Heteroatom Chemistry
Volume 12, Number 7, 2001

C-Phosphorylation of 5,10-Dimethyl-5, 10-dihydrophenazine and Its Carbo- and Heteroanalogs

Sergei P. Ivonin,[1] Svetlana D. Kopteva,[1] Viktor N. Serdyuk,[1] Andrei A. Tolmachev,[2] and Aleksandr M. Pinchuk[2]

[1] *Dnepropetrovsk State University, Department of Chemistry, Dnepropetrovsk-10, 320625, Ukraine*

[2] *Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kiev-94, 253660, Ukraine*

Received 12 December 2000; revised 18 June 2001

ABSTRACT: *This study covers phosphorylation of heterocyclic analogues of N-methyldiphenylamine with phosphorus tribromide in pyridine solution. The reaction is found to proceed regioselectively in accordance with the orienting effect of the amino group. Mono and bis-phosphorylated derivatives of the heterocycles have been isolated and characterized. It is pointed out that the heterocyclic systems under study exhibit reduced reactivity in electrophilic phosphorylation as compared to N-methyldiphenylamine. The results of calculations by the PM3 method are reported for the starting molecules and their σ-complexes.*
 Heteroatom Chem 12:652–657, 2001

INTRODUCTION

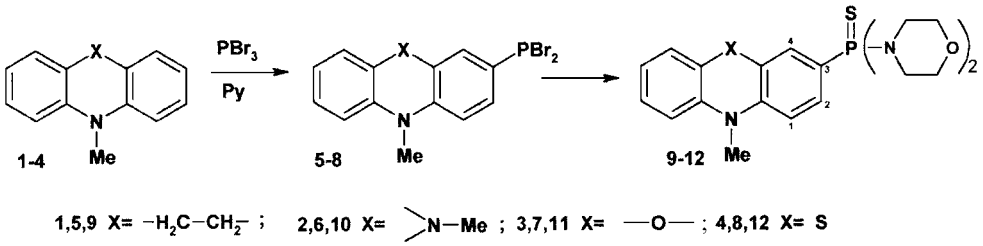
We have recently shown that *N*-methyldiphenylamine and *N*-methylphenylnaphthylamine, like other electron-rich benzene and naphthalene derivatives, are regioselectively phosphorylated with phosphorus tribromide in the presence of bases, the phosphorylation involving one or both aryl residues, as dictated by the reagent ratio [1,2].

Correspondence to: Sergei P. Ivonin, Heroev Stalingrada 133/60, Dnepropetrovsk, 49033, Ukraine, e-mail: ivonin@dp.ukrtel.net.

As might be expected, heterocyclic systems bearing a diphenylamino group, such as 5-methyl-10, 11-dihydro-5H-dibenzo[b,f]azepine (**1**), 5,10-dimethyl-5,10-dihydrophenazine (**2**), 10-methylphenoxazine (**3**), and 10-methylphenothiazine (**4**), should also undergo regioselective phosphorylation with phosphorus tribromide in the presence of bases, according to the orienting effect of the amino group. Phosphorylation of the mentioned heterocycles is interesting, both theoretically and practically, as they represent structural constituents of many medicinal agents [3]. It should also be noted that phosphorylation of these heterocyclic systems with phosphorus halides has not been investigated previously, and comparative analysis of their reactivity toward other electrophiles is still lacking in the literature [4–7]. PBr_3 has been found to be efficient in the phosphorylation of *N*-and *P*-heterocycles [8–10].

RESULTS AND DISCUSSION

We have found that 5,10-dimethyl-5,10-dihydrophenazine (**2**) and also its carbo- and heteroanalogs **1, 3**, and **4** enter into a phosphorylation reaction with phosphorus tribromide in pyridine at the 1:1 reagent ratio to provide the corresponding dibromophosphines **5–8** which were further converted to thioamido-phosphonates **9–12** in high yields (Scheme 1).



