

Metal Chelates of Dithiocarbazic Acid and Its Derivatives. IX. Metal Chelates of Ten New Schiff Bases derived from S-Methyldithiocarbamate

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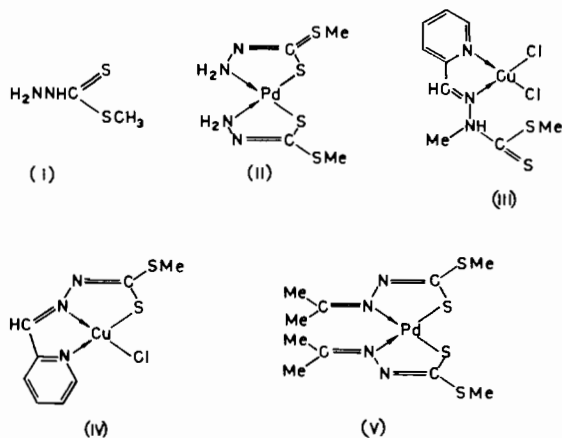
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The Schiff bases $RR'C=NNHC(S)SCH_3$ derived from S-methyldithiocarbamate have been prepared. The mass spectra of the Schiff bases having $R = Me$ and $R' = Ph$, 2-furyl, and 2-thienyl and $R = R' = Ph$ are similar and display strong peaks for the molecular ion M and the ions $M-CH_3S$, $M-CH_3SH$, $R'C=NH$, $R'CN$, $R'H$, R' , and $R'-H$. A mechanism of fragmentation is proposed. Complexes of the Schiff bases of the type $Met(RR'C=NN=CSSCH_3)_2$ ($Met = Ni, Cu, Zn, Pd$, and Pt) have been isolated in most instances. When $R' = Bu^n$ or Bu^i , nickel ion catalyses the hydrolysis of the Schiff base with the concomitant formation of the S-methyldithiocarbamate complex $[Ni(H_2NNHCSSCH_3)_3](NO_3)_2$. The metal complexes are being tested for anti-cancer activity.

Introduction

In Part I¹ of this series metal chelates of dithiocarbazic acid (I) were described, while in Parts II-VII metal chelates of a number of Schiff bases derived from (I) were reported.²⁻⁷ Some of the copper complexes display ferromagnetic and antiferromagnetic interactions.⁶⁻⁸ In Part VIII some metal ion induced rearrangements of thiazolines derived from (I) were reported.⁹

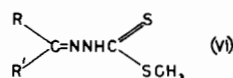


A number of these metal chelates were tested for anti-cancer activity: the palladium complex (II) and the copper complex (III) were found to show moderate anti-tumour activity. However, the copper complex (IV) and the palladium complex (V) displayed confirmed cytostatic activity in the 9KB test system, which is an *in vitro* human epidermoid carcinoma of the nasopharynx. This test system gives a better indication of carcinostatic activity over a wide range of cancers than most others.¹⁰

Since the carcinostatic and antiviral activity of metal chelates is often quite markedly altered by minor changes in the ligand,¹⁰⁻¹³ we, in collaboration with the U.S. National Cancer Institute, have commenced a systematic survey of the anti-tumour activity of metal chelates of dithiocarbamate derivatives. As part of this survey we have synthesized a number of Schiff bases derived from S-methyldithiocarbamate and we have characterized the chelates formed by these Schiff bases with nickel(II), copper(II), zinc(II), palladium(II), and platinum(II). These compounds are described below.

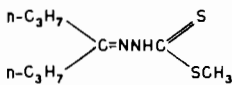
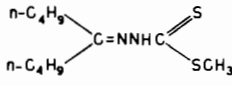
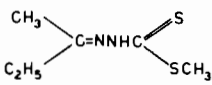
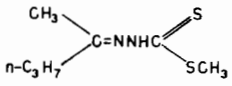
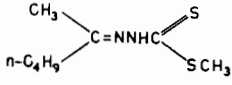
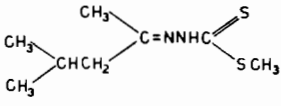
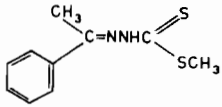
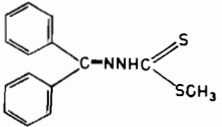
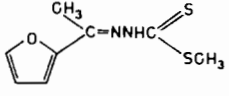
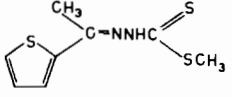
Results and Discussion

