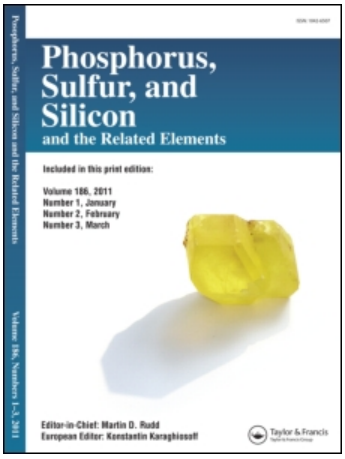

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SULFUR BONDED PALLADIUM(II) AND PLATINUM(II) COMPLEXES OF BIOLOGICALLY POTENT THIOAMIDES

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Sulfur bonded square planar complexes of the type, $[M(NSH)_2]Cl_2$ and $[M(NS)_2]$, where, $M=Pd^{II}$ and Pt^{II} and NSH = 2-[1-furanyl)-ethyledene]hydrazinecarbothioamide, 2-[1-(2-thienyl)-ethyledene]hydrazinecarbothioamide, 2[1-(2-naphthenyl)ethyledene]-hydrazinecarbothioamide with sulfur donor ligands have been synthesised and characterised. Chemical analysis, IR, UV-visible, ^1H NMR, magnetic measurements, conductance measurements and molecular weight determinations have been utilised for establishing the geometries of the free ligands and their metal complexes. The spectral data are consistent with a square planar geometry around Pd^{II} and Pt^{II} in which the ligand acts as a neutral bidentate and monoanionic bidentate ligand coordinating through nitrogen and sulfur atoms. To discuss bioinorganic aspects of the complexes, representative free ligands and their metal complexes were tested **in vitro** against a number of microorganisms and **in vivo** on male albino rats. Findings are positive.

INTRODUCTION

Thiosemicarbazones constitute an interesting class of N/S donor ligands which possess enormous pharmacological activities which in several cases are known to have been enhanced by the presence of transition metals. [1-3] Transition metal complexes of these ligands are gaining enormous importance on account of their inherent biological potential. They are known to function as antimicrobial, [4] antifertility, [5] antimalarial [6] and antileukemic agents. [7] In an efforts to gain more insight into the coordination pattern, stereochemistry and biological

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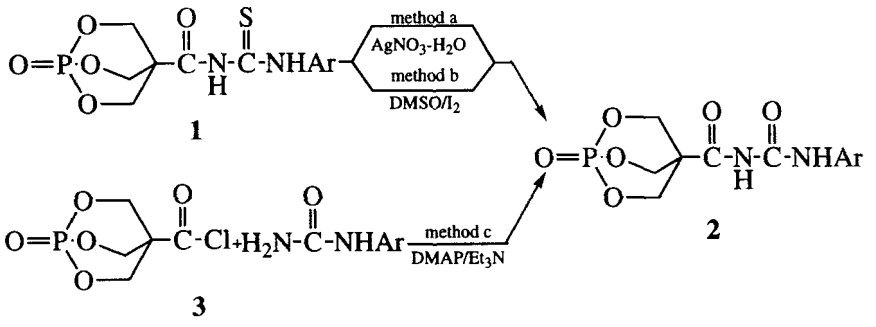


1 2 3

SCHEME 1

RESULTS AND DISCUSSION

Selection of Synthetic Methods

In general, carbonyl ureas can be synthesized by addition reactions, namely addition of carbonyl isocyanates to amines or amides to isocyanates. However, both reactions failed to give **2**. So we developed three different synthetic strategies to **2** as follows:

Method **a**, carbonyl ureas **2** are prepared by reaction of the corresponding carbonyl thioureas with silver nitrate solution. The method **a** has some outstanding merits:

a. The reaction is fast and complete because it proceeds in homogeneous phase.
b. Products **2** can be easily separated because of theirs poor solubilities in acetone.
c. Ag_2S can be quantitatively collected after the reaction.

