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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS—XXXVI[1]

SIMPLE NEW ROUTES TO PHOSPHORINS FROM 2-HYDROXY-, 2-MERCAPTO-, AND 2-AMINOBENZOIC ACIDS AND THEIR DERIVATIVES

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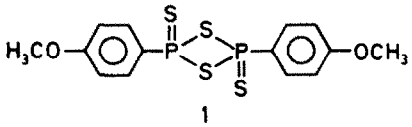
Abstract—2-Hydroxybenzoic acid heated with 2,4 - bis(4 - methoxyphenyl) - 1,3,2,4 - dithiadiphosphetane - 2,4 - disulfide, **1**, gave 2 - (*p* - methoxyphenyl) - 4H - 1,3,2 - benzoxathiaphosphorin - 4 - one 2 - sulfide, **3**, and its thio-analogue, **4**, while its ethyl or phenyl esters gave **4** as the sole product. 2 - Mercaptobenzoic acid and its ethyl ester when heated with **1** produced 3H - 1,2 - benzodithiole - 3 - one, **8**, 3H - 1,2 - benzodithiole - 3 - thione, **9**, and 2 - (*p* - methoxyphenyl) - 4H - 1,3,2 - benzodithia - phosphorin - 4 - one 2 - sulfide, **10**. The reaction of 2 - aminobenzoic acid with **1** gave 1,2 - dihydro - 2 - (*p* - methoxyphenyl) - 4H - 3,1,2 - benzoxaphosphorin - 4 - one 2 - sulfide, **12**. Reactions of **1** with methyl 2 - aminobenzoate and 2 - aminobenzamides are described. Mechanistic considerations for the formation of the heterocyclic phosphorus compounds are presented.

It has been found that 2,4 - bis(4 - methoxyphenyl) - 1,3,2,4 - dithiaphosphetane - 2,4 - disulfide, **1**, is a most effective thiation reagent for ketones,[2] carboxamides,[3-7] esters,[8-10] S-substituted thioesters,[8] lactones,[11] lactams,[12] imides,[12] enaminones,[13] hydrazides[14] and hydrazones.[15]

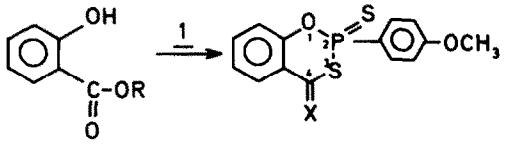


1

The reagent **1** is easily available and undergoes also ring-closure reactions with substrates containing two functional groups.[10,15] To extend the use of **1** to other bifunctional substrates, its reaction with 2 - hydroxy-, 2 - mercapto-, and 2 - aminobenzoic acid and their derivatives has been investigated and found to give new phosphorus heterocycles. Our results are reported in this paper.

RESULTS AND DISCUSSION

By refluxing 2-hydroxybenzoic acid, **2a**, with **1** in anhydrous toluene at 110° two new phosphorus heterocycles, 2 - (*p* - methoxyphenyl) - 4H - 1,3,2 - benzoxathia - phosphorin - 4 - one 2 - sulfide, **3**, (high yield) and its thioanalogue, **4**, (low yield) are formed.



2 a, R = H; b, R = C_2H_5; c, R = C_6H_5 — **3**, X = O; **4**, X = S

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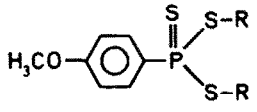
At higher temperature (140° in anhydrous xylene), the reaction between ethyl 2 - hydroxybenzoate, **2b**, and **1** gave **4** in 40% yield besides diethyl - 4 - methoxyphenylphosphonotrithioate, **5b**.[16]

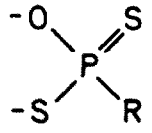


5

a, R = CH_3
b, R = C_2H_5

The highest yield of **4** (81%) was found when using phenyl 2 - hydroxbenzoate, **2c** at 140° in anhydrous xylene.

