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SYNTHETIC AND NMR SPECTROSCOPIC STUDIES ON THE 2,1,3-BENZOPHOSPHADIAZINE RING SYSTEM *

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Summary

Alkylation reactions of 2,3-dihydro-2-mercapto-2,1,3-benzophosphadiazine-4(1*H*)-thione-2-sulphide are described; reaction with methyl iodide occurs sequentially to produce mono-, di- and tri-methylated derivatives. Reaction of 1,2-dihydro-1-methyl-2,4-bis(methylthio)-2,1,3-benzophosphadiazine with *p*-chloroaniline leads to a product formed by displacement of SMe groups both from carbon and phosphorous. Lawesson's reagent reacts with *o*-aminobenzamide to yield 1,2-dihydro-2,4-bis(*p*-methoxyphenyl)-2,1,3-benzophosphadiazine-2-sulphide. Details of ^{13}C and ^{31}P NMR used to identify these compounds are discussed.

Introduction

Coppola has described the preparation of the 2,1,3-benzophosphadiazine system (**2**) from reaction of substituted aminobenzamides (**1**) and phosphorous trichloride [1]. As a result of an independent study we have also prepared this heterocycle and reported that reactions of aminobenzamides (**1**) with phosphorous pentasulphide in pyridine yield 2,3-dihydro-2-mercapto-2,1,3-benzophosphadiazine-4(1*H*)-thione-2-sulphide derivatives, the structure of the ring system **3** being proved by X-ray analysis [2]. This reaction provides a rare example of the encorporation of phosphorous derived from P_2S_5 into a heterocyclic system [3]. We now describe further studies on the chemistry of this novel heterocycle, the synthesis of new derivatives, and NMR spectroscopic studies on the systems.

Results and discussion

Synthetic studies

We have now demonstrated that methylation of compound **3** with methyl iodide occurs first at the sulphur atom, attached to phosphorous, as reaction of 1

* Dedicated to Professor G.E. Coates on the occassion of his 70th birthday.

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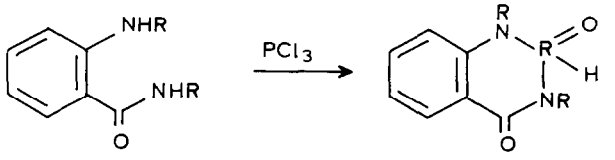
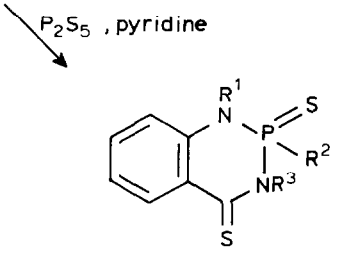
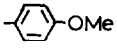
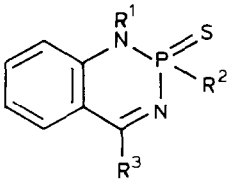
equivalent of methylating reagent with **3** leads to the isolation of monomethyl derivative **4** in good yield. Reaction of **4** with a further one equivalent of methyl iodide occurs at the sulphur atom of the thioamide group to give dimethylated



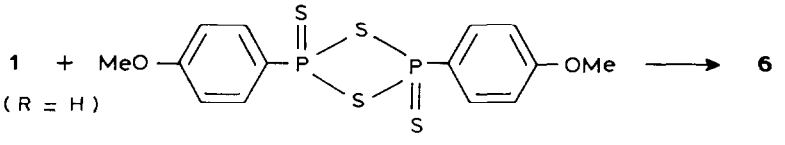
(1) (2) (R = alkyl, phenyl)



	R^1	R^2	R^3
3	H	SH	H
4	H	SMe	H
5	H	SH	Me
6	H		H



	R^1	R^2	R^3
7	H	SMe	SMe
8	Me	SMe	SMe
9	Et	SMe	SEt
10	Me	-NH-*p*-C_6H_4Cl	-NH-*p*-C_6H_4Cl
11	Me	SMe	-NHPh
12	Me	SMe	



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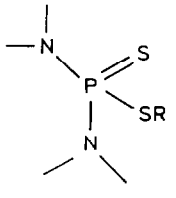

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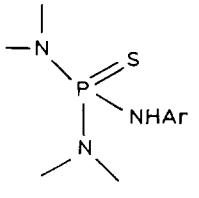

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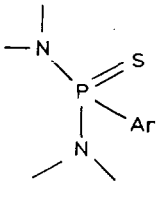

(16)

derivative **7**. Compound **7** is then readily alkylated further to yield trimethyl derivative **8**, prepared previously [2] in a one-step reaction of excess methyl iodide with compound **3**. This sequential alkylation methodology allows the preparation of mixed alkyl derivatives of system **3**, e.g. compound **9** which is obtained in a two-step procedure comprising reaction of the parent compound **3** with one equivalent of methyl iodide, followed by an excess of ethyl iodide.

