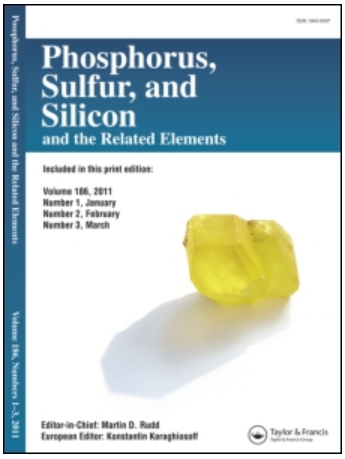


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# ORGANOPHOSPHORUS CHEMISTRY, 20.[1] THE BEHAVIOUR OF CERTAIN γ-PYRONE DERIVATIVES TOWARD 2,4-BIS-(4-METHOXYPHENYL)-1,3,2,4-DITHIAPHOSPHETAN-2,4-DISULPHIDE (LAWESSON REAGENT)

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# ORGANOPHOSPHORUS CHEMISTRY, 20.[1] THE BEHAVIOUR OF CERTAIN γ-PYRONE DERIVATIVES TOWARD 2,4-BIS-(4-METHOXYPHENYL)-1,3,2,4-DITHIAPHOSPHETAN-2,4-DISULPHIDE (LAWESSON REAGENT)

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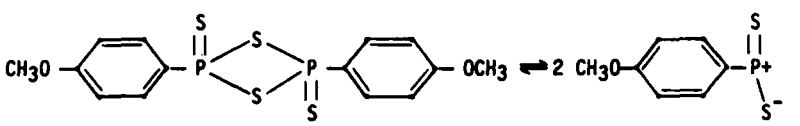
Lawesson reagent **LR,1** converts 2,6-dimethyl-γ-pyrone **2a**, flavone **3a** into their corresponding thioketones **2b** and **3b** in high yields. Thiation of flavone **3a** with Lawesson reagent **LR,1** can be also induced photochemically to give thioflavone **3b** together with the ring phosphorane product **6A**. Thiation of khellin **4a** by LR to give **4b** is accompanied by demethylation of **4b** to give desmethylthiokhellin **4c**. The behaviour of γ-pyrones **2a, 3a** and **4a** toward thiation with **LR,1** was discussed in the light of the principle of vinylogy.

*Key words:* Lawesson reagent; γ-pyrones; thiation; dealkylation; vinylogy.



## INTRODUCTION

The versatile utility of 2,4-bis-(4-methoxyphenyl)-1,3,2,4-dithiaphosphetane-2,4-disulphide (Lawesson Reagent, **LR,1**) as an efficient thiating agent for carbonyl compounds, is well recognized. This activity extends to include ketones,[2] carboxamides,[3] esters,[4,5] enaminones,[6] lactams[7] and lactones.[8] Moreover, we have recently[9] reported on the reactivity of reagent **1** toward monoanil derivatives of benzil.



**A** **LR,1** **B**

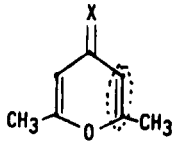
The behaviour of γ-pyrones toward reagent **1** has not been investigated. Therefore, we have now studied the reaction of **1** with 2,6-dimethyl-γ-pyrone **2a**, 2-phenyl-5,6-benz-γ-pyrone (flavone, **3a**) and 4,9-dimethoxy-7-methyl-5H-furo-benz-γ-pyrone (Khellin, **4a**). By virtue of presence of the (—CH=CH—) group in the

γ-pyrone ring of compounds **2a, 3a** and **4a,** the present study may also shed light on whether these substrates would or would not act as true vinylogs[10] of acetone, benzophenone and acetophenone respectively in their behaviour toward **LR,1**.

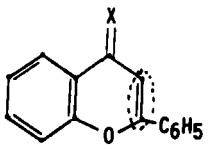
## RESULTS AND DISCUSSION

It has been found that **2a** reacts with **LR,1** in dry toluene at the reflux temperature to give 2,6-dimethylpyrane-4-thione **2b**.[11]

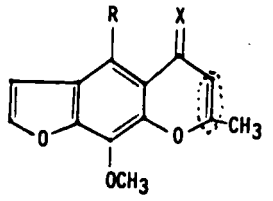
When a mixture of **2a** and **LR,1** in benzene was exposed to solar radiations (Schlenk tube), thione **2b** was yielded together with 4-methoxyphenyl phosphinic acid **5c**.[12]



**2a**, X = O
**b**, X = S



**3a**, X = O
**b**, X = S



**4a**, X = O, R = $OCH_3$
**b**, X = S, R = $OCH_3$
**c**, X = S, R = OH
**d**, X = O, R = OH

It seems that thiation of **2a** by **1A** to give **2b** produces species **5a** which is then photo-oxidized to produce betaine **5b**. Addition of elements of water (unavoidable moisture) to **5b** produces **5c** (Scheme 1).

