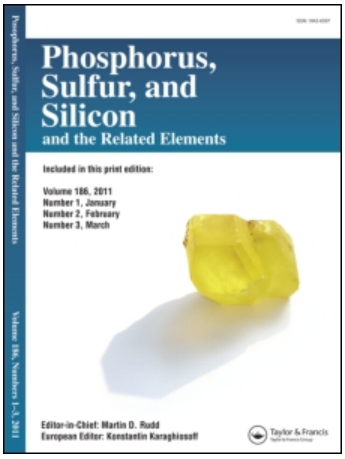

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THE REACTION OF 2,4-BIS(4-METHOXYPHENYL)-l,3,2,4-D1THIA DIPHOSPHETANE-2,4-DISULFIDE (LR) WITH COUMARIN OXIME AND HYDRAZONE DERIVATIVES. SYNTHESIS OF BENZOPYRANO (3,2-D)-Δ^5-2,1,3-OXAZA- AND 1,2,3-DIAZA-PHOSPHOLINES

A. B. A. G. Ghattas[a]; O. A. Abd Allah[a]; H. M. Moustafa[a]
[a] Chemistry Department, Faculty of Science, Sohag, Egypt

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THE REACTION OF 2,4-BIS(4-METHOXYPHENYL)-1,3,2,4-DITHIA DIPHOSPHETANE-2,4-DISULFIDE (LR) WITH COUMARIN OXIME AND HYDRAZONE DERIVATIVES. SYNTHESIS OF BENZOPYRANO (3,2-D)-Δ^5-2,1,3-OXAZA- AND 1,2,3-DIAZA-PHOSPHOLINES

A.-B.A.G. GHATTAS*, O.A. ABD ALLAH and H.M. MOUSTAFA

Chemistry Department, Faculty of Science, Sohag, Egypt

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2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent, LR, **1**) reacted with coumarin oxime (**2**) and its 6-methyl derivative (**3**) to give compounds **6** and **7**, respectively. Oxidation of **6** and **7** with $KMnO_4$ afforded the corresponding oxo- derivatives, **8** and **9**. Benzopyrano(3,2-d)-Δ^5-1,2,3-diazaphospholine-3-sulfide derivatives (**14** and **15**) were obtained through the reaction of LR with coumarin hydrazones (**10** and **11**), respectively. Mannich reaction using morpholine and/or benzylamine on compounds **14** and **15** afforded the Mannich bases **16–19**. Alkylation of **14** and **15** with ethyl iodide produced compounds **20** and **21**.

Keywords: 2; 4-Bis(4-methoxyphenyl)-1; 3; 2; 4-dithiadiphosphetane-2; 4-disulfide (LR) coumarin oxime; coumarin hydrazone; biological properties

INTRODUCTION

Benzopyran derivatives have a wide spectrum of biological activity[1–3]. Organophosphorus compounds have also been reported as effective insecticides[4]. In view of the above observations and in continuation of our studies in the same area[5–7], it was of interest to fuse P-heterocycles with

* Correspondence Author.

the benzopyran nucleus, with the hope that the newly synthesized compounds might exhibit enhanced biological properties.

2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent, LR, **1**) beside its effectiveness as a thiation reagent for different carbonyl compounds[8–14], undergoes ring closure reactions with oximes[15], hydrazones[16], and substrates containing two functional groups[5,17–20] forming phosphorus heterocycles. To extend the use of LR (**1**) for the synthesis of new fused P- heterocycles, its reaction with coumarin-oxime and -hydrazone derivatives has been investigated in this paper.

RESULTS AND DISCUSSION

The parent compounds coumarin oxime (**2**) and its 6-methyl derivative (**3**) were prepared in good yields by the reaction of the corresponding thio compounds with hydroxylamine hydrochloride[21,22] in the presence of sodium acetate. Compounds **2** and **3** were allowed to react with Lawesson's reagent (**1**) in acetonitrile at room temperature to give compounds **4** and **5** in good yield. Their structures were confirmed on the basis of their elemental and spectral analyses (cf. Tables I and II).