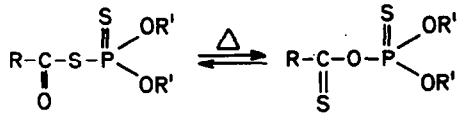
The structural proofs for **3** and **4** use spectroscopic data and elemental analyses. The IR spectrum of **3** showed a strong absorption band at 1670 cm^{-1} (C=O). In the ^{13}C NMR spectra the carbonyl carbon of **3** absorbs at 180.7 ppm and the thiocarbonyl carbon of **4** at 212.6 ppm. The mass spectra of **3** and **4** showed *m/e* 322 (M^+) and 338 (M^+), respectively. In the ^{31}P NMR spectra the chemical shifts of **3** and **4** were found at 84.3 and 78.3 ppm, respectively, which is in accordance with other compounds containing the following structure:[17a]



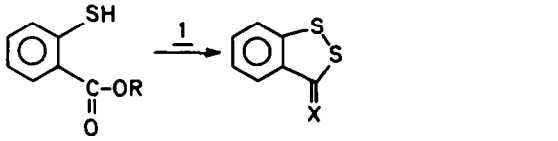
As to the formation of **5b** it is suggested that the ethanol, formed from the ring-closure reaction (Scheme 1), will react with **1** to give a 1:1-adduct, which then by a not too-well understood reaction will give the final product. The reaction between hydroxy compounds and **1** and other similar reagents is known.[18-20]

Compound **3** was also refluxed in CCl_4 for 30 hr but

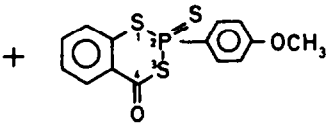
the starting material was recovered and no rearrangement[21] was observed:



The reaction of equimolecular amounts of 2 - mercaptobenzoic acid, **7a**, with **1** in anhydrous toluene at 110° gave the following products: 3H - 1,2 - benzodithiole - 3 - one, **8**,[22] 3H - 1,2 - benzodithiole - 3 - thione, **9**,[23-26] and a new phosphorus heterocycle, 2 - (*p* - methoxyphenyl) - 4H - 1,3,2 - benzodithiaphosphorin - 4 - one 2 - sulfide, **10**.



7 a, R = H b, R = C_2H_5 **8**, X = O **9**, X = S

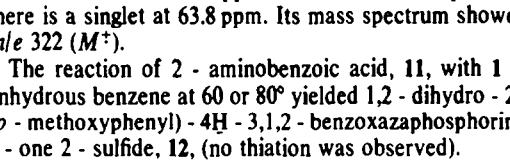


10

In the reaction of **7a** (1 mole) with excess of **1** (2 moles) in anhydrous toluene at 110°, **8** was not isolated while the yield of **9** increased (due to thiation of **8**) but the yield of **10** did not change. Compound **9** was also obtained in high yield by reacting ethyl 2 - mercaptobenzoate, **7b**, with **1** in anhydrous xylene at 140°. In addition also **5b** and **10** were isolated. The formation of **8** and **9** has also been observed in the reaction of P_4S_{10} with different derivatives of 2 - mercaptobenzoic acid.[24-26]

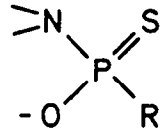
The structural proof of **10** is based on IR, ^1H, ^{13}C, ^{31}P NMR and mass spectroscopy and elemental analyses. In the IR spectrum a strong absorption at 1670 cm^{-1} (C=O) was observed. In the ^{13}C NMR spectrum the carbonyl carbon absorbs at 187.0 ppm and in ^{31}P NMR spectrum there is a singlet at 63.8 ppm. Its mass spectrum showed *m/e* 322 (M^+).

The reaction of 2 - aminobenzoic acid, **11**, with **1** in anhydrous benzene at 60 or 80° yielded 1,2 - dihydro - 2 - (*p* - methoxyphenyl) - 4H - 3,1,2 - benzoxazaphosphorin - 4 - one 2 - sulfide, **12**, (no thiation was observed).



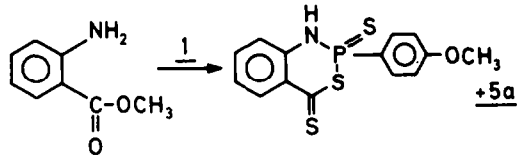
11 **12**

The structural proof of **12** is based on IR, ^1H, ^{13}C and ^{31}P and mass spectroscopy. In the IR spectrum strong absorptions at 1750 cm^{-1} (O–C=O) and 3200 cm^{-1} (NH stretching) were observed. In the ^1H NMR spectrum there are a singlet at 3.8 ppm (3H, OCH_3) and a doublet at 9.35 ppm (1H, J_{PH} 16 Hz) NH. In the ^{13}C spectrum, the carbonyl carbon absorbs at 170.2 ppm and in the ^{31}P NMR spectrum there is a singlet at 77.7 ppm in accordance with other compounds containing the following structure:[17b]



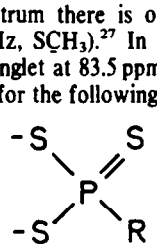
Its mass spectrum showed *m/e* 305 (M^+).

