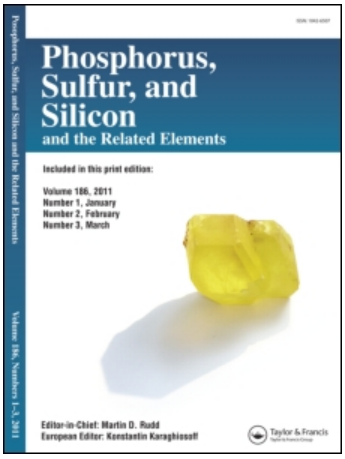

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The Synthesis of Novel Derivatives of 1,5-Dihydro-4-Mercapto-2,6-Dioxo-1,3,5,2-Triazaphosphorine and Their Antitumor Activity

Ruyu Chen[a]; Lijuan Mao[a]; Xiaoru Chen[a]
[a] Research Institute of Elemento-Organic Chemistry, Nankai University, Tianjin, People's Republic of China

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THE SYNTHESIS OF NOVEL DERIVATIVES OF 1,5-DIHYDRO-4-MERCAPTO-2,6-DIOXO-1,3,5,2-TRIAZAPHOSPHORINE AND THEIR ANTITUMOR ACTIVITY

RUYU CHEN,* LIJUAN MAO and XIAORU CHEN
Research Institute of Elemento-Organic Chemistry, Nankai University, Tianjin, 300071, People's Republic of China

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A series of new derivatives of 1,5-dihydro-4-mercapto-2,6-dioxo-1,3,5,2-triazaphosphorine have been synthesized. The most stable tautomer was proven to have the thioenol form by spectroscopic data and quantum chemistry calculation. The preliminary bioassay indicated that the title compounds significantly inhibited the growth of jurkat cells in vitro as well as S-180 tumor in vivo.

Key words: Triazaphosphorine; synthesis; derivatives; antitumor activity; structure confirmation.

INTRODUCTION

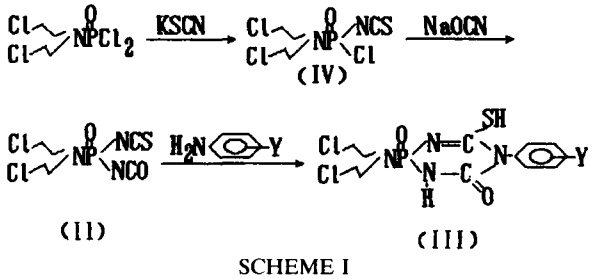
Since 1960's, the syntheses of 2,5-dihydro-4,6-dithio (or dioxo-) -1,3,5,2-triazaphosphorine derivatives have appeared in the literature.[1–8] However, neither the 4-mercapto-6-oxo form of this type of compounds nor the antitumor activity have been reported thus far.

In order to yield new antitumor compounds, a number of the analogues **III** were synthesized. The stability of the tautomeric structure of compounds **III** was examined by spectroscopic method and quantum chemistry calculation. The preliminary bioassay showed that compounds **III** have good antitumor activity.

DISCUSSION AND RESULTS

A. Synthesis of the Title Compounds

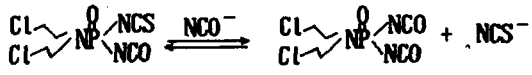
For synthesizing the title compounds, different routes were attempted. The route shown in Scheme I failed.



SCHEME I

*To whom correspondence should be addressed.

When equimolecular amounts of compound **IV** and NaOCN were used, the yields were low even after changing several solvents. When an excess of NaOCN was added, the exchange reaction occurred as follows.



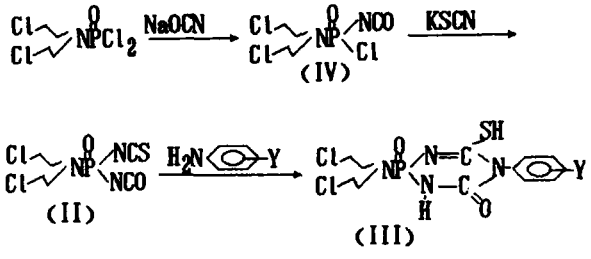
(A)

This might be due to the relatively weak nucleophilicity of OCN^- which is a weaker departing group than NCS^-, so that the by-product A is formed.