TABLE I Physical and Analytical Data of The New Compounds

Product No	*M.P (°C) Cryst. Solvent*	*Yield (%)*	*Mol. Form. (Mol. Wt)*	*Analytical Data (Cal./Found)*		
				C	*H*	*N*
4	130	89	$C_{16}H_{14}NO_3PS_2$	52.88	3.88	3.85
	(EtOH)		(363.381)	52.65	3.73	3.77
5	170	87	$C_{17}H_{16}NO_3PS_2$	54.11	4.27	3.71
	(EtOH)		(377.279)	54.00	4.15	3.60
6	210	76	$C_{16}H_{12}NO_3PS$	58.35	3.67	4.25
	(EtOH)		(329.301)	58.17	3.49	4.13
7	242	77	$C_{17}H_{14}NO_3PS$	59.47	4.11	4.08
	(EtOH)		(343.327)	59.26	3.99	3.96
8	138	65	$C_{16}H_{12}NO_4P$	61.35	3.86	4.47
	(EtOH)		(313.237)	61.23	3.69	4.68

Product No	M.P (°C) Cryst. Solvent	Yield (%)	Mol. Form. (Mol. Wt)	Analytical Data (Cal./Found)		
				C	H	N
9	>300	70	$C_{17}H_{14}NO_4P$	62.39	4.31	4.30
	(AcOH)		(327 263)	62.54	4.43	4.19
10	86	89	$C_9H_8N_2O$	67.48	5.03	17.49
	(Benzene)		(160.168)	67.01	4.50	17.92
11	166	81	$C_{10}H_{10}N_2O$	68.94	5.78	16.08
	(EtOH)		(174.194)	68.81	5.63	15.89
12	90	79	$C_{16}H_{15}N_2O_2PS_2$	53.02	4.17	7.73
	(EtOH)		(362 396)	52.85	4.01	7.61
13	180	77	$C_{17}H_{17}N_2O_2PS_2$	54.24	4.55	7.44
	(EtOH)		(376 422)	54.03	4.39	7.31
14	160	72	$C_{16}H_{13}N_2O_2PS$	58.53	3.99	8.53
	(Dioxan)		(328 316)	58.36	3.86	8.41
15	200	74	$C_{17}H_{15}N_2O_2PS$	59.64	4.42	8.18
	(Dioxan)		(342 342)	59.47	4.33	8.00
16	148	69	$C_{21}H_{22}N_3O_3PS$	59.00	5.19	9.83
	(EtOH)		(427 445)	58.87	5.01	9.68
17	176	70	$C_{24}H_{22}N_3O_2PS$	64.41	4.95	9.39
	(Dioxan)		(447 475)	64.21	4.83	9.24
18	115	76	$C_{22}H_{24}N_3O_3PS$	59.85	5.48	9.52
	(EtOH)		(441 471)	59.70	5.31	9.32
19	163	75	$C_{25}H_{24}N_3O_2PS$	69.58	5.61	9.74
	(EtOH)		(431 501)	69.37	5.45	9.60
20	136	66	$C_{18}H_{17}N_2O_2PS$	60.66	4.81	7.86
	(EtOH)		(356 368)	60.43	4.66	7.70
21	151	67	$C_{19}H_{19}N_2O_2PS$	61.61	5.17	7.56
	(EtOH)		(370 394)	61.43	5.00	7.39