SCHEME 1

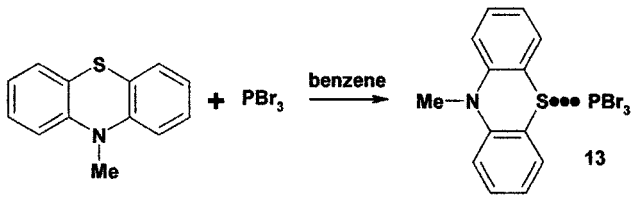
Dibromophosphines **5–8** appear as yellow crystalline substances readily hydrolyzable by atmospheric moisture, with their compositions and structures respectively, supported by elemental analyses (see Table 1), and ^{31}P and ^{1}H NMR spectra. The most characteristic ^{1}H resonances are the doublet H^4 in the region 6.96–7.18 ppm and the doublet of doublets H^2 in the region 7.29–7.72 ppm (see Tables 2 and 3).

It is noteworthy that heterocycles **1–4**, when phosphorylated, manifest different reactivities. As seen from Table 4, they are less reactive than *N*-methyldiphenylamine in the reaction of electrophilic phosphorylation. The most reactive member of these heterocyclic systems is 5,10-dimethyl-5,10-dihydrophenazine (**2**) that is comparable in this respect to *N*-methyldiphenylamine.

An increase in the reaction temperature causes the reaction time to shorten substantially for slow-reacting heterocycles such as phenoxazine (**3**) and diazepine (**1**) (see Table 4). At the same time, an increased temperature of the reaction mixture for the reaction with *N*-methylphenothiazine (**4**) results in the change of the reaction course leading to a thiophosphorylbromide and polymeric products of undetermined structure.

We deem the low reactivity of *N*-methylphenothiazine in electrophilic phosphorylation to be due to the fact that the initial attack of phosphorus tribromide occurs at the sulfur atom, characterized by an increased nucleophilicity. In support of this conjecture, *N*-methylphenothiazine was reacted with phosphorus tribromide in benzene to form the corresponding complex **13** (Scheme 2).

Complex **13** is a light-green powder with a characteristic melting temperature; its composition is corroborated by elemental analysis. The ^{31}P NMR



SCHEME 2

TABLE 1 ^{31}P NMR Spectral Data (δ, ppm; *J*, Hz.), Yields, Melting Temperatures, and Data of Elemental Analysis

				Found			*Calculated*	
Compound	δ_P *(ppm) (solvent)*	*Yield (%)*	*m.p. (°C) (solvent)*	*N (%)*	*P (%)*	*Empirical formula*	*N (%)*	*P (%)*
5	154.7 (pyridine)	77	134–135 (octane)	3.53	7.75	$C_{15}H_{14}Br_2NP$	3.51	7.76
6	155 (benzene)	78	128 (octane)	7.01	7.78	$C_{14}H_{13}Br_2N_2P$	7.00	7.74
7	158.6 (pyridine)	76	78 (benzene/hexane)	3.67	7.98	$C_{13}H_{10}Br_2NOP$	3.62	8.00
9	77.2 (benzene)	84	70–71 (octane)	9.49	6.97	$C_{23}H_{30}N_3O_2PS$	9.47	6.98
10	77 (chloroform)	83	193–195 (octane)	12.61	6.94	$C_{22}H_{29}N_4O_2PS$	12.60	6.97
11	76.4 (benzene)	71	86–88 (octane)	9.73	7.16	$C_{21}H_{26}N_3O_3PS$	9.74	7.18
12	68.3 (benzene)	81	85 (ethanol)	9.38	6.91	$C_{21}H_{26}N_3O_2PS_2$	9.39	6.92
13	200 (chloroform)	90	78 (hexane)	3.95	4.34	$C_{13}H_{13}Br_3NPS$	3.92	4.33
14	152 (benzene)	75	157 (hexane/benzene)	2.39	10.51	$C_{15}H_{13}Br_4NP_2$	2.38	10.52
15	153.7 (pyridine)	75	174 (hexane/benzene)	4.78	10.48	$C_{14}H_{12}Br_4N_2P_2$	4.75	10.50
16	150.6 (benzene)	70	132 (hexane)	2.47	10.74	$C_{13}H_9Br_4NOP_2$	2.43	10.74
17	152 (benzene)	83	250–251 (ethanol)	10.33	9.12	$C_{31}H_{45}N_5O_4P_2S_2$	10.33	9.14
18	77.1 (chloroform)	87	205–206 (octane)	12.39	9.13	$C_{30}H_{44}N_6O_4P_2S_2$	12.38	9.13
19	76.3 (benzene)	79	147–148 (methanol)	10.51	9.29	$C_{29}H_{41}N_5O_5P_2S_2$	10.52	9.30

spectrum of the compound contains a signal at $\delta = 200.1$, and its ^{1}H spectrum is identical with that of *N*-methylphenothiazine, which suggests complexation at the sulfur atom.