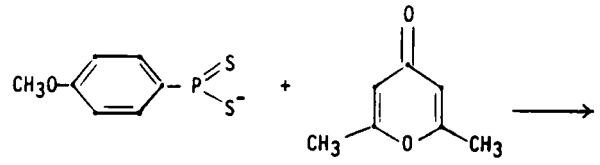
When a mixture of flavone **3a** and **LR,1** was refluxed in dry toluene, it produced thioflavone **3b**.[3]

It has been found that when a mixture of **3a** and **LR,1** in dry benzene was exposed to sunlight (Schlenk tube), an orange crystalline substance that contained both sulfur and phosphorus was isolated. It was assigned a ring phosphorane structure **6A** based on spectral measurements (cf. experimental). An alternative structure like **6B** may be excluded due to the absence of signals in the δ 4.5–5.5 ppm region in which the ring methine proton is expected to appear.

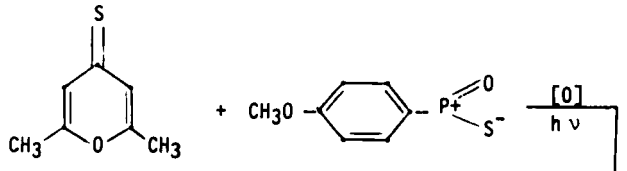
The same product **6A** was obtained when a mixture of **3a** and **LR,1**, in dry benzene, was irradiated with a high pressure lamp.

A mechanism accounting for the formation of the ring phosphorane structure **6** is depicted in **Scheme 2**. It is based on the assumption of initial thiation of flavone to give thioflavone **3b** which can exist in the dipolar form **3c**. The latter structure facilitates the approach of the betaine **5b** to give the intermediate **7** which cyclizes *via* electrophilic attack by phosphorus on the pyran ring carbanion yielding **6A**.

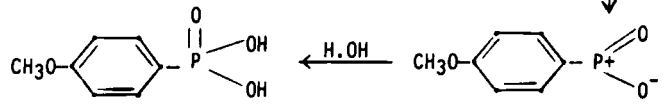
After refluxing **LR,1** and khellin **4a** in dry toluene, two pure substances (devoid of phosphorus) were isolated in a sequence. The first was proved to be thiokhellin **4b**.[14] The second was obtained in golden yellow needles and formulated as desmethyl thiokhellin **4c** based on spectral data[15,16] (cf. experimental). Moreover, compound **4c** underwent the reactions characteristic for hydroxychromones wherein the OH group is of a chelated nature.[17–19] Thus, it is insoluble in 50% aqueous NaOH solution and is recovered practically unchanged upon treatment with an



1B 2a

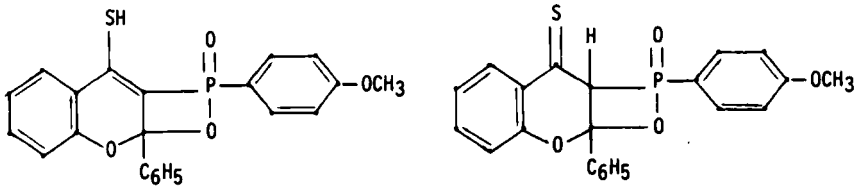


5a



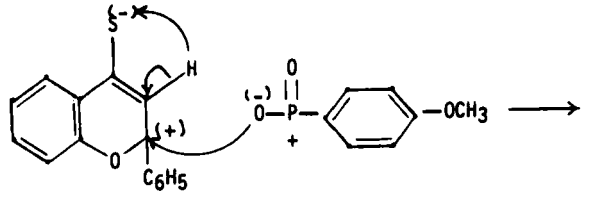
5c 5b

Scheme (1)