TABLE II Spectral Data of The New Compounds

Product No.	*IR (Cm^{-1})*	*^{1}H-NMR (δ ppm)*
4	3100(CH, arom.); 2830(CH, aliph.); 2359(P-SH); 1600 (C=N); 652(P=S).	8.7–6.8 (m,9H,arom.+vinylic); 6.3(d,1H, proton at C_3); 3.9(s,3H, OCH_3); 3.7(s, 1H, SH).
5	3040(CH, arom.); 2960(CH, aliph.); 2400(P-SH); 1602 (C=N); 648(P=S).	8.5–6.8 (m,8H,arom.+vinylic); 6.3(d,1H, proton at C_3); 3.9(s,3H,OCH_3); 3.7(s, 1H, SH); 2.3(s,3H,CH_3).
6	3050(CH, arom.); 2963(CH, aliph.); 1602(C=N); 657(P=S).	8.7–6.8 (m,9H,arom.+vinylic); 3.9(s,3H, OCH_3).
7	3093(CH, arom.); 2950(CH, aliph.); 1600(C=N). 649(P=S).	8.6–6.8 (m,8H,arom.+vinylic); 3.9(s,3H, OCH_3); 2.4(s,3H,CH_3).
8	3099(CH, arom.); 2957(CH, aliph.); 1257(P=O); 1600(C=N).	8.7–6.8 (m,9H,arom.+vinylic); 3.9(s,3H, OCH_3).
9	3079(CH, arom.); 2960(CH, aliph.); 1250(P=O); 1601(C=N).	8.6–6.9 (m,8H,arom.+vinylic); 3.9(s,3H,OCH_3); 2.4(s,3H,CH_3).
10	3300,3200(NH_2); 1600(C=N).	8.0–6.8 (m,5H,arom.+vinylic); 6.3 (d, 1H, proton at C_3); 5.2–4.9(br,2H,NH_2).
11	3320,3253(NH_2); 3036(CH, arom.); 1611(C=N).	8.1–6.7(m,4H,arom.+vinylic), 6.3(d, 1H, proton at C_3); 5.6–5.3(br,2H,NH_2); 2.33(s,3H,CH_3).
12	3263(NH); 3008(CH, arom.); 2856(CH, aliph.); 1611(C=N); 649(P=S).	10.0–9.8(br,1H,NH), 8.7–6.8(m,9H,arom.+ vinylic); 6.4(d, 1H, proton at C_3); 3.75(s, 1H,SH); 3.9(s,3H,OCH_3).
13	3263(NH); 3008(CH, arom.); 2856(CH, aliph.); 1005(C=N); 649(P=S).	10.1–9.9(br, 1H,NH), 8.7–6.8(m,8H,arom.+ vinylic); 6.4(d, 1H, proton at C_3); 3.68(s, 1H,SH); 3.9(s,3H,OCH_3); 2.3(s,3H,CH_3).
14	3233(NH); 3038(CH,arom.); 2899 (CH,aliph.); 1015(C=N); 655(P=S).	11.0–10.8(br, 1H,NH); 8.6–6.8(m,9H, arom.+ vinylic), 3.9(s,3H,OCH_3). MS : (rel.Int. %)328.1(M^+, 21); 326.1(46); 304