The Schiff bases (VI; $R = Me, Pr^n, Bu^n$ or Ph ; $R' = Et, Pr^n, Bu^n, Bu^i, Ph, 2-furyl$, or 2-thienyl) have been prepared by condensation of S-methyldithiocarbamate with the appropriate ketone in alcohol solution. These compounds are listed in Table I. The Schiff base with $R = R' = Et$ is a liquid at room temperature and it was not isolated.

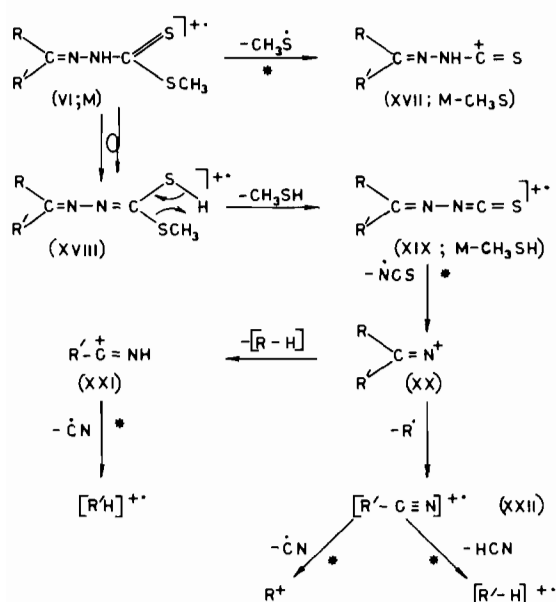


Mass spectra were obtained for the Schiff bases where $R' = Ph, 2-furyl$, or 2-thienyl. However, when both R and R' are alkyl, the Schiff bases undergo pyrolysis in the mass spectrometer and satisfactory spectra were not obtained.

TABLE I. Analytical Data for Schiff Bases.

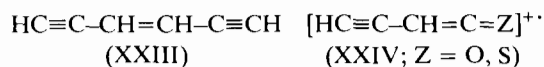
Compound	Structural Formula	Colour	M.p.	Analyses %			
				Calcd. Found			
				C	H	N	
VII	<i>S</i> -Methyl- β - <i>N</i> -hept-4-ylidene-dithiocarbazate		White	45–46°	49.5 49.7	8.3 8.4	12.8 12.8
VIII	<i>S</i> -Methyl- β - <i>N</i> -non-5-ylidene-dithiocarbazate		White	59	53.6 54.0	9.0 9.2	11.4 11.8
IX	<i>S</i> -Methyl- β - <i>N</i> -but-2-ylidene-dithiocarbazate		White	57	40.9 41.0	6.9 6.8	15.9 15.2
X	<i>S</i> -Methyl- β - <i>N</i> -pent-2-ylidene-dithiocarbazate		Cream	62	44.2 44.9	7.4 7.6	14.7 14.3
XI	<i>S</i> -Methyl- β - <i>N</i> -hex-2-ylidene-dithiocarbazate		White	58	47.0 47.3	7.9 8.1	13.7 13.8
XII	<i>S</i> -Methyl- β - <i>N</i> -(4-methylpent-2-ylidene)dithiocarbazate		White	42	47.0 47.0	7.9 7.6	13.7 13.5
XIII	<i>S</i> -Methyl- β - <i>N</i> -(phenylethylidene)-dithiocarbazate		Cream	140	53.5 54.1	5.4 5.7	12.5 12.7
XIV	<i>S</i> -Methyl- β - <i>N</i> -(diphenylmethylene)-dithiocarbazate		Yellow	119	62.9 63.2	4.9 4.9	9.8 9.6
XV	<i>S</i> -Methyl- β - <i>N</i> -(fur-2-ylethylidene)-dithiocarbazate		Deep Cream	122	44.8 44.5	4.7 4.9	13.1 12.7
XVI	<i>S</i> -Methyl- β - <i>N</i> -(thien-2-ylethylidene)-dithiocarbazate		Deep Yellow	139–141	41.7 41.3	4.4 4.3	12.2 11.8

Where $R' = \text{aryl}$, the mass spectra of the Schiff bases are similar and display strong peaks for the molecular ion M and for the ions $M-\text{CH}_3\text{S}$, $M-\text{CH}_3\text{SH}$, $R'\text{C}=\text{NH}$, $R'\text{CN}$, $R'\text{H}$, R' , and $R'-\text{H}$. The proposed fragmentation pattern is given in Scheme 1. Reactions which were confirmed by the presence of metastable peaks are denoted by asterisks.