Method **b**, carbonyl ureas **2** can be synthesized by oxidation of carbonyl thioureas **1** in DMSO in the presence of a catalytic amount of iodine. This method is limited by long reaction times (about 8 hours at 80°C) and low reaction yields (only about 50%).

Method **c**, The reaction must be catalyzed by DMAP because of large steric effects arising from the cage structure of the acid chloride **3**, and the yields are only about 70%.

In conclusion, method **a**, the desulfurization of the corresponding carbonyl thioureas **1** by $AgNO_3$-H_2O, is an optimal route to synthesize the carbonyl ureas **2**, summarized in Table I.

TABLE I Physical and spectral data of compounds 2

No	Ar	Recryst. Solv.	Yield (%)	m.p. (°C)	Element. Anal. (%)[a]			^1H NMR (DMSO-d_6, TMS, δ) ppm			
					C	H	N	3×P-CH_2 (^3J=7.2Hz)	Ar-H	C(O)NH	NHAr
2a	C_6H_5	DMF-H_2O	92	265–267	46.18 (46.16)	4.00 (4.20)	8.74 (8.97)	4.92–5.00(d)	7.10–7.50(m)	10.96 (s)	10.16 (s)
2b	p-Me C_6H_4	HOAc	97	264–268	47.64 (47.86)	4.57 (4.63)	8.55 (8.59)	5.00–5.08(d)	7.12–7.46(q)	10.96 (s)	10.11 (s)
2c	o-Cl C_6H_4	HOAc-H_2O	96	261	41.92 (41.58)	3.24 (3.49)	7.99 (8.08)	5.04–5.12(d)	6.48–8.38(m)	11.28 (s)	10.82 (s)
2d	m-Cl C_6H_4	DMF-H_2O	95	259–260	41.89 (41.58)	3.22 (3.49)	8.06 (8.08)	4.96–5.04(d)	7.20–7.76(m)	11.04 (s)	10.26 (s)
2e	p-Cl C_6H_4	HOAc	100	260–261	41.64 (41.58)	3.42 (3.49)	8.04 (8.08)	5.02–5.10(d)	7.36–7.76(q)	11.04 (s)	10.26 (s)
2f	2,3-Cl_2 C_6H_3	DMF-H_2O	81	249–251	37.76 (37.82)	2.53 (2.91)	7.40 (7.35)	4.96–5.04(d)	7.40–8.32(m)	11.10 (s)	10.88 (s)
2g	2,4,5-Cl_3 C_6H_2	HOAc	90	280–282	34.74 (34.68)	2.82 (2.43)	6.71 (6.74)	4.98–5.06(d)	8.20(s) 8.52(s)	11.42 (s)	10.96 (s)
2h	p-Br C_6H_4	DMF-H_2O	91	247–248	36.77 (36.85)	2.95 (3.09)	7.09 (7.16)	4.96–5.04(d)	7.54(s)	11.02 (s)	10.24 (s)
2i	m-$NO_2C_6H_4$	HOAC-H_2O	87	261–263	40.30 (40.35)	3.17 (3.39)	11.75 (11.76)	4.94–5.02(d)	7.54–8.62(m)	11.12 (s)	10.48 (s)
2j	o-OMe C_6H_4	DMF-H_2O	90	266–268	45.47 (45.62)	4.15 (4.42)	8.16 (8.19)	4.96–5.04(d)	6.92–8.24(m)	11.04 (s)	10.64 (s)

[a]Found(Calcd.).

Reaction Mechanism of Desulfurization of Carbonyl Thioureas 1 by $AgNO_3$-H_2O

Generally, thiourea derivatives are much easier to prepare than the corresponding urea derivatives. In this paper, we report that carbonyl ureas **2** can be prepared in very high yield by desulfurization of the corresponding thioureas **1**, which have been synthesized very easily in our previous publication.[7] Moreover, we expect that many other important urea derivatives,[8] such as sulfonylureas and phosphorylureas can also be obtained by this desulfurization reaction from their corresponding thioureas. However, the detailed mechanism of this reaction has not been reported yet.