Product No.	*IR (Cm^{-1})*	*^{1}H-NMR (δ ppm)*
15	3303(NH); 3058(CH,arom.); 2939 (CH,aliph.); 1010(C=N); 651(P=S)	(39); 226(49); 126.9(45); 110.9(100); 58.3(33). 10.2–10.0(br, 1H,NH); 8.7–6.8(m,8H, arom.+ vinylic), 3.9(s,3H,OCH_3); 2.3(s,3H,CH_3).
16	3058(CH, arom.); 2939, 2834(CH, aliph.); 1010(C=N); CH_2); 3.9(s,3H,OCH_3); 656(P=S).	8.6 –6.8(m,9H,arom.+ vinylic); 4.5(s,2H 3.7–3.4(m,4H, CH_2-O-CH_2),2.7–2.4(m,4H,CH_2-N-CH_2).
17	3323(NH); 3028(CH, 2959, 2864(CH, aliph.); 1011 (C=N); 652(P=S).	arom.); 9.9–9.7(br, 1H,NH),8.6–6.8 (m, 14H, arom. + vinylic); 4.5(s,2H,N-CH_2-N); 3.9(s,3H, OCH_3); 3.0(s,2H, N-CH_2Ph).
18	3088(CH, arom.); 2949, 2894(CH, aliph.); 1009(C=N); 3.9(s,3H,OCH_3); 653(P=S).	8.6–6.8(m,9H,arom.+ vinylic); 4.5(s,2H, CH_2); 3.7–3.4(m,4H, CH_2-O-CH_2), 2.7–2.4(m,4H,CH_2-N-CH_2); 2.3(s,3H,CH_3).
19	3298(NH); 3088(CH, arom.); 2959, 2894(CH, aliph.); 1019 (C=N); 647(P=S).	9.9–9.7(br, 1H,NH), 8.6–6.8 (m, 14H, arom. + vinylic); 4.5(s,2H,N-CH_2-N); 3.9(s,3H, OCH_3); 3.0(s,2H,N-CH_2Ph); 2.3(s,3H,CH_3)
20	3058(CH, arom.); 2939(CH, aliph.); 1010(C=N).	8.6 –6.8(m,9H,arom.+ vinylic); 3.7(q,2H CH_2); 3.9(s,3H,OCH_3); 1.2(t,3H,CH_3).
swa21	3068(CH, arom.); 2939(CH, aliph.); 1010(C=N).	8.6 –6.8(m,9H,arom.+vinylic); 3.9(s,3H, OCH_3); 3.7(q,2H,CH_2); 1.2(t,3H,CH_3); 2.3(s,3H,CH_3Ph).

The IR spectra of compounds **4** and **5** showed the absence of the absorption bands corresponding to the hydroxyl group while exhibiting characteristic bands corresponding to P=S at 652 and 648 cm^{-1}, respectively. The ^{1}H-NMR spectrum ($CDCl_3$,δ) of compound **4** showed the absence of signal corresponding to N-OH while exhibiting a signal corresponding to three aliphatic protons at 3.9 (-OCH_3,s). The ^{1}H-NMR spectrum of compound **5** (DMSO,δ) showed the absence of a signal corresponding to N-OH while exhibiting bands corresponding to three aliphatic protons at 3.85 (-OCH_3,s) and three aliphatic ones at 2.3 (CH_3,s). The cyclization of compounds **4** and **5** to 3-(4-methoxyphenyl)benzopyrano(3,2-d)-Δ^5-2,1,3-oxazaphospholine-3-sulphide (**6**) and 3-(4-methoxyphenyl)-6-methyl-benzopyrano(3,2-d)-Δ^5-2,1,3-oxazaphospholine-3-sulphide (**7**), respectively was achieved by using the Prasad Roa method[23], the same products could be obtained in good yields in one step by the reaction of **1** with **2** and/or **3** in boiling N,N-dimethylaniline. The structure of these compounds were proved by elemental analyses, IR and ^{1}H-NMR spectra (cf. Table II). The functionality P=S was converted to P=O for compounds **6** and **7** by the reaction of these compounds with $KMnO_4$ in acetic acid at room temperature. The IR spectra of products **8** and **9** showed the characteristic absorption bands corresponding to P=O at 1257 and 1250 cm^{-1}, respectively.

Coumarin hydrazone[6] (**10**) and its 6-methyl derivative (**11**) were prepared in good yields by the reaction of the corresponding thio compounds with hydrazine hydrate. Compounds **10** and **11** were allowed to react with Lawesson's reagent (**1**) in acetonitrile at room temperature to give the opened products **12** and **13** in good yields. The IR spectra of compounds **12** and **13** showed the absence of the -NH_2 absorption bands. The ^{1}H-NMR spectra of these compounds are in agreement with the proposed structures (cf. Table II). The cyclized products 3-(4-methoxyphenyl)benzopyrano(3,2-d)-Δ^5-1,2,3-diazaphospholine-3-sulfide (**14**) and 3-(4-methoxyphenyl)-6-methyl-benzopyrano(3,2-d)-Δ^5-1,2,3-diazaphospholine-3-sulfide (**15**) were obtained by refluxing compounds **12** and **13** in N,N-dimethylaniline. The same products **14** and **15** were also obtained in one step through the reaction of **1** with **10** and/or **11** in boiling N,N-dimethylaniline. The IR and ^{1}H-NMR spectra of these compounds confirm the proposed structures (cf. Table II). The mas spectrum of compound **14** showed the molecular ion at *m/e* (rel. int. %) 328(22).