We have shown that reaction of trimethylated compound **8** with amines leads to nucleophilic displacement of SMe from the imine carbon e.g. to yield compounds **11** and **12** [2]. We have now found that on prolonged heating amines will also displace the SMe group that is attached to phosphorous. Thus, reaction of **8** with *p*-chloroaniline in xylene affords phosphadiazine derivative **10**.

A further variation in the substitution pattern at phosphorous in this heterocycle is obtained when the phosphorous atom is derived from Lawesson's reagent (**13**) instead of P_2S_5. Reaction of aminobenzamide **1** with reagent **13** yields phosphadiazine derivative **6**. Lawesson's reagent is well established as an alternative reagent to P_2S_5 for many sulphur-transfer reactions [4], but the use of reagent **13** as a source of a phosphorous-containing fragment in a reaction is uncommon. We therefore have facile entry into the 2,1,3-benzophosphadiazine system with three different substitution patterns, viz. 14–16, at phosphorous.

Spectroscopic studies

The structures of the new compounds we have prepared follow from analytical, mass spectroscopic and NMR spectroscopic data. In particular $^{1}H-^{31}P$ coupling constants, in combination with ^{13}C, ^{31}P and ^{1}H NMR chemical shifts, confirmed the different sub-structures present in the heterocyclic ring for compounds **3–12**. In general, however, attempts at separating long range couplings to phosphorous proved fruitless. The two systems represented by structures **3–6** and **7–12** could be clearly distinguished by their ^{13}C NMR spectra where C(4) occurred at either δ ca. 195 or δ ca. 177 ppm, appropriate for the C=S or C=N groups, respectively. The ^{1}H NMR spectra of compound **7** exhibited $^{1}H-^{31}P$ couplings to the NH proton (^{2}J(HP) 12 Hz) and to the SMe group attached to phosphorus (^{3}J(HP) 16 Hz) whereas ^{5}J(HP) for the C(4)-SMe group was not observed. For compounds containing the MeN-P grouping, e.g. **8** [2] and **10**, values ^{3}J(HP) ca. 11 Hz were observed. Replacing the SMe group attached to phosphorous by an NHR or an aryl group caused an upfield shift for the phosphorus resonance consistent with data presented in an earlier compilation [5] (cf. compounds **8** δ(P) 67.7; **10** 46.6; **6** 48.3 ppm).

Experimental

Starting materials were obtained commercially (Aldrich or Fluka) and used without further purification. All solvents were dried and distilled before use. Melting points were obtained on a Kofler heating stage and are uncorrected. Mass spectra were obtained by electron impact using a VG 7070E mass spectrometer operating at 70 eV.

NMR spectra were obtained in $CDCl_3$ solution with TMS as internal reference at 250 MHz using a Bruker AC 250 spectrometer.

Preparation of 2,3-dihydro-2-methylthio-2,1,3-benzophosphadiazine-4(1H)-thione-2-sulphide (4)

Compound **3** [2] (1.25 g, 5 mmol) was dissolved in methanol (10 ml). Methyl iodide (710 mg, 5 mmol) was added and the solution stirred at 0 °C for 1 h. The yellow precipitate was collected and recrystallised from nitromethane to yield product **4** (1.0 g, 75%) yellow crystals, m.p. 134–138 °C.

Analysis: Found: C, 37.3; H, 3.5; N, 10.6; S, 36.5. $C_8H_9N_2PS_3$ calc: C, 36.9; H, 3.5; N, 10.8; S, 36.9%. Mass spectrum: *m/e* 260 (M^+). ^{1}H NMR: δ 8.70 (d, *J*(HP) 13.1 Hz, NH), 7.81–6.81 (4H, m, ArH), 6.20 (d, *J*(HP) 12 Hz, NH), 2.21 (3H, d, *J* 16.2 Hz, P-SMe). ^{13}C NMR: δ 192.0 (*J* 3Hz, C=S), 142.0, 134.3, 121.1, 119.0, 117.0, 15.6 (*J* 5.9 Hz, P-SMe). ^{31}P NMR: δ 67.5 ppm.

Preparation of 1,2-dihydro-2,4-bis(methylthio)-2,1,3-benzophosphadiazine-2-sulphide (7)

Compound **4** (520 mg, 2 mmol) was partially dissolved in methanol (20 ml). Methyl iodide (250 mg, 2 mmol) was added and the solution stirred at room temperature for 12 h to give a yellow precipitate which was filtered, dried and recrystallised from nitromethane to yield product **7**, (175 mg, 65%) m.p. 121–123 °C.