Penn[9] suggested that N,N′-diphenyl urea is formed via the N,N′-diphenyl carbodiimide intermediate when N,N′-diphenyl thiourea is caused to react with ammonical silver nitrate. Therefore we assum that the reaction of **1** with $AgNO_3$-H_2O proceeds by a similar mechanism. At first, carbonyl thioureas **1** react with $[Ag(OH)_2]^-$ to form complexes **A** because of the strong coordination ability of the sulfur atom. After intramolecular elimination, the carbodiimide intermediate **B** can be obtained, which subsequently reacts with H_2O to form the carbonyl ureas **2**.

Since the carbonyl and phenyl group conjugate with the -N=C=N- group, **B** should have characteristic absorption in the UV spectra, and most of reactions keep $k_1 \gg k_2$; therefore, it is possible to detect **B** by UV.

The results of UV measurements reveal that: Carbonyl thioureas **1** were rapidly transformed into intermediates **B** with a characteristic absorption peak at 288 nm; afterwards, H_2O was added to **B** and the products **2** were obtained. Compared to the formation of carbodiimide **B**, the second step is much slower.

Furthermore, we observed that the reaction rate was affected by the solution's pH value. A lower pH value can increase the reaction rate. It means that H^+ participated in the addition reaction of H_2O to intermediate **B** by electrophilicly attacking the C=N bond.

To determine which nitrogen atom, carbonyl-N or aryl-N, was attacked by H^+, we allowed **1a** to react with $AgNO_3$-anhydrous CH_3OH. As a result, only compound **4** rather than its constitutional isomer **5** was obtained. **4** can be distinguished from **5** by the ^1H NMR. It is known that δ_H N-H is 8–12 ppm for the amide group and 3–5 ppm for the arylamine group,[10] and our product's δ_H N-H is 11.2 ppm.

Now, it is clear that **B** is the reaction intermediate of the desulfurization reaction, H^+ only attacks the nitrogen atom that is attached to the carbonyl group when it participates in this reaction. So, we can postulate a possible mechanism as follows:

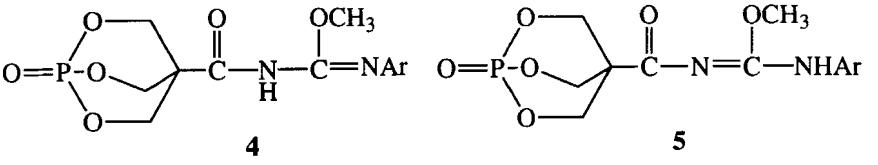
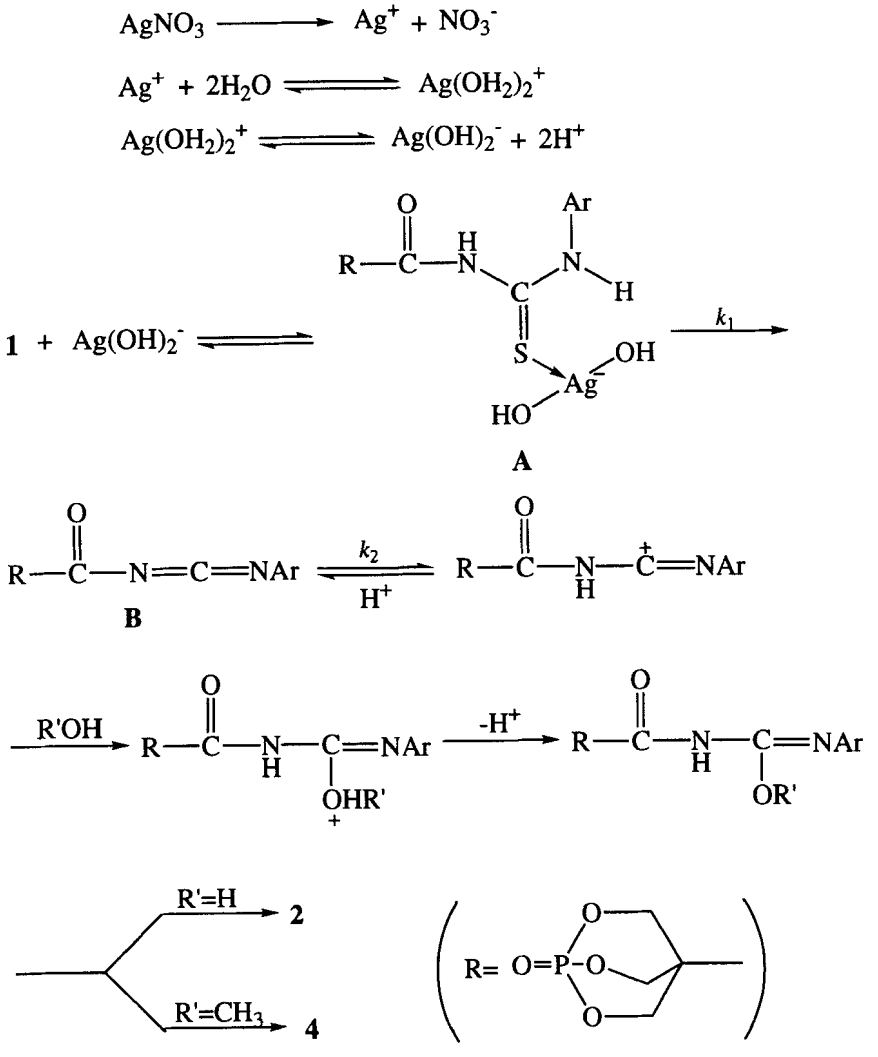
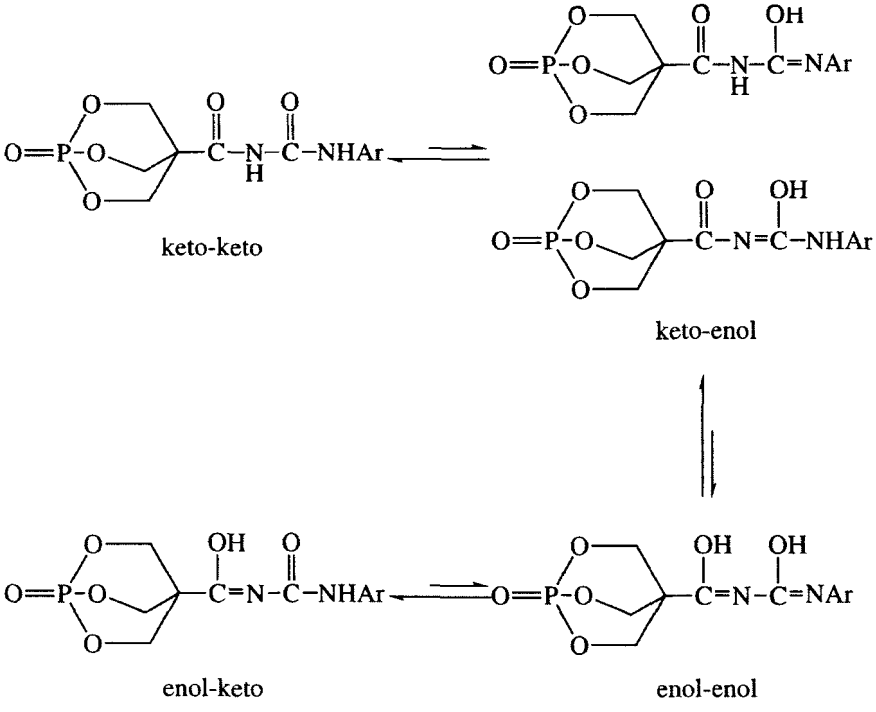


FIGURE 1



SCHEME 2



SCHEME 3

Spectral Characteristics and Structure of Compounds 2

In principle, carbonyl ureas **2** have four kinds of keto-enol tautomers at the most:

The IR and ^{1}H NMR spectra show that most compounds of **2** exist in the keto-keto form. IR spectra of **2** show strong characteristic absorption bands at about 1699 cm^{-1} and 1595 cm^{-1} (two C=O). In the ^{1}H NMR spectra only one set of doublet were observed at δ 5.00–5.20 ppm due to cyclic CH_2. Shifting of the amide proton (C(O)NHAr) to lower field indicates the existence of intramolecular hydrogen bonds.