The other synthetic route is shown in Scheme II.

By changing the sequence of addition of KSCN and NaOCN and keeping the amount of KSCN a little less than NaOCN, compounds **III** were prepared smoothly in a one-pot reaction. Electronic and steric effects of substituents on the aniline derivatives gave different results under the given reaction conditions (see Table I).

Compared with $(ClCH_2CH_2)_2NP(O)(NCS)_2$,[4] the reaction of $(ClCH_2CH_2)_2$-NP(O)(NCO)(NCS) with amines was more complex and the yields were lower, so that the o-substituted anilines were only weakly reactive.



Y = P-Me, m-Me, H, P-Cl, m-Cl, m-NO_2

SCHEME II

TABLE I

Reaction condition and experimental data

No.	Y Group	State*	Temperature(℃)	Time(h.)	Yield(%)	m.p.(℃)
III_1	p-Me	W. S.	-20~(-10)	4.0	61.5	108~109
III_2	m-Me	W. S.	-20~(-10)	4.5	50.1	124~126
III_3	H	W. S.	-20~(-10)	4.5	40.7	120~122
III_4	p-Cl	W. S.	-20~(-10)	4.5	34.2	116~118
III_5	m-Cl	W. S.	-10~0	4.5	28.3	118~120
III_6	m-NO_2	Y. S.	-10~25	6.0	20.8	106~107

*W = white, S = solid, and Y = yellow.

B. *Confirmation of Structure*

All compounds **III** have been analyzed by ^{1}H NMR, IR, MS and elemental analysis (see Table II).

^{1}H NMR spectra determined on a 90 MHz NMR spectrometer in deuterioacetone showed that the protons of nitrogen mustard and the substituted phenyl groups gave normal chemical shifts but the proton peak in the phosphorus heterocycle was

TABLE II

Data of spectra and results from elemental analysis

No.	Group (Y)	^{1}H NMR (δ, ppm)	IR(cm^{-1})	Elemental Analyses(%)		
				C	H	N
III_1	p-Me	2.3(s,3 H,CH_3), 3.3~3.9(m,8 H, 2 CH_2 ,CH_2N),7.1~7.3(m,2H),7.4~7.7 (m, 2 H)	3205(w,NH), 3080,2977, 2819, 1975(wb, N=C-SH), 1610(S), 1590(S),1320(m,P=O), 1162	39.72 (39.50)	4.24 (4.33)	14.22 (14.17)
III_2	m-Me	3.35(s,3 H,2 $ClCH_2CH_2N$), 6.8~7.7(m,4 H)	3230,3080,2905,1986, 1609(s.),1588,1429,1223(m,P=O), 1188, 1085,923	39.41 (39.50)	4.20 (4.33)	13.88 (14.17)
III_3	H	3.4~4.0(m,8 H,2 $ClCH_2CH_2N$),7.2~7.6(m,3 H,Ph), 7.6~7.9(m,2 H,Ph)	3217(w,NH), 2991, 1925(wb,N=CSH), 1605,1583, 1490, 1318(m,P=O), 1119, 1085, 923	37.49 (39.50)	4.20 (4.33)	14.44 (14.68)
III_4	p-Cl	3.2~4.0(m,8 H,2 CH_2CH_2N), 7.3~7.5(d,2 H), 7.6~7.9(m,2 H)	3225(w,NH), 3090, 2972, 1974(wb,N=CSH), 1601(s), 1508(s), 1537, 1312(m, P=O), 1192, 1089	34.82 (34.66)	3.11 (3.39)	13.35 (13.48)
III_5	m-Cl	3.4~4(m,8 H, 2 $ClCH_2CH_2N$), 7.1~7.7(m,4 H)	3213(m,NH), 3081,2977, 1972(w,N=CSH), 1602,1573, 1309(m,P=O), 1198, 1161, 931	34.48 (34.66)	3.23 (3.39)	13.28 (13.46)
III_6	m-NO_2	3.45~4.0(m,8 H,2 $ClCH_2CH_2N$),7.6~9(tmb,4 H)	3284(w,NH),3053,2981, 1983(wb,N=CSH), 1619(m, C=O), 1587, 1519, 1203(m ,P=O), 1180, 998	34.07 (33.81)	3.46 (3.31)	16.68 (16.42)