Thereafter, we investigated phosphorylation of compounds **1–3** with excess phosphorus tribromide. It was found, that they reacted with excess phosphorus tribromide in boiling pyridine to give bisdibromphosphines **14–16**, characterized further by conversion to bisthioamidophosphonates **17–19** in high yields (Scheme 3).

Compounds **14–16** were obtained as solid crystalline substances, with their compositions confirmed by elemental analysis and their structures attested by ^{31}P and ^{1}H NMR spectra. The most characteristic signals in the ^{1}H NMR spectrum are the doublet $H^{4,6}$ at $\delta = 7.75$ (14) and at $\delta = 6.76$ (16). Bisdibromophosphine (**15**) exhibits the doublet $H^{4,9}$ at $\delta = 6.37$, a doublet of doublets ($H^{2,7}$) at $\delta = 7.29$, and a singlet at $\delta = 3.14$ originating from the protons of the $N-CH_3$ groups and indicating their equivalence. Thus, the second dibromophosphino group is introduced at the position 8 of the heterocyclic system. Among the heterocycles in question, the most reactive in bis-phosphorylation is 5,10-dimethyl-5,10-dihydrophenazine (**2**) (see Table 5), the two nitrogen atoms independently affecting the phosphorylation.

The above-presented experimental findings suggest that the ring closure in the molecule of *N*-methyldiphenylamine results in reduced reactivity of the concerned heterocycles toward the reaction of phosphorylation, which may be attributed to inhibition of conjugation between the lone electron pair of the nitrogen atom and the aromatic moiety.

To verify this assumption, we have calculated, by the PM3 method, structural parameters of the starting molecules as well as heats of formation for σ-complexes generated on protonation (see Table 6).

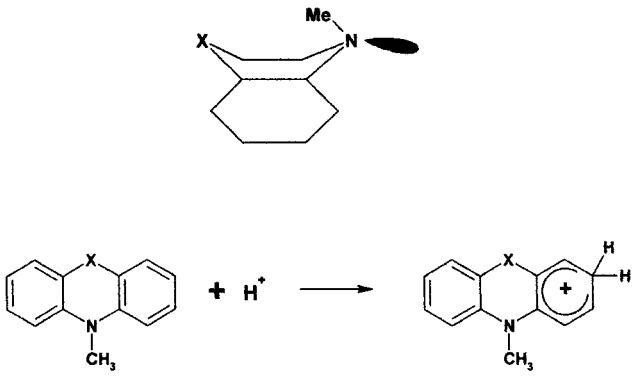


TABLE 2 H NMR Spectral Data for Compounds **7**, **11**, **12**, **16**, and **19**

Compound	H^4 (ppm)	J_{HP} (Hz)	H^2 (ppm)	J_{HH} (Hz)	J_{HP} (Hz)	H^8 (ppm)	J_{HH} (Hz)	J_{HP} (Hz)	H^6 (ppm)	J_{HP} (Hz)	Other signals (δ, ppm; J, Hz)
7	7.18 d	8.74	7.34 t	8.4	8.4						3.04s (3H,N—CH_3); 6.40–6.80m (5H,$H^{1,6,7,8,9}$)
11	7.08 d	14.1	7.38 dd	8.2	14.1						2.83–2.95m (8H,CH_2N); 3.08s (3H,N—Me); 3.56s* (8H,CH_2O); 6.65–6.95m (5H,$H^{1,6,7,8,9}$)
12	6.65	8.2	6.90 t	8.2	8.2						3.13s (3H, CH_3); 3.14m (8H,N—CH_2); 3.68m (8H,O—CH_2) 7.11–7.18m (2H,$H^{6,8}$); 6.21–6.35m (3H,$H^{1,7,9}$)
16	7.33 d	8.4	6.76 dd	8.2	9.6	6.76 dd	8.02	9.6	7.33 d	8.4	3.11s (3H,CH_3); 6.57d (2H,$H^{1,9}$) $J_{HH} = 9.6$
19	7.11 d	12.6	7.39 dd	8.1	12.3	7.39 dd	8.1	12.3	7.11 d	12.6	2.92s[a] (16H,CH_2N); 3.12s (3H,N—Me); 3.56s[a] (16H, CH_2O); 6.88dd (2H,$H^{1,9}$) $J_{HH} = 8.1$, $J_{HP} = 3.0$