On the other hand, at elevated temperature (140°, xylene) the reaction of methyl 2 - aminobenzoate, **13**, with **1** produced 1,2 - dihydro - 2 - (*p* - methoxyphenyl) - 4H - 3,1,2 - benzothiazaphosphorin - 4 - thione 2 - sulfide, **14**, and dimethyl - 4 - methoxyphenylphosphonotrithioate, **5a**.



13 **14** **+5a**

The structural proof of **14** is based on ^1H NMR and mass spectroscopy. In the ^1H NMR there is a singlet at 3.8 ppm (3H, OCH_3) and a doublet at 9.5 ppm (1H, J_{PH} 15 Hz) NH. Its mass spectrum showed the mass peak at *m/e* 337 (M^+). The structure elucidation of **5a** is based on ^1H, ^{13}C, and ^{31}P NMR, mass spectrometry and elemental analyses. Its ^1H NMR spectrum contains a doublet (3H and 3H) at 2.3 ppm corresponding to the two (SCH_3) group protons, one singlet (3H) at 3.85 ppm (OCH_3). In the ^{13}C NMR spectrum there is one methyl signal at 15.3 ppm ($^2J_{cp}$ 3.5 Hz, SCH_3).[27] In the ^{31}P NMR spectrum there is one singlet at 83.5 ppm also in accordance with literature data for the following structure.[28,29]

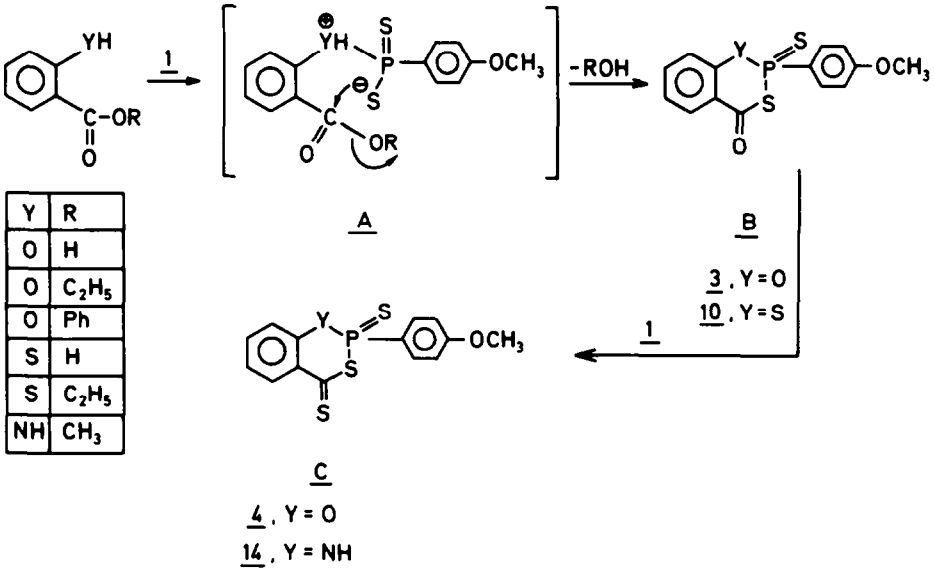


The mass spectrum of **5a** showed peaks at *m/e* 264 (M^+) and *m/e* 217 (M^+-SCH_3, base peak).

As to the mechanism for the formation of the *p*-heterocycles **3**, **4**, **10** and **14** (R ≠ H) it is suggested (Scheme 1) that a nucleophilic attack on **1** gives A, followed by ring closure and expulsion of the alcohol (ROH) to give B. Subsequent thiation produces C. When R = H (Y = O or S) the same mechanism as above is suggested, but with anthranilic acid it is assumed that the carboxylate of the betaine, **11'** attacks **1** on phosphorus giving a salt, which at elevated temperature loses H_2S[1] to give **12**.

By reacting 2-aminobenzamide, **15a**, and 2 - aminocyclohexylbenzamide, **15b**, with **1** the respective phosphorus heterocycles, 2,3 - dihydro - 2 - (*p* - methoxyphenyl) - 1,3,2 - benzodiazaphosphorine - 4 (1H) - thione - 2 - sulfide, **16a** and **16b** were formed.

