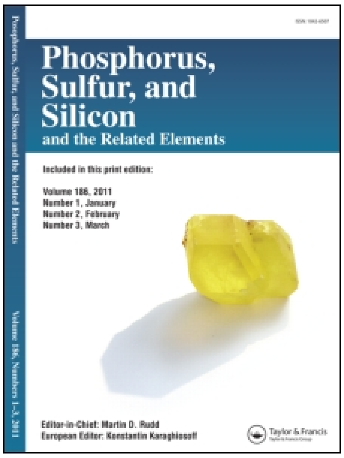

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HETEROCYCLIC SULFUR COMPOUNDS

LXXXIV: 3-Alkoxy-1,2-dithio-isocoumarins and 3-Alkylthio-1,2-dithio-isocoumarins

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Reaction of phosphorus pentasulfide with alkyl hydrogen homophthalates or dialkyl homophthalates gives a mixture of 3-alkoxy-1,2-dithio-isocoumarins and of 3-alkylthio-1,2-dithio-isocoumarins; some of these compounds resulting from a migration of an alkoxy or of an alkylthio group.

Oxidation of these dithio-isocoumarins into 2-thio-isocoumarins has been performed either by potassium permanganate or by benzonitrile N-oxide.

INTRODUCTION

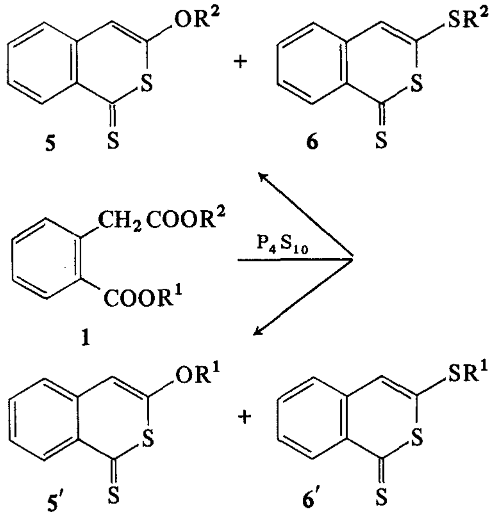
In a previous paper[1] we have described the synthesis of 1,2-dithio-isocoumarins by reaction of phosphorus pentasulfide upon 2-(aroylmethyl)-benzoic esters. This method gives simultaneously 1-thio- and 1,2-dithio-isocoumarins and isolation of both products is difficult. A better synthesis, giving only 1,2-dithio-isocoumarins consists in the action of phosphorus pentasulfide on 2-aroylmethyl-*N*,*N*-dialkyl-thiobenzamides.[2] Isocoumarins obtained according to these methods always had an aryl radical fixed at position 3.

This paper reports studies of the action of phosphorus pentasulfide on alkyl hydrogen homophthalates or on dialkyl homophthalates. We had hoped to obtain in this way, according to the above mentioned literature, 3-alkoxy-1-thio-isocoumarins and/or 3-alkoxy-1,2-dithio-isocoumarins. In fact, no 1-thio-isocoumarin could be characterized but we obtained instead 3-alkylthio-1,2-dithio-isocoumarins.

Alkoxy- and alkylthio-1,2-dithio-isocoumarins are separated by adsorption chromatography either on alumina or on silica gel. When the reaction has been carried out with an ester containing two different alkyl groups, methyl and ethyl for instance, nmr of the fractions obtained by chromatography shows that generally both alkyls can be traced either in the alkoxy fraction or in the alkylthio fraction. Chromatography does not permit isolating each compound and crystallization gives only the major component of a given fraction.

RESULTS

Our results are summarized in Scheme 1.

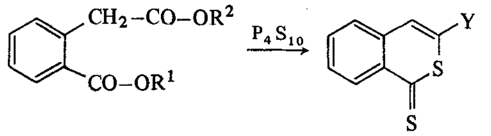


SCHEME 1

These first results showed the existence of various reaction paths, some of them involving an alkyl migration. This system appears capable of giving more information on the reactivity of phosphorus pentasulfide and, accordingly, we wanted to obtain a more precise knowledge of the various yields in at least one case.

For this reason, we selected a dimethyl ester in

TABLE I
Reaction of phosphorus pentasulfide with homophthalic esters



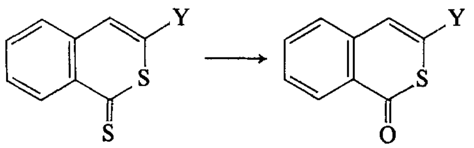
5: Y = OR^2 **5'**: Y = OR^1

6: Y = SR^2 **6'**: Y = SR^1

Starting material:			Yields of 1,2-dithio-isocoumarin:			
Ref:	R^1	R^2	Y = OR^2	Y = OR^1	Y = SR^2	Y = SR^1
2A[3]	CH_3	H	–	1	–	10
2B[3]	C_2H_5	H	–	3.2	–	2.7
3a[3]	H	CH_3	2.6	–	5.4	–
3b[3]	H	C_2H_5	7	–	1.5	–
4Aa[3]	CH_3	CH_3	14*	3*	4.3*	8.7*
4Ab	CH_3	C_2H_5	15	–	–	4.5
4Ba	C_2H_5	CH_3	12.5	traces	traces	traces
4Bb[3]	C_2H_5	C_2H_5	25		1.5	

which one methyl was fully deuterated: ($^2H_3$)methyl *o*-(methoxycarbonylmethyl)benzoate (**4A'a**). Overall yields were established with the isotopically normal dimethyl ester. Nmr of both alkoxy and alkylthio fractions from the reaction of the deuterated compound gave in each case the proportion of alkyl migration. Results calculated in this way are marked in Table I by a star (*).