[a]lines are broadening.

TABLE 3 ^{1}H NMR Spectra Data for Compounds **5, 6, 9, 10, 14, 15, 17**, and **18**

Compound No	*Solvent*	*δ, (ppm), J (Hz)*
5	$CDCl_3$	3.21s (4H,CH_2); 3.49s (3H,CH_3); 7.00–7.25m (5H,$H^{4,9,8,7,6}$); 7.63d (1H,H^1) $J_{HP} = 8.4$; 7.72t (1H,H^3) $J_{HH} = 8.4$, $J_{HP} = 8.4$
6	$CDCl_3$	3.05m (6H;CH_3); 6.45–6.62m (3H,$H^{4,6,9}$); 6.70–6.80m (3H; $H^{1,7,8}$); 7.25 dd (1H,H^3) $J_{HP} = 2.5$, $J_{HH} = 8.8$
9	$CDCl_3$	2.84–3.08m (8H,CH_2N); 3.10s (4H,CH_2); 3.34s (3H,N—Me); 3.50–3.60m (8H,CH_2O); 6.99t (1H,H^8) $J_{HH} = 8.7$;7.14–7.22m (4H,$H^{4,6,7,9}$); 7.55d (1H,H^1) $J_{HP} = 12.9$; 7.62t (1H,H^3) $J_{HH} = 8.7$, $J_{HP} = 8.7$
10	DMSO-d_6	3.01m (6H,CH_3); 6.48–6.59m (3H, $H^{4,6,9}$); 6.70–6.80m (3H, $H^{1,7,8}$); 7.22 dd (1H,H^3) $J_{HP} = 12.6$, $J_{HH} = 9.3$
14	$CDCl_3$	3.22s (4H,CH_2); 3.48s (3H,CH_3); 7.16d (2H,$H^{4,6}$) $J_{HH} = 8.2$; 7.66d (2H,$H^{1,9}$) $J_{HP} = 8.7$; 7.75dd (2H,$H^{3,7}$) $J_{HP} = 8.7$, $J_{HH} = 8.4$
15	$CDCl_3$	3,14s (6H,CH_3); 6.37d (2H,$H^{4,9}$) $J_{HH} = 8.6$; 6.96d (2H,$H^{1,6}$) $J_{HH} = 3.5$; 7.29 dd (2H,$H^{3,8}$) $J_{HP} = 3.5$, $J_{HH} = 8.6$
17	DMSO-d_6	3.15s (4H,CH_2); 3.39s (3H,CH_3); 3.35m (16H,CH_2N); 3.55s[a] (16H,CH_2O); 7.26d (2H,$H^{4,6}$) $J_{HH} = 8.2$; 7.59–7.70m (4H,$H^{1,3,7,9}$)
18	DMSO-d_6	2.97m (8H,CH_2N); 3,08s[a] (6H,CH_3); 3.56s[a] (8H,OCH_2); 6.34d (2H,$H^{4,9}$) $J_{HH} = 8.2$; 6.98d (2H,$H^{1,6}$) $J_{HP} = 12.1$; 7.36dd (H,$H^{3,8}$) $J_{HH} = 8.2$, $J_{HP} = 12.1$