The structural proof of **16** is based on spectroscopic



Y	R
O	H
O	C_2H_5
O	Ph
S	H
S	C_2H_5
NH	CH_3

A

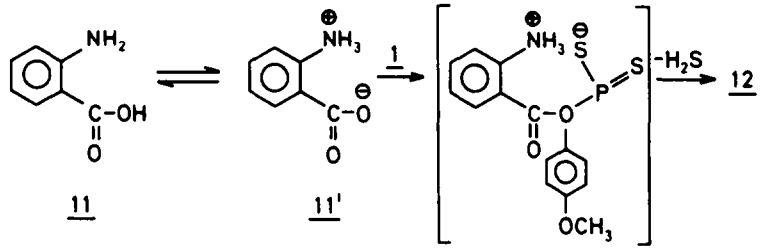
B

3, Y = O
10, Y = S

C

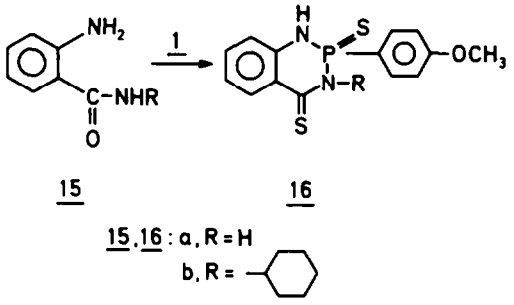
4, Y = O
14, Y = NH

Scheme 1.



11 11' 12

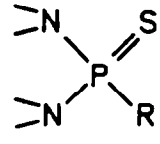
Scheme 2.



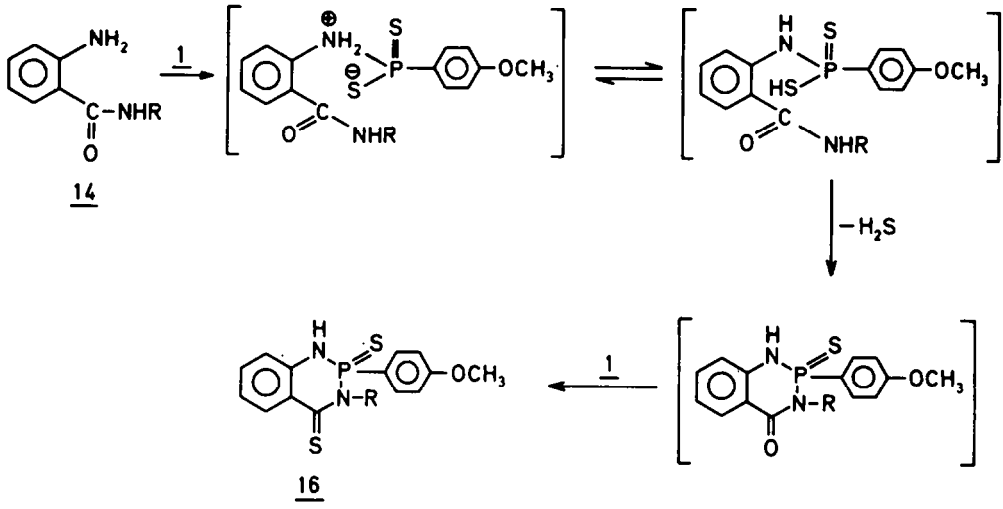
15 16

15,16 : a, R = H
b, R =

data and elemental analyses. In **16a** the IR spectrum (KBr) showed absorption band at 3260 cm^{-1} (NH–P–) stretching frequency and a band at 3150 cm^{-1} (NH–C–) stretching frequency.[30] The IR spectrum (film) of **16b** showed a band at 3300 cm^{-1} (broad) corresponding to the NH stretching frequency.[30] In the ^1H NMR spectra of **16a** and **16b** there are singlets at 3.80 and 3.85 ppm corresponding to the OCH_3 group protons, respectively. In **16b** there is a multiplet at 0.7–1.8 ppm (10H, cyclohexyl group) and a multiplet at 2.6–2.8 ppm (1H, CH proton). In ^{13}C NMR of **16a** and **16b** the thiocarbonyl carbon at 194.6 and 196.4 ppm, respectively. The ^{31}P NMR spectra showed a singlet at 48.4 and 51.5 ppm corresponding to the absorption of **16a** and **16b**, respectively, which is in accordance with other compounds containing the following structure:[31]



Concerning the mechanism for the formation of **16a** and **16b** the following is suggested:



Scheme 3.