Mannich reaction on compounds **14** and **15** using formaldehyde and amines morpholine and benzylamine afforded the corresponding Mannich

bases **16–19**. The IR and ^{1}H-NMR spectra of these compounds confirm the proposed structures (cf. Table II).

Alkylation of compounds **14** and/or **15** with ethyl iodide in presence of sodium hydroxide solution gave 3-ethylthio-3-(4-methoxyphenyl)benzopyrano(3,2-d)-Δ^5-1,2,3-diazaphospholine (**20**) and 3-ethylthio-3-(4-methoxyphenyl)-6-methyl-benzopyrano(3,2-d)-Δ^5-1,2,3-diazaphospholine (**21**), respectively. The IR and ^{1}H-NMR spectra of the resulted sulfides were in agreement with the proposed structures (cf. Table II).

Experimental

All melting points were determined on a Kofler melting point apparatus and were uncorrected. IR spectra (cm^{-1}) were recorded on a nicolet, 710 FT-IR Spectrophotometer in KBr, ^{1}H-NMR spectra were recorded at 60 MHz on a varian A-60 Spectrophotometer using TMS as an internal reference standard. The mas spectra were recorded on a CEC 21–104 single focusing mass spectrometer operating at 70 ev using direct inlet. Elemental analyses were carried out on an elemental analyzer model 240 C. All compounds were checked for their purity on TLC plates.

Compound 1 was prepared as described earlier[8]

Starting compounds 2, 3, 10 and 11

Coumarin oximes (**2 & 3**) and Coumarin hydrazones (**10 & 11**) were prepared from the corresponding thiocoumarin derivatives according to known methods[6,21–22]. The physical and spectroscopic data of the new derivatives **10** and **11** are presented in Tables I and II.

Preparation of compounds 4, 5, 12 and 13 : (General procedure)

Lawesson's reagent (2.02 g, 0.01 mol) was added to a solution of oxime and/or hydrazone derivatives (0.01 mol) in 50 ml acetonitrile and stirred for 10 hr. The solvent was evaporated at reduced pressure and the residual solid was crystallized from the appropriate solvent (cf. Table I).

Preparation of benzopyrano(3,2-d)-Δ^5-2,1,3-oxazaphospholine-3-sulphide derivatives (6, 7) and benzopyrano(3,2-d)-Δ^5-1,2,3-diazaphospholine-3-sulfide derivatives (14, 15). Method A (general procedure)

Compouds **4, 5, 12** and/or **13** (0.01 mol) was refluxed in N,N-dimethylaniline (10 ml) until hydrogen sulfide ceased (18 hr). The solvent was con-

centrated, cooled and filtered. The solid product was recrystallized from the appropriate solvent (cf. Table I).

Method B (general procedure)

Lawesson's reagent (2.02 g, 0.01 mol) was added to a solution of oxime and/or hydrazone derivatives (0.01 mol) in 50 ml N,N-dimethylaniline and refluxed until hydrogen sulfide ceased (18 hr). The reaction mixture was concentrated. After cooling, the formed precipitate was filtered off and recrystallized from the appropriate solvent (cf. Table I)

Preparation of benzopyrano(3,2-d)-Δ^5-2,1,3-oxazaphospholine-3-one derivatives (8, 9) : (General procedure)