However, **2c** and **2e** have other isomers; in the ^{1}H NMR spectra, two sets of doublets were observed at δ 5.00–5.20 ppm. The existence of isomers can affect the aromatic protons' chemical shift value and make them shift to higher field, but the P atom's chemical shift value is not changed. For example, in the ^{31}P NMR spectra of **2c** there is only one absorption peak at δ −8.2 ppm. The probable explanation is that the isomeric position (amide group) is much further away from the P atom and can not affect its chemical shift value.

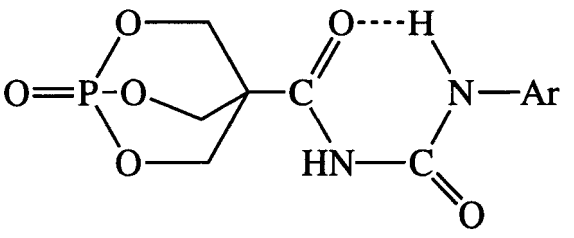


FIGURE 2

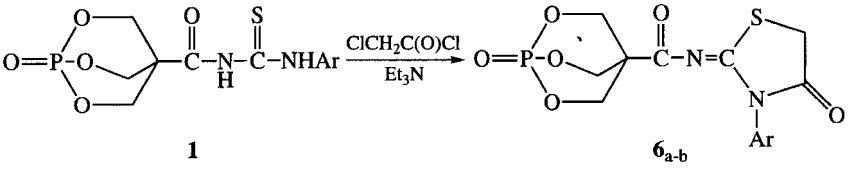
Reaction of 1 with Chloroacetyl Chloride

Carbonyl thioureas **1** should have some general reactive characters because they have an entire -NHC(S)NH- group. For example, when **1** react with chloroacetyl chloride,[11] the desired cyclic products $\mathbf{6}_{\mathbf{a\text{-}b}}$ can be obtained, which have high bactericidal activities.

EXPERIMENTAL

Melting points were measured on a YANACO micro melting point apparatus and were not corrected. IR spectra were obtained on a JSCODS-301 IR spectrometer(KBr). UV was recorded on a UV-240 spectrometer(CH_3CN). ^1H NMR and ^{31}P NMR measurements were carried out on a JEDLFX-9Q NMR spectrometer. MS spectra were taken on a HP-5988 MASS spectrometer(EI).

Triethylamine and chloroacetyl chloride were distilled before used. Solvents for chemical reactions were generally distilled from proper drying agents prior to use: methanol from Mg and I_2, acetone from $CaSO_4 \cdot 0.5H_2O$, THF from benzophenone ketyl. Carbonyl thioureas **1** were prepared by the methods described previously.[7]



1 **$6_{a\text{-}b}$**

SCHEME 4

N-(1-oxo-4-carbonyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane)-N′-phenyl urea 2a:

Method **a**: To a stirred solution of 3.28g (10 mmol) **1a** in 30 ml of acetone was added dropwise a solution of 3.40g (20 mmol) silver nitrate in 6 ml of water. After stirring for 4 hrs at room temperature, 60 ml of water was added and the resulting mixture was filtered. The black precipitate was extracted with DMF (10ml × 3). To the combined extracts a large amount of water was added and the white precipitate was filtered and recrystallized from DMF-H_2O to give 2.87g (92%) **2a**, m.p. 265.5–267°C.

Method **b**: To a 50ml four-necked flask equipped with a condenser ($CaCl_2$ dry tube) was added successively 3.28g (10mmol) **1a**, 20ml of DMSO and a catalytic amount of iodine. The stirred mixture was heated to 80°C for 8 hrs until **1a** had disappeared, monitored by means of TLC. After removing most of DMSO (about 15ml), the reaction mixture was filtered and the filtrate was poured into a large amount of water, and a white precipitate was formed. Work-up was the same as described in method **a**. Yield 51%, m.p. 264–267°C.