Scheme 1. Proposed mechanism for fragmentation of Schiff bases ($R' = \text{aryl}$).

The molecular ion (VI) by loss of the radical $\text{CH}_3\text{S}\cdot$ gives the ion (XVII). The tautomeric molecular ion (XVIII) loses a molecule of methyl mercaptan to give (XIX), which by loss of the radical $\cdot\text{NCS}$ gives (XX). The ion (XX) loses $\text{R}-\text{H}$ to yield (XXI), which in turn loses the radical $\cdot\text{CN}$ to give the ion $[\text{R}'\text{H}]^{\cdot+}$. When $\text{R} = \text{Me}$, $\text{R}-\text{H}$ is the even-electron radical $:\text{CH}_2$; when $\text{R} = \text{Ph}$, the molecule $\text{R}-\text{H}$ is considered most likely to have the open-chain structure (XXIII).



The ion (XX) also fragments by loss of the radical R' to yield the ion (XXII), which can lose a $\cdot\text{CN}$ radical to give R'^+ or a molecule of HCN to yield $[\text{R}'-\text{H}]^{\cdot+}$. The ion $[\text{R}'-\text{H}]^{\cdot+}$ is also considered to have the open-chain structure (XXIII) when $\text{R}' = \text{Ph}$ and the structure (XXIV) when $\text{R}' = \text{thienyl}$ or furyl .

The Schiff bases listed in Table I by loss of a proton from their tautomeric thiol form can act as singly negatively charged bidentate ligands coordinating to metal ions via the mercapto sulphur and β -nitrogen atoms. The metal chelates which have been charac-

terized are listed in Table II. These compounds are being screened for anti-cancer activity in the P388 lymphocytic leukaemia test system.

In some instances pure products were not obtained. However, with the ligands VIII, XI, and XII, *i.e.* when $\text{R}' = \text{Bu}^n$ or Bu^i , nickel nitrate gave the pale blue paramagnetic complex of *S*-methyldithiocarbazate, *viz.* $[\text{Ni}(\text{H}_2\text{NNHCSSCH}_3)_3](\text{NO}_3)_2$,¹ indicating that hydrolysis of the Schiff base had occurred. Nickel(II)¹⁴⁻¹⁶ and copper(II)¹⁷ are known to catalyse the hydrolysis of the $\text{C}=\text{N}$ bond of Schiff bases with concomitant formation of a metal complex of the amine. When the nitrogen of the Schiff base becomes coordinated, the electronic cloud becomes reorientated in the direction of the metal ion and away from the $\text{C}=\text{N}$ double bond, thereby weakening it so that it becomes more readily susceptible to hydrolytic cleavage. In the present study this phenomenon was observed only with nickel and Schiff bases having $\text{R}' = \text{Bu}^n$ or Bu^i .

Experimental

S-Methyldithiocarbazate

This compound was prepared by the method of Bähr and Schleitzer.¹⁸ Since their details are rather brief and the conditions for a high yield are critical, the method is given here in detail.

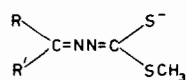
Potassium hydroxide (22.8 g) was completely dissolved in 9:1 alcohol-water mixture (140 ml) and the mixture was cooled in ice. To the cooled solution hydrazine hydrate (20 g) was added slowly with stirring. A solution of carbon disulphide (30.4 g) in alcohol (25 ml) was then added dropwise from a burette, with constant stirring, over a period of 1 hr. The temperature of the mixture was kept below 10°C during the addition. The resulting yellow oil was separated by means of a separatory funnel and dissolved in 2:3 alcohol-water mixture (100 ml) and this solution was cooled in ice. Methyl iodide (58 g) was added slowly with vigorous mechanical stirring; after the addition the mixture was stirred for a further 10 min while a white product separated. Ice-cold water (100 ml) was then added and the stirring was continued for another 10 min.