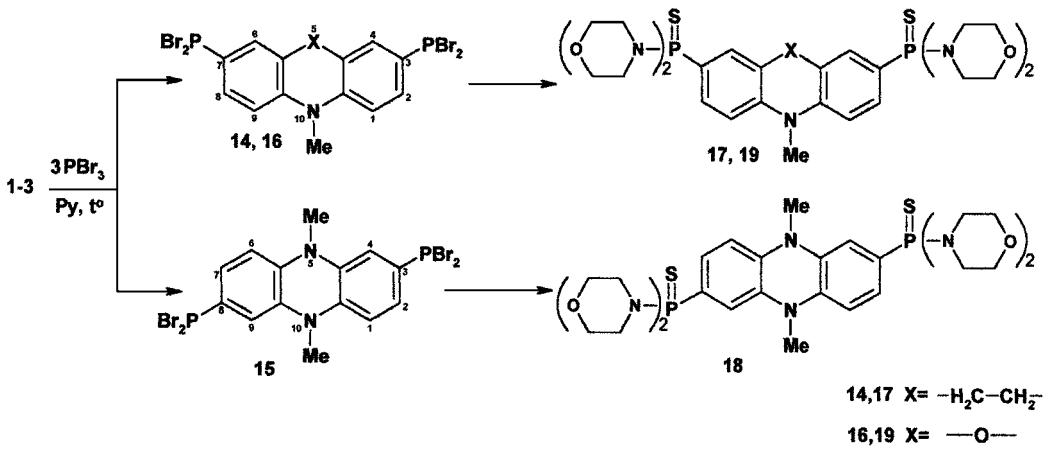
[a]Lines are broadening.

As seen from the computed data, the heats of formation for σ-complexes produced by the compounds of interest increase as their reactivity in phosphorylation decreases. On analyzing the spatial structure of starting molecules, one can conclude that the reactivity decreases more, the larger is the deviation (Δφ) of the lone electron pair of the nitrogen atom from the orthogonality to the plane of phenyl rings.

Thus, the experimentally obtained reactivity series for the heterocycles under study in the phosphorylation reaction correlates well with the PM3 computed structural data for starting molecules and the heats of formation of the corresponding protonic σ-complexes.

EXPERIMENTAL

The ^{31}P and ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer, TMS being used as an internal standard for ^{1}H signals and 85% H_3PO_4 as an external standard for ^{31}P signals. All reactions were carried out in anhydrous solvents. The reaction completion time was monitored by ^{31}P NMR spectroscopy. Monophosphorylation was considered to be ended as soon as the signal of phosphorus tribromide disappeared from the spectrum of the reaction mixture. The time needed for bis-phosphorylation to come to completion was determined by the vanishing signal of monodibromophosphine.



SCHEME 3

TABLE 4 The Time Taken for the Phosphorylation of Compounds 1–4 at the 1:1 Reagent Ratio

	Time	
x	*20°C*	*115°C*
N-Methyldiphenylamine[a]	8 h	–
>N—CH_3	12 h	–
—H_2C—CH_2—	6 days	6 h
—O—	14 days	12 h
—S—	1 year[b]	Different outcome

[a]From Ref. [1].
[b]The reaction proceeds to the extent of 25% at the reagent ratio 1:3.

The general procedure for the preparation of dibromophosphines 5–8. To a solution of the corresponding compound from the series **1–4** (0.01 mol) in pyridine (20 ml), phosphorus tribromide (0.01 mol) was added. The reaction mixture was held at 20°C for an appropriate time (see Table 4) and then evaporated under vacuum. The residue was dissolved in benzene (50 ml) and the resulting precipitate was filtered off. On evaporation of the filtrate under vacuum, the residue crystallized (See Table 1).

The general procedure for the preparation of dithiophosphonates 9–11. To a stirred solution of the corresponding dibromophosphine from the series **5–8** (0.01 mol) in benzene, a solution of morpholine (0.02 mol) and triethylamine (0.03 mol) in benzene (30 ml) was added. After having been allowed to stand at room temperature for 5 h, the reaction mixture was filtered and sulfur (0.01 mol) was added to the filtrate. Then the mixture was boiled for 2 h and evaporated under vacuum. The residue was crystallized from the solvent listed in Table 1.

Dimorpholinothiophosphonate (**12**). To a solution of *N*-methylphenothiazine (0.01 mol) in pyridine (30 ml), phosphorus tribromide (0.03 mol) was added. The reaction mixture was allowed to stand at room temperature for 1 year. The resulting precipitate was filtered off, and a solution of morpholine (0.02 mol) and triethylamine (0.03 mol) in benzene (30 ml) was added to the filtrate. After the mixture had been held at 20°C for 5 h, it was filtered and sulfur (0.01 mol) was added to the filtrate. Then the mixture was boiled for 2 h and evaporated under vacuum. The residue was boiled twice with water (70 ml) and crystallized from the solvent indicated in Table 1.