Analysis: Found: C, 39.7; H, 4.4; N, 10.0; S, 34.5. $C_9H_{11}N_2PS_3$ calc: C, 39.4; H. 4.0; N, 10.2; S, 35.0%. Mass spectrum: *m/e* 274 (M^+). ^{1}H NMR δ 7.81–6.83 (4H, m, ArH), 6.20 (d, *J*(HP) 12 Hz, NH), 2.59 (s, 3H, C(4)-SMe), 2.16 (d, 3H, *J* 16 Hz, P-SMe). ^{13}C NMR 177.3 (d, *J*(PC) 14.4 Hz, 4-C) 143.0, 136.1, 127.2, 120.1, 116.8 (*J*(PC) 22.4 Hz, 8a-C), 115.3, 15.2 (*J*(PC) 5.5 Hz, 2-SMe) and 13.0 (4-C-SMe), ^{31}P NMR 67.7 ppm.

Reaction of compound **7** with excess methyl iodide yielded trimethyl derivative **8**, identical (by ^{1}H NMR and m.p.) with a sample described previously [2].

Preparation of 1,2-dihydro-1-ethyl-2-methylthio-4-ethylthio-2,1,3-benzophosphadiazine-2-sulphide (9)

A mixture of compound **4** (520 mg, 2 mmol) and ethyl iodide (3.0 g, excess) in ethanol (20 ml) was stirred at room temperature for 12 h. Workup and purification as described for product **7** yielded compound **9**, (512 mg, 81%), m.p. 164–167 °C.

Analysis: Found: C, 45.9; H, 5.4; N, 8.8; S, 30.0. $C_{12}H_{17}N_2PS_3$ calc: C, 45.6; H, 5.4; N, 8.9; S, 30.4%. Mass spectrum: *m/e* 316 (M^+) ^{1}H NMR δ 7.90–6.80 (4H, m, ArH), 3.40 (2H, m, *J*(HP) 10 Hz N(1)-CH_2-), 2.60 (2H, q, C(4)-CH_2-), 2.16 (3H, d, *J*(HP) 16 Hz, 2-SMe), 1.74 and 1.68 (both 3H, t, CH_3). ^{13}C NMR 177.2 (d, *J*(PC) 14.0 Hz, 4-C). ^{31}P NMR 67.3 ppm.

Preparation of 1,2-dihydro-1-methyl-2,4-bis(p-chloroanilino)-2,1,3-benzophosphadiazine-2-sulphide (10)

Trimethyl derivative **8** (850 mg, 3 mmol) was refluxed for 24 h with *p*-chloroaniline (2.5 g, 20 mmol) in xylene (20 ml). Solvent was evaporated in vacuo to yield a gum which was extracted into hot methanol. Cooling of the methanol solution yielded product **10**, white needles (660 mg, 50%), m.p. 262–264 °C.

Analysis: Found: C, 53.6; H, 4.0; N, 12.2; S, 7.7. $C_{20}H_{17}N_4PSCl_2$ calc: C, 53.8; H, 3.8; N, 12.6; S, 7.2%. Mass spectrum: *m/e* 446 (M^+). ^{1}H NMR δ 8.01–6.75 (12H, m, ArH), 9.4 and 9.0 (both br, NH) and 3.09 (d, *J* 10 Hz, N(1)-Me). ^{31}P NMR δ 57.8 ppm.

Preparation of 1,2-dihydro-2,4-bis(p-methoxyphenyl)-2,1,3-benzophosphadiazine-2-sulphide (6)

Lawesson's reagent (**13**) (8.0 g, 20 mmol) was added to a solution of 2-aminobenzamide (**1**) (650 mg, 5 mmol) dissolved in toluene (25 ml) and the mixture was stirred at room temperature for 24 h. The mixture was filtered and the filtrate evaporated onto alumina and eluted through an alumina column using chloroform as eluent. An oil was obtained which after storage for 24 h at 0 °C solidified to yellow crystals (400 mg, 28%) m.p. 92–95 °C.

Analysis: Found: C, 52.8; H, 3.9; N, 8.8; S, 20.3. $C_{14}H_{15}N_2OPS_2$ calc: C, 52.5; H, 4.1; N, 8.8; S, 20.0%. Mass spectrum: *m/e* 320 (M^+). ^{1}H NMR δ 8.73 (d, *J*(HP) 12.0 Hz, NH). 7.82–6.89 (8H, m, NH), 6.5 (d, *J* 11.4 Hz, NH), 3.75 (3H, s, OMe). ^{13}C NMR 194.9 (C=S), 163.6 (C-OMe), 138.4, 135.7, 134.7, 133.6, 133.5, 122.6, 118.5 (d, *J*(HP) 11.0 Hz), 114.6 (d, *J*(HP) 15.0 Hz), and 55.9 (OMe). ^{21}P NMR δ 48.3 ppm.

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