P and Crowe, A J *Polyhedron*, 1985, 4: 1085
13. Prasad, R N and Tandon, J P *Indian J. Chem.*, 1973, 11: 366
14. Mohan, M, Sharma, P and Jha, N K *Inorg. Chim. Acta*, 1985, 107: 91
15. Kadish, K M, Xu, Q Y, Barbe, J M and Guilard, R *Inorg. Chem.*, 1988, 27: 1191
16. Dashora, R, Singh, R V and Tandon, J P *Synth. React. Inorg. Met.-Org. Chem.*, 1983, 13: 209
17. Singh, D and Singh, R V *Main Group Met. Chem.*, 1990, 13: 21
18. Sharma, R K, Singh, R V and Tandon, J P *Synth. React. Inorg. Met.-Org. Chem.*, 1980, 10: 221
19. Saxena, A and Tandon, J P *Indian J. Chem.*, 1985, 24A: 419
20. Singh, D and Singh, R V *Proc. 1st ANAIC Kuala Lumpur*, 1990 (unpublished)
21. Tweedy, B G *Phytopathology*, 1964, 54: 910
22. Henzliek, R P and William, H S *J. Med. Chem.*, 1979, 22: 124
23. Levier, R R and Jarkowiak, M E *Biol. Reprod.*, 1972, 7: 260