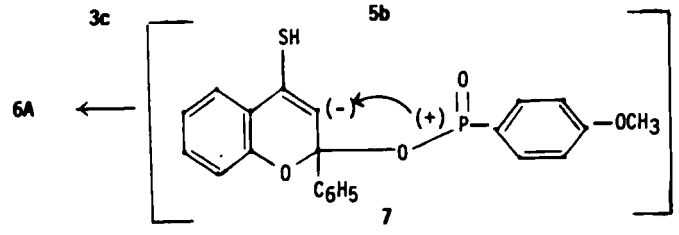


A B

6



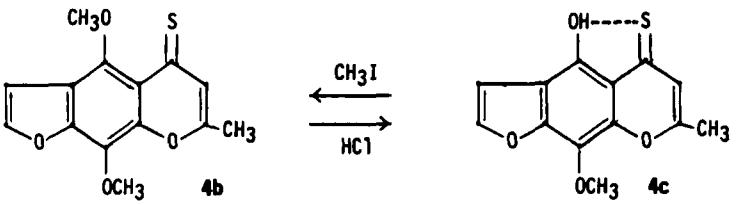
3c 5b



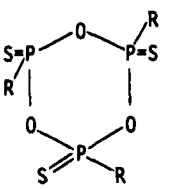
6A 7

Scheme 2

ethereal diazomethane solution. Besides, compound **4c** exhibits a green colouration upon treatment with 1% alcoholic ferric chloride and a deep yellow colouration upon treatment with 0.1% aqueous uranyl acetate solution.[18] Upon treatment with methyl iodide in dry acetone in presence of anhydrous $K_2CO_3$, compound **4c** yielded thiokhellin **4b** whose m.p. was not depressed upon admixture with an authentic sample[14] and their IR spectra were superimposable. On the other hand, demethylation of **4b** with dilute aqueous hydrochloric acid yielded **4c**.




It is worthy to mention that in all the thiation reactions of **2a, 3a** and **4a** with **LR,1** a colourless crystalline phosphorus containing product was isolated or detected by thin layer chromatography (TLC) and proved to be trimer **8** by comparing its m.p. as well as its IR and PMR spectra with those of an authentic sample.[1-4]




## CONCLUSION

It could be concluded that **LR,1** can be used as a specific and effective thiating agent for the carbonyl-oxygen atom of the γ-pyrone derivatives **2a, 3a** and **4a** with leaving the heterocyclic oxygen atom of the γ-pyrone ring unaffected. It has an advantage over thiation using phosphorus pentasulfide as a new method giving higher yields.

Apparently, the thiation process is associated with existence of the monomeric dipolar form **1B** in equilibrium with the dimeric form **1A**. Prior formation of **1B** which undergoes photo-oxidation to betaine **5b**, also accounts for the production of 4-methylphenyl phosphinic acid **5c** and a ring phosphorane structure like **6** through the photo-induced reaction of **LR** with **2a** and **3a**, respectively.

Besides, structure **1B** seems to be implicated in the process of demethylating thiokhellin **4b** to produce desmethylthiokhellin **4c**. This finding also explores a new potentiality for reagent **1** as a specific dealkylating agent for alkoxy groups in a *peri*-position to a carbonyl (or thiocarbonyl) group. In this sense, the effect of **LR,1** simulates that of thiols which converts khellin into desmethylkhelline **4d**,[20] but without thiating the γ-pyrone carbonyl oxygen.

The successful thiation of γ-pyrone carbonyl oxygen in **2a, 3a** and **4a** by **LR,1** is thus in good accord with the concept that these γ-pyrones are vinylogs of acetone, benzophenone and acetophenone respectively, which are known to be converted into their corresponding thioketones[2] under the influence of the same thiating agent.

## EXPERIMENTAL

All melting points were uncorrected. Benzene and toluene were dried over sodium. The IR spectra (run in KBr and expressed in $cm^{-1}$) were recorded with a Bechmann 4220 Infracord. The $^1$H-NMR spectra were measured (in $CDCl_3$ or DMSO-$d_6$ and expressed in the δ-scale, ppm) at 60 MHz or 90 MHz on a Varian instrument using TMS as an internal standard. The mass spectra were performed at 70 eV using a Varian MAT 112 Mass Spectrometer.

Lawesson reagent **1** was prepared according to an established procedure[21] and twice crystallized before use.