The product was separated by filtration, washed with water, and dried in air. The crude product was recrystallized from benzene (150 ml); yield, 20 g (40%); m.p. $81-82^\circ\text{C}$ (Found: C, 19.9; H, 4.9; N, 23.3; Calcd. for $\text{C}_2\text{H}_6\text{N}_2\text{S}_2$: C, 19.7; H, 4.95; N, 22.95%).

Preparation of the Schiff Bases

A solution of *S*-methyldithiocarbazate (5 g; 0.04 mol) and the appropriate ketone (0.04 mol) in alcohol (50 ml) containing 10M hydrochloric acid (5 drops) was heated at the reflux for 2 hr. Upon cooling in ice, the mixture deposited crystals of the Schiff base; the

TABLE II. Metal Chelates of Schiff Bases. L =



Compound	R	R'	Colour	Analyses %			
				Calcd.			
				Found			
C	H	N	Met				
PdL ₂	Et	Et	Deep Orange	34.7	5.4	11.55	21.95
				34.5	5.3	10.9	22.1
PtL ₂	Et	Et	Yellow	29.3	4.6	9.8	34.0
				29.3	4.7	9.4	33.9
CuL ₂	Pr ⁿ	Pr ⁿ	Black	43.4	6.9	11.2	12.75
				43.7	6.6	11.4	12.7
ZnL ₂	Pr ⁿ	Pr ⁿ	White	43.2	6.8	11.2	
				43.4	7.0	11.5	
PdL ₂	Pr ⁿ	Pr ⁿ	Orange	40.0	6.3	10.35	19.7
				40.1	6.3	10.3	19.5
PtL ₂	Pr ⁿ	Pr ⁿ	Deep Yellow	34.3	5.4	8.9	31.0
				34.3	5.5	8.8	30.6
PdL ₂ · 2C ₂ H ₅ OH	Bu ⁿ	Bu ⁿ	Deep Orange	45.3	7.9	8.1	15.4
				45.2	7.5	8.9	15.3
NiL ₂	Me	Et	Purplish Brown	35.2	5.4	13.6	14.35
				35.3	5.5	13.0	14.3
CuL ₂	Me	Et	Black	34.8	5.4	13.5	15.3
				34.5	5.3	13.5	15.4
ZnL ₂	Me	Et	White	34.6	5.3	13.5	
				34.6	5.2	13.4	
PdL ₂	Me	Et	Orange	31.5	4.85	12.3	23.3
				31.5	4.9	12.3	23.5
PtL ₂	Me	Et	Yellow	26.4	4.1	10.3	35.7
				27.3	4.4	10.2	35.6
NiL ₂	Me	Pr ⁿ	Dark Purple	33.5	6.0	12.8	13.4
				33.5	6.1	12.8	13.35
CuL ₂	Me	Pr ⁿ	Black	38.05	5.9	12.7	14.4
				38.0	5.95	12.7	14.4
ZnL ₂	Me	Pr ⁿ	White	37.9	5.9	12.6	
				38.6	6.0	12.6	
PdL ₂	Me	Pr ⁿ	Orange	34.7	5.4	11.55	21.9
				34.7	5.5	11.6	21.9
CuL ₂	Me	Bu ⁿ	Black	40.9	6.4	11.9	13.5
				40.6	6.2	11.9	13.65
ZnL ₂	Me	Bu ⁿ	White	40.7	6.4	11.9	
				41.0	6.3	11.85	
NiL ₂	Me	Ph	Bronze Green	47.5	4.4	11.1	11.6
				47.3	4.2	11.0	11.5
CuL ₂	Me	Ph	Greenish Black	47.1	4.35	11.0	12.5
				47.2	4.3	10.9	12.5
ZnL ₂	Me	Ph	White	46.9	4.3	10.9	
				47.3	4.4	10.8	
PdL ₂	Me	Ph	Orange	43.4	4.0	10.1	19.25
				43.5	4.0	10.1	19.4
PtL ₂	Me	Ph	Yellowish Orange	37.4	3.45	8.7	30.4
				37.95	3.6	8.7	30.5
NiL ₂	Ph	Ph	Bronze Green	57.2	4.2	8.9	9.3
				56.9	4.1	8.6	9.3
CuL ₂	Ph	Ph	Black	56.8	4.1	8.8	10.0
				56.9	3.95	8.3	10.0
ZnL ₂	Ph	Ph	Yellow	56.6	4.1	8.8	
				56.9	4.3	8.5	

TABLE II. (Cont.)