EXPERIMENTAL

^{1}H NMR spectra were recorded at 60 MHz on a Varian EM-360 spectrometer. ^{13}C and ^{31}P NMR spectra were obtained on a Varian CFT-20 instrument at 20.14 and 32.19 MHz, respectively. $CDCl_3$ was used as solvent and TMS as internal reference standard. Chemical shifts are expressed as δ-values. Also ^{31}P chemical shifts are reported positive low field to (external) H_3PO_4. IR spectra were recorded on a Beckman IR-18A spectrometer. Mass spectra were recorded on a Micromass 7070 F mass spectrometer operating at 70 eV using direct inlet. Elementary analyses were carried out by Novo Microanalytical Laboratory, Novo Industri A/S, Novo Allé, DK-2880 Bagsvaerd.

Table 1. Experimental and analytical data of the products

Starting Compound	Product	Reaction Time (h)	Solvent[d]	Reaction Temp. (°C)	Yield (%)	M.p. (°C)	Analyses Calc./Found (%) C	H	P	S
2a	3	3½	T	110	72	98	52.17 52.20	3.42 3.64	9.62 9.39	19.90 18.72
	4				10	102	49.70 49.70	3.25 3.32	9.17 9.87	28.40 28.37
2b	4	2	X	140	40					
	5b				7	oil[15]				
2c	4	2½	X	140	81					
7a[a]	8	3	T	110	15	78[20]				
	9				52	94[24]				
	10				32	130	49.70 50.51	3.25 3.38	9.17 9.06	28.40 27.60
7a[b]	9	2	T	110	75					
	10				30					
7b	5b	2	X	140	10					
	9				80					
	10				33					
11	12	2½	B	60	50	168	(e)			
13	5a	2½	X	140	31	oil	40.91 41.33	4.92 4.96	11.74 10.36	36.36 37.28
	14				10	135				
15a	16a	24	B	25	24	95[c]	52.44 51.92	4.06 4.08	9.69 9.32	20.00 19.99
15b	16b	6	T	110	20	110	(e)			

a) 7a (1 mole) + 1 (1 mole)

b) (1 mole 7a:2 mole 1)

c) (N;Calc. 8.75, Found 8.81%)

d) T = toluene, X = xylene, B = benzene

e) M.S.

Table 2. IR, ^{13}C and ^{31}P NMR spectra of the products

Compound	IR (cm^{-1})	^{13}C δ(ppm)	^{31}P *δ(ppm)
3	1670 (C=O)	180.7 (C=O)	84.3
4		212.6 (C=S)	78.3
5a		14.8 (S-$\underline{C}H_3$)	83.5
		55.3 (O$\underline{C}H_3$)	
10	1670 (C=O)	187.0 (C=O)	63.8
12	1750 (O-C=O)	170.2 (C=O)	77.7
	3200 (NH)		
	3260 (NH)		
16a	3150 (NH-C-)	194.6 (C=S)	48.4
16b	3300 (NH,b)	196.4 (C=S)	51.5

* δ-Values relative to 85% H_3PO_4 (external) $CDCl_3$

Silica gel 60 (Merck) was used for column chromatography. The light petroleum used boiled below 45°C. M.p.'s are uncorrected.

Starting materials. Compound **1** (now available from Fluka AG, CH-9470 Buch SG) was prepared as described earlier.[1] Compounds **2**, **7**, **11** and **13** were commercially available. The others, **15a**[32] and **15b**[33] were prepared by known methods.

General procedure for the reaction of **2a–c**, **7a, b**, **13** *and* **15b** *with* **1**

0.01 mole of the starting compound and 4.04 g (0.01 mole) of **1** were refluxed in 10 ml of anhydrous toluene at 110° or xylene at 140° (see Table 1) with stirring until no more of the starting material could be detected (tlc). After cooling to room temperature, the excess of **1** was filtered off. Then the reaction mixture was evaporated on silica gel under reduced pressure and applied to silica gel column using ether/light petroleum as eluant. The reaction conditions and the physical data are summarized in Table 1.

In molar ratio of (1:2) of **7a**:**1**, when reacted under identical conditions as above gave results with varying yields and different compounds. Reaction of **11** with **1**: As above, reaction temperature 60°. Reaction of **15a** with **1**: As above, reaction temperature 25°.