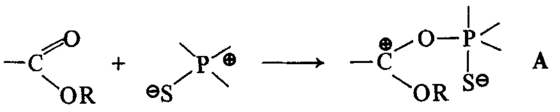
The structure of these dithio-isocoumarins has been confirmed by their oxidation to the corresponding 2-thio-isocoumarins either by potassium permanganate or by benzonitrile-*N*-oxide.[4]



7a: Y = OCH_3
7b: Y = OC_2H_5
8a: Y = SCH_3

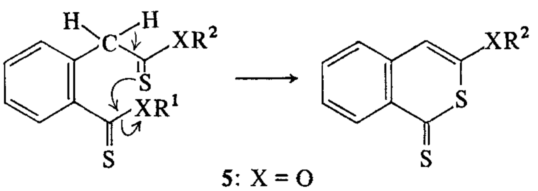
DISCUSSION

In order to explain the migration of an alkyl belonging to a benzoate group, we may assume that, in every case, primary attack of an ester group by phosphorus pentasulfide leads to a type **A** structure:



Structures of type **A** may evolve in various ways leading possibly to four different compounds from one diester containing two different alkyl groups.

In what can be considered as the "normal" reaction, compounds of type **A** yield a phosphorus oxysulfide and an *O*-alkyl thioester which, in turn, may isomerize into an *S*-alkyl thioester. The latter, by further reaction of phosphorus pentasulfide, may lead to a dithioester. These classical reactions and subsequent cyclization explain the formation of compounds **5** and/or **6**:

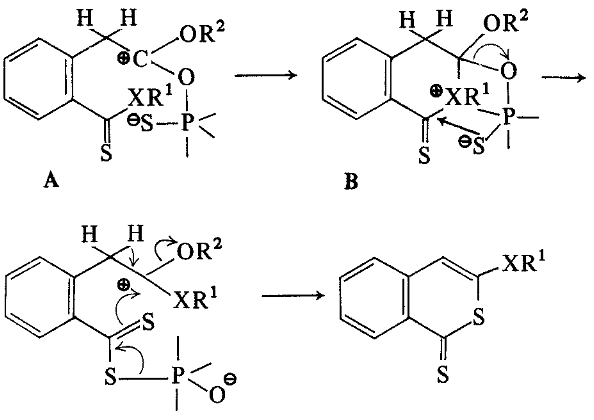


5: X = O
6: X = S

Another reaction path, involving the transient formation of a cyclic oxonium or sulfonium structure **B**, permits us to explain why the resulting dithio-isocoumarin may retain, instead of R^2, the alkyl R^1 coming from the benzoate ester group (Scheme 2). It should be noted also that this scheme may apply as well to the formation of the "normal" products (e.g. at stage **C**, elimination of XR^1 instead of OR^2).

The mechanism for elimination of R^{2}OH from (**C**) has not been detailed. It consists most probably in the formation of a thiophosphate if R^2 is alkyl, or of a thiophosphoric acid group when R^2 is hydrogen.

The significance of the transfer reaction is particularly clear for the formation of 3-alkylthio-1,2-dithio-isocoumarins from alkyl hydrogen homophthalates:



5': X = O
6': X = S

SCHEME 2

the best yields are obtained from the alkyl benzoate type esters and not from the alkyl phenylacetate type esters.

EXPERIMENTAL

Alkyl homophthalates. Methyl hydrogen homophthalates (**2A** and **3a**), ethyl hydrogen homophthalates (**2B** and **3b**), dimethyl homophthalate (**4Aa**) and diethyl homophthalate (**4Bb**) have been prepared as described in literature.[3]

Ethyl methyl homophthalates **4Ab** and **4Ba** have been obtained by reaction of diazomethane in ethyl ether upon the corresponding ethyl hydrogen homophthalates, **3b** and **2B** respectively:

Methyl *o*-(ethoxycarbonylmethyl)benzoate **4Ab**, from *o*-(ethoxycarbonylmethyl)benzoic acid (**3b**). mp = 48–49°C (cyclohexane); yield 75%.

Ethyl *o*-(methoxycarbonylmethyl)benzoate **4Ba**, from (*o*-ethoxycarbonylphenyl)acetic acid **2B**. bp_{15} = 158°C; yield 62%.