Compound	R	R'	Colour	Analyses %			
				Calcd. Found			
				C	H	N	Met
PdL ₂	Ph	Ph	Orange	53.2	3.9	8.3	15.7
				53.35	3.9	8.0	15.5
PtL ₂	Ph	Ph	Orange	47.0	3.4	7.3	25.5
				47.8	3.7	7.0	24.85
NiL ₂	Me	C ₄ H ₃ O	Bronze	39.6	3.7	11.5	12.1
				39.9	4.2	11.5	12.0
CuL ₂	Me	C ₄ H ₃ O	Black	39.2	3.7	11.4	13.0
				39.4	3.8	11.45	13.0
ZnL ₂	Me	C ₄ H ₃ O	Pale Yellow	39.05	3.7	11.4	
				39.25	3.9	11.6	
PdL ₂	Me	C ₄ H ₃ O	Reddish Orange	36.1	3.4	10.5	20.0
				36.4	3.6	10.6	19.9
PtL ₂	Me	C ₄ H ₃ O	Orange	31.7	3.3	8.7	30.3
				31.6	3.4	8.6	30.2
CuL ₂	Me	C ₄ H ₃ S	Black	36.8	3.5	10.7	12.1
				36.2	3.3	10.3	11.8
ZnL ₂	Me	C ₄ H ₃ S	Yellow	36.7	3.5	10.7	
				36.9	3.6	10.6	
PdL ₂	Me	C ₄ H ₃ S	Orange	34.0	3.2	9.9	18.8
				34.3	3.3	9.9	18.0
PtL ₂	Me	C ₄ H ₃ S	Yellowish Orange	29.4	2.8	8.6	29.8
				29.7	2.8	8.4	29.5

crystals were filtered off and washed with a little ice-cold alcohol, and dried *in vacuo*; yield, 50–80%.

Preparation of the Metal Complexes

Nickel complexes

A solution of nickel nitrate hexahydrate (1 g; 3.4 mmol) in alcohol (50 ml) was added to a hot solution of the Schiff base (6.8 mmol) in alcohol (50 ml). The mixture was heated for 10 min and then cooled in ice. On cooling, the mixture deposited crystals of the metal complex; these were separated, washed with ice-cold alcohol, and dried *in vacuo* over silica gel; yield, 30–70%.

Copper complexes

The copper complexes were prepared from copper nitrate trihydrate as described for the nickel complexes; yield, 40–60%.

Zinc complexes

The zinc complexes were prepared from zinc nitrate hexahydrate as described above. However, in some cases the complex did not deposit immediately and it was necessary to allow the mixture to stand overnight in the refrigerator; yield, 40–50%.

Palladium and Platinum complexes

A solution of potassium chlorometallate K₂MetCl₄ (Met = Pd, Pt) (3.5 mmol) in water (40 ml) was added slowly, with stirring, to a hot solution of the Schiff base (7.0 mmol) in alcohol (40 ml). The mixture was heated on the steam bath for 10 min and the deposited complex was then filtered off from the hot mixture, washed first with water, then with alcohol, and dried *in vacuo* over silica gel; yield, 30–60%.

Hydrolysis of the Schiff Bases

When an alcoholic solution of nickel nitrate hexahydrate was added to a solution of the Schiff base VIII, pale blue crystals of tris(*S*-methylthiocarbazate)nickel(II) nitrate were obtained (Found: C, 13.9; H, 3.2; N, 20.0; Ni, 10.8. Calcd. for C₆H₁₈N₈NiO₆S₆: C, 13.1; H, 3.3; N, 20.4; Ni, 10.7%). The Schiff bases XI and XII gave the same product with similar analysis.

Mass Spectra

The mass spectra were obtained on an AEI MS-12 mass spectrometer at 70eV at a temperature of 25 to 40°C.

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