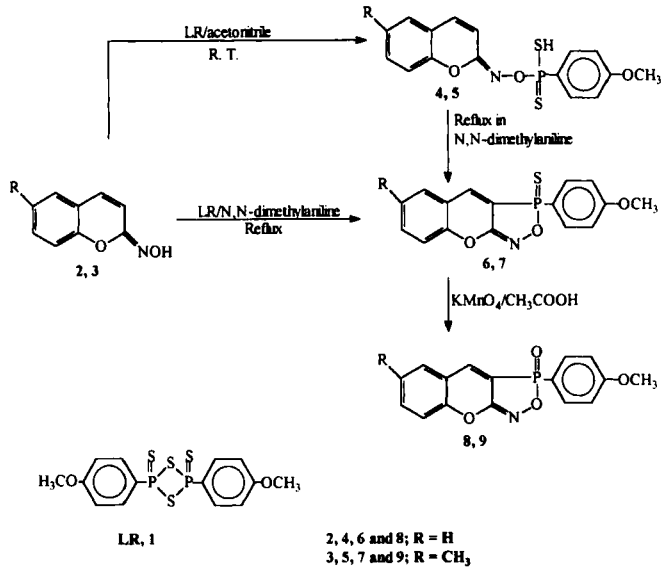
A solution of $KMnO_4$ (0.158 g, 0.01 mol) in 10 ml of water was added drop by drop to a solution of compound **6** and/or **7** (0.01 mol) in 20 ml acetic acid with stirring at room temperature for 3 hr. The reaction mixture was poured into 100 ml of ice cooled water. The precipitate was filtered off and recrystallized from the appropriate solvent (Cf. Table I).

Preparation of 2-(Morphlinomethyl or benzylaminomethyl)-3-(4-methoxyphenyl)benzo-pyrano(3,2-d)-Δ^5-1,2,3-diazaphospholine-3-sulfide derivatives (16–19) : (General procedure)

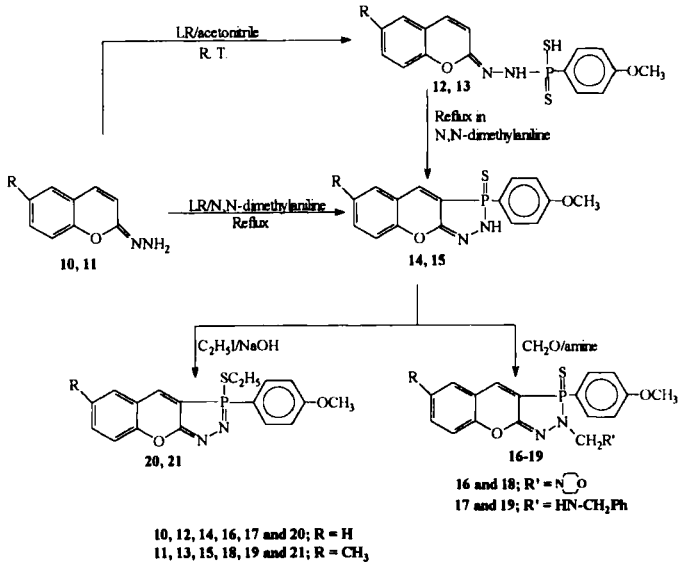
Formaldehyde (1.5 ml; 40% solution) was added to a solution of compound **14** and/or **15** (0.001 mol) in absolute ethanol (10 ml). The reaction mixture was refluxed for 1 hr. After cooling to room temperature the appropriate amines (morpholine and/or benzylamine) (0.001 mol) was added. The reaction mixture was refluxed for 4 hr. The formed precipitate was filtered off and recrystallized from the appropriate solvent to give the corresponding Mannich bases (**16–19**) (Cf. Table I).

Preparation of 3-Ethylthio-3(4-methoxyphenyl)benzopyrano(3,2-d)-Δ^5-1,2,3-diazaphospholine derivatives (20, 21) : (General procedure)

Compound **14** and/or **15** (0.001 mol) was dissolved in sodium hydroxide solution (30 ml, 10%) and ethanolic solution of ethyl iodide (0.001 mol, in 30 ml ethanol) was added. The reaction mixture was refluxed for 1hr. After cooling, the formed precipitate was filtered off and recrystallized from the appropriate solvent (cf. Table I).



SCHEME 1



SCHEME 2

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