Rearrangement of **3**. 1.61 g (0.005 mole) of **3** was refluxed in anhydrous CCl_4 at 80° for 30 hr. The solvent was evaporated under vacuum till dryness. The solid obtained (1.60 g) was recrystallized from ethanol. Its m.p. and mixed m.p. with an authentic sample of **3** gave no depression.

Compound **3**. MS: *m/e* 322 (M^+, 100%), 294 ($M^+ - CO$, 24%), 259 (54%), 202 (17%), 183 (26%). ^1H NMR ($CDCl_3$): δ3.8 (3H, S, OCH_3), 7.1 (2H, dd, $^4J_{PH}$ 5 Hz, J_{HH} 9 Hz), 7.2–7.9 (m, aromatic), 8.1 (2H, dd, $^3J_{PH}$ 15 Hz, J_{HH} 9 Hz).

Compound **4**. MS: *m/e* 338 (M^+, 100%), 274 (66%), 227 (42%), 136 (67%). ^1H NMR ($CDCl_3$): δ 3.8 (3H, S, OCH_3), 7.0 (2H, dd, $^4J_{PH}$ 5 Hz, J_{HH} 9 Hz), 7.1–7.9 (4H, m, aromatic), 8.2 (2H, dd, $^3J_{PH}$ 15 Hz, J_{HH} 9 Hz).

Compound **5a**. MS: *m/e* 264 (M^+, 33%), 217 ($M^+ - SCH_3$, 100%), 185 (15%), 139 (16%). ^1H NMR ($CDCl_3$): δ 2.3 (6H, d, $^3J_{PH}$ 16 Hz, 2 SCH_3), 3.8 (3H, OCH_3), 6.9 (2H, dd, $^4J_{PH}$ 5 Hz, J_{HH} 9 Hz), 7.9 (2H, dd, $^3J_{PH}$ 15 Hz, J_{HH} 9 Hz).

Compound **10**. MS: *m/e* 338 (M^+, 23%), 310 ($M^+ - CO$, 7%), 272 (25%), 202 (7%), 170 (100%), 136 (100%). ^1H NMR ($CDCl_3$): δ 3.8 (3H, S, OCH_3), 6.9 (2H, dd, $^4J_{PH}$ 5 Hz, J_{HH} 9 Hz), 7.0–7.7 (4H, m, aromatic), 8.0 (2H, dd, $^3J_{PH}$ 15 Hz, J_{HH} 9 Hz).

Compound **12**. MS: *m/e* 305 (M^+, 100%), 289 (40%), 272 (35%), 241 (45%), 119 (32%). ^1H NMR ($CDCl_3$ + DMSO): δ 3.8 (3H, S, OCH_3), 6.9 (2H, dd, $^4J_{PH}$ 5 Hz, J_{HH} 9 Hz), 7.1–7.8 (m, aromatic), 7.9 (2H, dd, $^3J_{PH}$ 15 Hz, J_{HH} 9 Hz), 9.4 (1H, d, $^2J_{PH}$ 16 Hz, NH).

Compound **14**. MS: *m/e* 337 (M^+, 100%), 304 ($M^+ - SH$, 10%), 273 (100%), 202 (10%). ^1H NMR ($CDCl_3$): δ 3.8 (3H, S, OCH_3), 6.9–8.1 (8H, m, aromatic protons), 9.5 (d, 1H, NH).

Compound **16a**. MS: *m/e* 320 (M^+, 100%), 287 ($M^+ - SH$, 30%), 202 (11%), 150 (54%). ^1H NMR ($CDCl_3$): δ 3.8 (3H, S, OCH_3), 6.2

(1H, d, $^2J_{PH}$ 13 Hz, NH–P), 6.8–8.0 (7H, m, aromatic), 8.5 (1H, dd, *J* 8 Hz), 8.7 (1H, m, NH – C).

Compound **16b**. MS: *m/e* 402 (M^+, 55%), 369 ($M^+ - SH$, 30%), 320 (27%), 234 (100%), 202 (24%). ^1H NMR ($CDCl_3$): δ 0.7–1.8 (10H, m, cyclohexyl), 2.4–2.9 (1H, m, CH), 3.8 (3H, S, OCH_3), 6.1 (1H, d, $^2J_{PH}$ 13 Hz, NH), 6.6–7.6 (6H m, aromatic), 7.6–8.0 (1H, m), 8.2 (1H, dd, *J* 8 Hz).

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