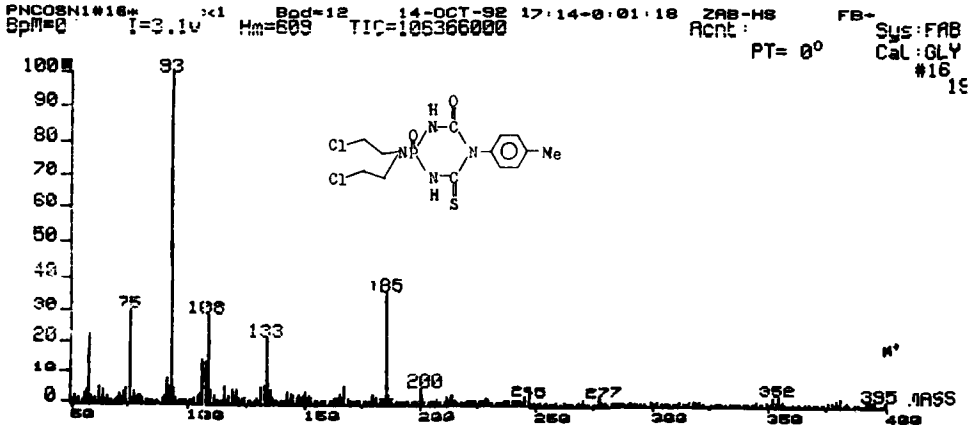


FIGURE 1

not observed. Determination on 200 MHz NMR spectrometer in deuteriochloroform indicated that a single sharp peak appeared around 3 ppm which seemed very similar to that of the 4,6-dimercapto analogue, known as the peak of HS-group.[4] On the contrary, the proton in the group "—NH—C(O)—" did not show any peak.

For IR spectra, a strong absorption band around 1650 cm^{-1} and a weak broad band around 1900 cm^{-1} may separately belong to C=O or N=C and —N=C—SH.[6] The others could all be rationalized.

The EI-MS spectra showed that compounds **III** always cleaved to give fragments which exactly equaled M^+-HNCO but not M^+-HNCS. Both FAB-MS and EI-MS gave the molecular ion peak (see Figure 1).

The quantum chemistry calculations by MNDO and PM3 methods have been done to further prove the structure of the stable tautomer (see Table III).

By MNDO method, $\Delta ET = 0.2718$, between thione-keto and thioenol-keto forms, corresponding to about 7 Kcal/mol, by PM3 method, $\Delta ET = 11$ kcal/mol, while, by MNDO method, $\Delta ET = -0.3490$, between thioenol-keto form and thioenol-enol form, corresponding to about -8 Kcal/mol and by PM3 method, $\Delta ET = -12$ Kcal/mol, indicating that the thioenol-keto form has the lowest energy, so the most stable tautomeric structure is the thioenol-keto form, and the three tautomers are interexchangeable at room temperature.

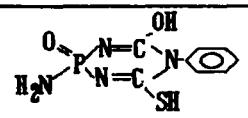
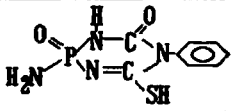
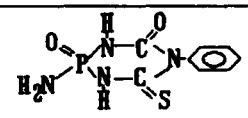
According to the above ^1H NMR and IR spectral analyses and quantum chemistry calculations, a conclusion could be drawn, that at room temperature the thioenol-keto form would be the most stable one and that there might be an equilibrium among thioenol-enol, thioenol-keto and thione-keto forms (see Figure 2).

C. *Antitumor Activity*

Results from the preliminary tests indicate that the compound $\mathbf{III}_6$ possesses antisarcoma-180 activity in rats, and the inhibition rate on weight of tumor was 56.5% in vivo, when drug concentration was 1 mg/kg.