Method **c**: To a 50ml four-necked flask equipped with a condenser($CaCl_2$ dry tube) was added successively 3.13g (10mmol) of freshly prepared **3**, 15ml of anhydrous acetone, 1.11g (11mmol) of triethylamine and a catalytic amount of 4-dimethylaminopyridine. To this stirred solution was added dropwise a solution of 1.36g (10mmol) phenylurea in 20ml of anhydrous acetone. After stirring for 30 min. at room temperature and refluxing for 2 hrs, the solvent was removed *in vacuo* and 20ml of water was added under stirring. The formed white precipitate was purified as described in method **a**. Yield 77%, m.p. 265–267°C.

Other compounds **2** were obtained by method **a**, (Table I).

Reaction of N-(1-oxo-4-carbonyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane) -N′-phenyl thiourea **1a** with $AgNO_3$-CH_3OH: To a 100ml flask equipped with a magnetic stirrer was added successively 0.66g (2mmol) **1a**, 0.68g (4mmol) silver nitrate and 50ml of anhydrous methanol. The mixture was stirred for 15 hrs at room temperature until **1a** disappeared (monitored by TLC). The reaction mixture was filtered, evaporated *in vacuo*, and the residue was added to 50ml water. The white precipitate formed was filtered and the precipitate recrystallized from HOAc-H_2O (1:1) to give 0.50g (81%) **4**, m.p. 194–196°C. IR(KBr): 1606.4(s, C=O), 1571.6(s, C=N), 1310.0(s, P=O), 837.2(s, bicyclo) cm^{-1}. ^1H NMR (DMSO-d_6, 90 MHz): 11.12(s, 1H, C(O)NH), 7.36(s, 5H, Ar-H), 4.96–4.88(d, ^3J = 7.2Hz, 6H, 3xP-OCH_2), 3.92(s, 3H, -OCH_3). Anal: Calc. for $C_{13}H_{15}N_2O_6P$ (326.25): C 47.86, H 4.63, N 8.59; found: C 47.43, H 4.16, N 8.56.

Reaction of N-(1-oxo-4-carbonyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane) -N′-phenyl thiourea **1a** with chloroacetyl chloride: To a 100 ml four-necked flask

equipped with a condenser ($CaCl_2$ dry tube) was added successively 1.64g (5mmol) **1a**, 1.11g (11mmol) of triethylamine and 40ml of anhydrous THF. To the stirred solution was added dropwise a solution of 0.57g (5mmol) of chloroacetyl chloride in 20ml of anhydrous THF at -5°C. The reaction mixture was stirred for 30 minutes at 0°C and thereafter for 4 hrs at room temperature. The mixture was filtered and the solvent removed *in vacuo*. The residue was purified by means of flash chromatography, petroleum ether/ethyl acetate(2:1) as eluent. 0.87g (47%) **6a** was obtained as a yellow solid, m.p. 213–215°C. IR(KBr): 1741.7(s, C=O), 1632.7(s, C=O); 1302.0(s, P=O)cm^{-1}. ^1H NMR ($CDCl_3$. 90 MHz): 7.54–7.20 (m, 5H, Ar-H), 4.64–4.56(d, ^3J = 7.2 Hz, 6H, 3xP-OCH_2), 3.96(s, 2H, CH_2). EI-MS: 368 (4.1, M^+). Anal: Calc. for $C_{14}H_{13}N_2O_6PS$ (368.30): C 45.66, H 3.56, N 7.61; found: C 45.60, H 3.08, N7.69.

6b was obtained in the same manner as described for the synthesis of product **6a** as an orange red solid, Yield 65%, m.p. 215–215.5°C. ^1H NMR($CDCl_3$, 90 MHz): 7.32–6.92(m, 4H, Ar-H), 4.62–4.54(d, ^3J = 7.2Hz, 6H, 3xP-OCH_2), 3.94(s, 2H, CH_2), 2.32(3H, s, CH_3). Anal: Calc. for $C_{15}H_{15}N_2O_6PS$(382.33): C 47.12, H 3.93, N 7.33; found: 47.10, H 3.78. N 7.30.

Acknowledgements

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