Silica gel (Kieselgel 60, particle size 0.2.0.5 mm, E. Merck, Darmstadt) was used for column chromatography. A pyrex glass column was used, 60 cm long and 2 cm diameter.

*The action of 1,3,2,4-dithiaphosphetane-2,4-disulfide LR,1 on 2,6-dimethyl-γ-pyrone* (**2a**), *2-phenyl-[5,6-benz]-γ-pyrone* (*flavone*, **3a**) *and 4,9-dimethoxy-7-methyl-5H-furo-benz-γ-pyrone* (*Khellin*, **4a**):

*General procedure.* A mixture of 0.005 mol of the γ-pyrone derivative (**2a, 3a** or **4a**) and 0.0025 mol of **LR,1** was heated in 25 ml dry toluene under reflux with stirring for about 12 hr until no more of the starting material could be detected (TLC). After cooling to room temperature, the reaction mixture was evaporated till dryness, *in vacuo*, in the presence of 5 g of silica gel. This mixture was introduced into a column charged with silica gel and packed with the appropriate eluent stated below. The following thioketones were isolated and identified.

I) *2,6-dimethyl-pyrane-4-thione*, **2b**
($C_7H_8OS$)
m.p. 144°C [Reported:[11] 145°C] yield 85%
Eluent used (ether-light petroleum, 4:6; v/v).
IR: no band at 1665 $cm^{-1}$ (C=O)
$^1$H-NMR: Signals at 2.25 (6H, $2CH_3$, *d*, $J_{III}$ = 1.5 Hz) and 6.85 (2H, vinyl, quartet, $J_{III}$ = 1.5 Hz).

II) *2-phenyl-5,6-benzpyran-4-thione* (*thioflavone*, **3b**)
($C_{15}H_{10}OS$)
m.p. 89°C [Reported:[13] 89°C] yield 90%
Eluent used (benzene-light petroleum, 1:9, v/v).

III) *4,9-Dimethoxy-7-methyl-5H-furo-[3,2-g]*-benzopyrane-5-thione (*thiokhellin* **4b**)
($C_{14}H_{12}O_4S$)
m.p. 133°C [Reported:[14] 135°C] yield 30%
Eluent used (benzene-pet-ether, 1:9, v/v).

Thiokhellin **4b** was obtained together with 4-hydroxy-9-methoxy-7-methyl-5H-furo-[3,2-g]-benzopyrane-5-thione (desmethylthiokhellin **4c**). Eluent used (benzene-petroleum-ether; 3:7, v/v).
Analysis calcd for $C_{13}H_{10}O_4S$: C, 59.54; H, 3.81; S, 12.21.
Found: C, 59.33; H, 3.44; S, 11.98.

$^1$H-NMR: signals at 2.35 (3H, $CH_3$, *d*, $J_{III}$ = 1.5 Hz); 6.80 (H, vinyl, quartet, $J_{III}$ = 1.5 Hz); 4.05 (3H, $OCH_3$, S); at 7.45 and 6.95 (2H, furan, 2d, each with $J_{III}$ = 3 Hz).
MS: m/z, 262; $M^+$, 30%.

*Action of phosphorus pentasulfide* ($P_2S_5$)$_x$ *on* **2a, 3a** *and* **4a**. A mixture of 0.005 mol of γ-pyrone derivative **2a, 3a** or **4a** and 0.005 mol of ($P_2S_5$)$_x$ was heated in 25 ml dry toluene under reflux with stirring for about 12 hr. After evaporation of the solvent, the solid material was recrystallized from the appropriate solvent to give **2b, 3b** and **4b** at yields 40%, 55% and 45% respectively.

*Action of phosphorus pentasulfide* ($P_2S_5$)$_x$ *on desmethylkhellin* **4d**. A mixture of 0.005 mol of desmethylkhellin **4d**[18] and 0.005 mol of ($P_2S_5$)$_x$ was heated in 50 ml dry benzene under reflux for 6 hr until no more of the starting material could be detected (TLC). After evaporation of the solvent, the solid

material was recrystallized from benzene-ethylacetate to give desmethylthiokhellin **4c** (m.p., mixed m.p. 220°C and comparative IR spectra).