TABLE III

Data of quantum chemistry calculations

Model	Hf (Kcal/mol)		ET (ev)	
	MNDO	PM3	MNDO	PM3
	-21.90	-67.38	-3007.6236	-2631.5119
	-29.95	-79.72	-3007.9726	-2632.0272
	-23.68	-68.36	-3007.7008	-2631.5544

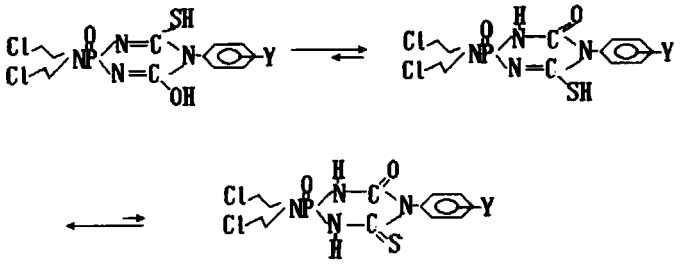


FIGURE 2

The compound $\mathbf{III}_6$ also appeared to exert a significant effect in suppressing Jurkat cell growth, but it was not observed with inhibition of thymidine uptake. This suggested that the growth inhibitory effect may involve a mechanism other than direct inhibition of DNA synthesis.

Biological activity of other compounds are currently being tested.

EXPERIMENTAL

Elemental analysis was carried out with a CHN CORDER MT-3 elementary analyzer. ^{1}H NMR was recorded with a JEOL-FX-90Q and Bruker AC-P200 SPECTROMETER, TMS was used as an internal standard. The IR spectra were measured by using a SHIMADZU-435 instrument. The MS was performed with VG-7070E spectrometer using the FAB method. Melting points were determined with Thomas-Hoover capillary melting point apparatus and uncorrected.

N,N-Bis-(2-chloroethyl) Chlorophosphoramide. The title compounds were prepared according to the method in literature.[5] Yield 75.6%, m.p. 52–54°C [Lit[5] 80%, m.p. 54–56°C].

Compound (**I**) *and* (**II**). 2 g (7.72 mmol) of N,N-bis-(2-chloroethyl)dichlorophosphoramide and 40 ml of anhydrous acetonitrile were added into a flask. Below 10°C, 0.5 g (7.70 mmol) of NaOCN was added stepwise into the reaction system, and the mixture was kept stirred for 3–4.5 h between 30–40°C until the TLC showed that the spot of dichlorophosphoramide almost disappeared. After the temperature decreased to about 0°C, 0.7 g (7.20 mmol) of KSCN was added in portions with stirring for 2–3 h, and the temperature was raised to about 10°C. Stirring was continued for another 40 min. The solvent was removed under reduced pressure and the product was purified by flash chromatography on a silica gel column using a mixture of chloroform, ether, and petroleum ether (1:1:4) as the eluent. A viscous substance was obtained and solidified gradually, m.p. 48–51°C, yield 46.3%.

^{1}H NMR (δ, ppm) 3.3–3.9 (m, 8 H, 2 $ClCH_2CH_2N$)
^{31}P NMR (δ, ppm) −17.50
IR (cm^{-1}) 2900 (w), 2090 (m, —N=C=O), 1965 (s, —N=C=S), 1264 (m, P=O), 1115, 1042, 981.
MS (CI, m/e) 287 (M+), 238 (M+—$ClCH_2$, base peak), 252, 147, 147, 163, 176, 63, 42.

Compounds (**III**). 1.5 g (5.21 mmol) of compound **II** was dissolved in 50 ml of anhydrous toluene, and after the temperature decreased to −25– −20°C, a mixture of equimolar quantities of substituted aniline and 20 ml of anhydrous toluene was added slowly with stirring. The reaction mixture was stirred for 4–8 h between −20–30°C until no more solid products formed. The solvent was removed by filtration, and the white or yellow solid products were obtained and recrystallized from acetone and ether (1:3), yield 30–65%.

ACKNOWLEDGEMENTS

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