TABLE 5 The Time Taken for the Phosphorylation of Compounds 1–3 at the 1:3 Reagent Ratio

x	*Time at 115°C*
N-Methyldiphenylamine[a]	12 h
>N—CH_3	36 h
—H_2C–CH_2—	48 h
—O—	6 days

[a]From Ref. [1].

TABLE 6 Deviation of the Lone Electron Pair of the Nitrogen Atom From the Orthogonality to the Aromatic Moiety and Heats of Formation for Protonic σ-Complexes

X	$\Delta\varphi^\circ$	ΔH *(Kcal/mol)*
–	0	156.9
NMe	22	159.1
O	38	176.1
S	39	176.4

The complex of *N*-methylphenothiazine with phosphorus tribromide (**13**). To a solution of *N*-methylphenothiazine (0.01 mol) in benzene (5 ml), phosphorus tribromide (0.05 mol) was added. The reaction mixture became deep-green. Hexane (20 ml) was added to the reaction mixture and it was left to stand at 20°C for 4h. The precipitated oil solidified on treatment twice with hexane. Its m.p. is listed in Table 1.

The general procedure for the preparation of bis-dibromophosphines 14–16. To a solution of the corresponding compound from the series **1–3** (0.01 mol) in pyridine (20 ml), phosphorus tribromide (0.03 mol) was added. The reaction mixture was boiled for an appropriate time (see Table 5) and then evaporated under vacuum. The residue was dissolved in benzene (50 ml) and the resulting precipitate was filtered off. On evaporation of the filtrate under vacuum, the residue was purified by reprecipitation from benzene by addition of hexane. (See Table 1).

The general procedure for the preparation of bis-dithiophosphonates 17–19. To a stirred solution of the corresponding bis-dibromophosphine from the series **14–16** (0.01 mol) in benzene (20 ml), a solution of morpholine (0.04 mol) and triethylamine (0.06 mol) in benzene (50 ml) was added. After having been allowed to stand at room temperature for 5 h, the reaction mixture was filtered and sulfur (0.02 mol) was added to the filtrate. Then the mixture was boiled for 2h and evaporated under vacuum. The residue was crystallized from the solvent listed in Table 1.

REFERENCES

[1] Kopteva, S. D.; Tolmachev, A. A. Zh Obshch Khim 1999, 69, 164.

[2] Ivonin, S. P.; Kopteva, S. D.; Serdyuk, V. N. Zh Org Khim 2000, 36(3), 422–428.
[3] Roth, H. J.; Kluman, A.; Bessiwenger, T. Pharmaceutical Chemistry; Wiley: New York, 1988; Vol. 1, p. 410.
[4] Jitt Norton, H.; Summers, J. W.; Shimko, T. M. J Org Chem 1972, 37(7), 1045–1047.
[5] Vanderhaeghe, H.; Phenoxazines. I. J Amer Chem Soc 1960, 25(5), 747–753.
[6] Kricka Larry, I.; Ledwith Antony. J Chem Soc Perkin Trans 2 1973, 1(8), 859–863.
[7] Koshechko, V. G.; Inozemtseva, A. N. Khim Geterotsikl Soed 1984, (5), 1110–1111.
[8] Ivonin, S. P.; Terikovska, T. E.; Chaikovskaya, A. A.; Marchenko, A. P.; Koydan, G. N.; Pinchuk, A. M.; Tolmachev, A. A. Heteroat Chem 1999, 10(3), 213–221.
[9] Tolmachev, A. A.; Ivonin, S. P.; Chaikovskaya, A. A.; Terikovska, T. E.; Kudrya, T. N.; Pinchuk, A. M. Heteroat Chem 1999, 10(3), 223–230.
[10] Keglevich, T.; Chuluunbaatar, A.; Dobo, A.; Toke, L. J. Chem Soc Perkin Trans 2000, 1, 1495.