*Action of diazomethane on desmethylthiokhellin* (**4c**). To a suspension of compound **4c** (0.2 g) in dry ether (20 ml) was added an ethereal solution of diazomethane (from 5 g N-nitrosomethylurea) and the mixture kept at 10°C for 24 hr. After removing the solvent, *in vacuo*, the residue was recrystallized from benzene-ethyl acetate to give golden yellow needles proved to be unchanged **4c** (m.p. and mixed m.p. 220°C).

*Methylation of desmethylthiokhellin* **4c**. To a solution of compound **4c** (0.5 g) in dry acetone (100 ml) was added anhydrous $K_2CO_3$ (6 g) and freshly distilled methyl iodide (20 ml). After boiling under reflux for 10 hr, the mixture was filtered while hot and the inorganic residue washed with boiling acetone. The filterate and washings were then freed from the volatile materials, *in vacuo*. The residual material was recrystallized from pet-ether 100–120°C to give compound **4b** (65% yield) (m.p., mixed m.p. and comparative IR spectra).

*The reaction of 1,3,2,4-dithiaphosphetane-2,4-disulfide* (*LR, 1A*) *with 2,6-dimethyl-γ-pyrone* (**2a**) *and 2-phenyl-5,6-benz-γ-pyrone* (*flavone*, **3a**) *in sunlight and in high pressure lamp:*

*General procedure*. A mixture of 0.005 mol of **2a** or **3a** and 0.0025 mol of **LR,1** in dry benzene was sealed under dry $N_2$ gas in a Schlenk tube then exposed to sunlight for 30 days (June). The reaction mixture was evaporated till dryness, *in vacuo*, in the presence of 5 g of silica gel. This mixture was column-chromatographed on silica gel using the appropriate eluent.

I) *The following products were isolated and identified in the case of* **2a**:
   a) *2,6-Dimethyl-pyrane-4-thione* **2b**, (*yield 60%*)
      Eluent used (ether-pet-ether, 4:6, v/v).
   b) *4-Methoxyphenyl phosphinic acid* **5c**:
      m.p. 158°C [Reported[12]: 158°C); yield 70%
      $C_7H_9O_4P$
      Eluent used (ether-pet-ether, 2:8, v/v)
      IR: Bands at 1600–1500 (C=C, aromatic), 1250 (P=O) and at 2800 (—OH).
      $^1$H-NMR: signals at 3.6 (3H, $OCH_3$, S); 6.8–7.5 (4H, aromatic, quartet with $J_{HH}$ = 1.5 Hz) and (2H, OH, bs, exchangeable with $D_2O$).
      MS: m/z = 188; $M^+$, 100%) and m/z = 170, $M^+$-$H_2O$, 33%.

II) *The following substances were isolated in the case of* **3a**
   a) *2-Phenyl-5,6-benzpyrane-4-thione* (*thioflavone*, **3b**), *yield 40%*
      Eluent used (benzene-light petroleum, 1:9, v/v).
   b) *The ring phosphorane product* **6A**
      m.p. 174°C yield 60%
      Eluent used (benzene-ethyl acetate, 3:7 v/v).
      Analysis calcd. for $C_{22}H_{17}O_4PS$: C, 64.70; H, 4.16; P, 7.59; S, 7.84.
      Found: C, 64.40; H, 3.88; P, 7.38; S, 7.50.
      IR: Bands at 1600–1500 (C=C, aromatic), 1260 (P=O); 1130 (P—O-aryl) and at 2650 (SH, broad).
      $^1$H-NMR: signal at 3.8 (3H, $OCH_3$, S), 9.4 (H, SH, S, exchangeable with $D_2O$), 6.8–7.8 (13H, aromatic, *m*) and at 6.9 and 7.7 (4H, aromatic linked to phosphorus, 2d, each with $J_{HH}$ = 6 Hz).
      MS: m/z, 408, $M^+$, 15%.

III) *Photoreaction of* **3a** *and* **LR,1** *with a high pressure lamp in dry benzene*

A mixture of 0.005 mol of **3a** and 0.0025 mol of **LR,1** was irradiated in a Pyrex vessel ($\lambda > 313$ nm) with a high pressure lamp (Philip HPK 125 w) for 24 hr whereby substantial reaction of materials has taken place as indicated from a TLC examination of the reaction mixture. Benzene was removed and the mixture was applied to a silica gel column chromatography. The product **6A** was obtained and identified in 65% yield together with thioflavone **3b**.

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