($^2H_3$)Methyl *o*-(methoxycarbonylmethyl)benzoate has been prepared from *o*-(methoxycarbonylmethyl)benzoic acid (**3b**). To 50 cm^3 of anhydrous methanol are successively added 0.74 g of sodium and 5.7 g of **3b**. After 15 min refluxing, the solution is cooled and 5 g of IC^2H_3 (CD_3I) is added. Refluxing is resumed for one hour and the methanol is distilled under vacuum. The residue is extracted with benzene and the resulting solution is washed with aqueous sodium carbonate and water and is finally dried on calcium chloride. After distillation of the solvent, the desired ester **4A'a** is crystallized in cyclohexane. White crystals, mp = 42°C, yield 50%.

1,2-Dithio-isocoumarins. Phosphorus pentasulfide is allowed to react with homophthalates in xylene according to a procedure already described,[1] with a refluxing time of 3 hours. The resulting compounds are purified by adsorption chromatography on alumina (activity 4) or on silica gel. Elution gives first generally the 3-alkylthio-1,2-dithio-isocoumarin(s). The 3-alkoxy-1,2-dithio-isocoumarin(s) are obtained afterwards. All these compounds are purified by crystallization in ethanol and form red crystals. The following 1,2-dithio-isocoumarins have been obtained:

5a: 3-Methoxy- mp = 128°C, yields: 17% from **4Aa**; 1% from **2A**; 2.6% from **3a**.

5b: 3-Ethoxy- mp = 108°C, yields: 25% from **4Bb**; 3.2% from **2B**; 7% from **3b**.

6a: 3-Methylthio- mp = 122°C, yields: 13% from **4Aa**; 10% from **2A**; 5.4% from **3a**.

6b: 3-Ethylthio- mp = 65°C, yields: 1.5% from **4Bb**; 2.7% from **2B**; 1.5% from **3b**.

2-Thio-isocoumarins. Oxidation of dithio-isocoumarins may be realized by potassium permanganate in acetone[1] and 2-thio-isocoumarins are crystallized in cyclohexane.

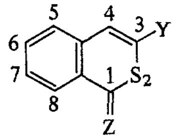
Another method uses benzonitrile *N*-oxide.[4] The dithio-isocoumarin is dissolved in benzene and an equivalent weight of triethylamine is added. This solution is brought to refluxing and a benzene solution of benzhydroximoyl chloride is added until the red color disappears. After cooling, the benzene solution is washed with water and dried on magnesium sulfate.

TABLE II
Nmr signals for aliphatic protons of homophthalic esters **2**, **3** and **4**

Ref:	CH_2CO (s)	$R^1 = H$ (s)	$R^1 = CH_3$ (s)	$R^1 = CH_3{-}CH_2$ (t)*	(q)	$R^2 = H$ (s)	$R^2 = CH_3$ (s)	$R^2 = CH_3{-}CH_2$ (t)*	(q)
2A	4.05	–	3.86	–	–	10.8	–	–	–
2B	4.05	–	–	1.35	4.34	11.3	–	–	–
3a	4.08	12.1	–	–	–	–	3.68	–	–
3b	4.08	11.8	–	–	–	–	–	1.25	4.19
4Aa	4.00	–	3,80	–	–	–	3.63	–	–
4A'a	4.00	–	(C^2H_3)	–	–	–	3.66	–	–
4Ab	4.01	–	3.86	–	–	–	–	1.23	4.17
4Ba	4.00	–	–	1.32	4.30	–	3.63	–	–
4Bb	4.00	–	–	1.32	4.30	–	–	1.18	4.12

* Coupling constant of CH_3 and CH_2 in ethyl groups: 7.0 Hz.

TABLE III
Nmr Spectra of dithio-isocoumarins and of 2-thio-isocoumarins



Ref:	Y	Z	δY	δH at 4	δH at 5, 6, 7	δH at 8
5a	CH_3O	S	3.88(s)	6.38(s)	7.1–7.8(m)	8.50–8.75(m)
5b	C_2H_5O	S	1.40(t), 4.11(q), $J = 7.0$ Hz	6.40(s)	7.06–7.63(m)	8.50–8.73(m)
6a	CH_3S	S	2.56(s)	7.28(s)	7.29–7.75(m)	8.50–8.73(m)
6b	C_2H_5S	S	1.36(t), 2.97(q), $J = 7.0$ Hz	7.31(s)	7.32–7.65(m)	8.50–8.75(m)
7a	CH_3O	O	3.95(s)	6.37(s)	7.15–7.82(m)	8.05–8.32(m)
7b	C_2H_5O	O	1.48(t), 4.17(q), $J = 7.0$ Hz	6.31(s)	7.23–7.58(m)	8.00–8.20(m)
8a	CH_3S	O	2.53(s)	7.06(s)	7.21–7.83(m)	7.96–8.20(m)

The 2-thio-isocoumarin is purified by chromatography on alumina and crystallization in cyclohexane.

The following 2-thio-isocoumarins have been prepared:
7a: 3-Methoxy- mp = 83°C
7b: 3-Ethoxy- mp = 113°C
8a: 3-Methylthio- mp = 62°C.

Nmr Spectra. All spectra are taken in C^2HCl_3 ($CDCl_3$) with TMS as internal reference. Data for homophthalic esters are given in Table II and for dithio- and 2-thio-isocoumarins are given in Table III.

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