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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS XLVIII[a)]

Synthesis of Dithioesters from P,S-Containing Reagents and Carboxylic Acids and Their Derivatives

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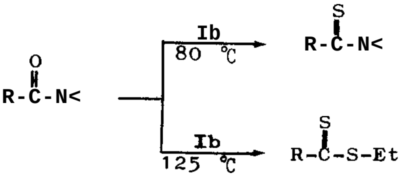
Abstract - 2,4-Bismethylthio-1,3,2,4-dithiadiphosphetane 2,4-disulfide, IIa, is prepared from O,O-dimethyldithiophosphoric acid, Ia, and P_4S_{10} at 160 °C. 2,4-Bis(4-phenoxyphenyl)-1,3,2,4-dithiadiphsophetane 2,4-disulfide, IIc, and 2,4-bis(4-phenylthiolophenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide, IId, are prepared at 160°C from P_4S_{10} and diphenylether and diphenylsulfides, respectively. Carboxylic acids RCOOH (R = CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, $C_6H_5CH_2$, C_6H_5) react with compound Ia at 130 °C to give the corresponding methyl dithioesters. Carboxylic acids RCOOH (R = C_6H_5-CH_2, C_6H_5) react with compound Ib at 200 °C for 15 min to give the corresponding ethyl dithioesters, while low boiling acids (R = CH,, C_2H_5, n-C_3H_7) yielded mixtures of the corresponding ethyl dithioester and ethyl carboxylate. Carboxylic acid chlorides RCOCl (R = $ClCH_2$, C_2H_5, t-C_4H_9, $C_6H_5CH_2$, C_6H_5, p-$NO_2C_6H_4$) react with compound IIa at 80 °C to give the corresponding methyl dithioesters in good yields. S-Substituted thioesters react with IIc at 85 °C to give the corresponding dithioesters in good yields. Dihydro-2(3H)-furanone, VI, and 5-methyl-2(3H)-furanone, VII, react with IIa at 80 °C to give dihydro-2(3H)-thiophenethione, VIII and 2,2'-dithiobis(5-methyl thiophene), IX, respectively. Also XI reacts with IIa, IIc, and IId to give VIII in nearly quantitative yields.

Dithioesters are of great importance because of their wide application in organic synthesis and industry (e.g. as vulcanization inhibitors,[1] starting material for the synthesis of Dyes,[2] photosensitizers,[3] polymers,[4] . . . ...). Some methods for their preparation are mentioned in a recent review.[6] Another more recent method is the reaction of tertiary amides[8] with O,O-diethyldithiophosphoric acid, Ib,



Scheme 1

[a)] XLVII B. Yde, N.M.Yousif, U.Pedersen, I.Thomsen and S.-O.Lawesson, Tetrahedron 40 (1984)

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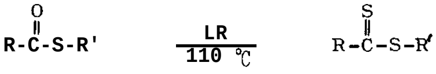
or thiation of S-substituted thioesters [7,8] with IIb (LR)



$$R-\overset{O}{\overset{\|}{C}}-S-R' \xrightarrow[110\ ^\circ C]{LR} R-\overset{S}{\overset{\|}{C}}-S-R'$$

Scheme 2

For the preparation of thiopeptides [9,10] dithioesters of N-protected amino acids can be used, which are prepared by mild methods to avoid racemization.

In attempts to find effective and mild methods for the preparation of dithioesters we have studied the P,S-containing reagents Ia,b and IIa-d.

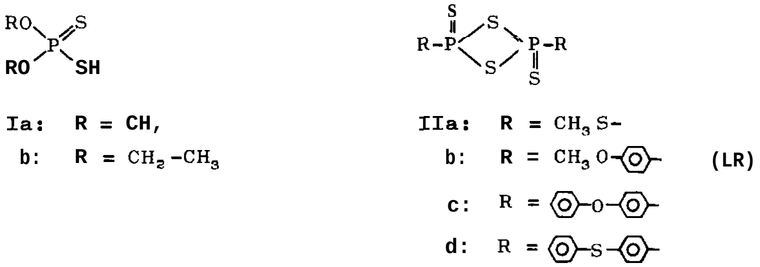


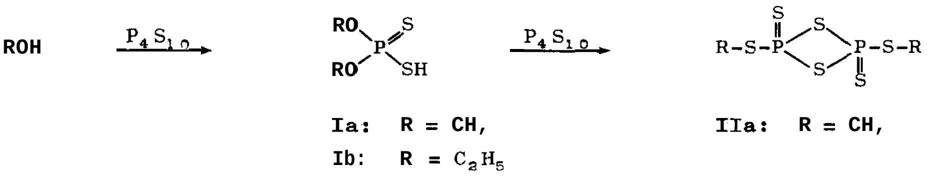
Fig.1

This paper reports on the reactions of I and II with carboxylic acids and their derivatives.

RESULTS AND DISCUSSIONS.

A, Starting materials

The commercially available O,O-dimethyldithiophosphoric acid, Ia, and O,O-diethyl dithiophosphoric acid, Ib, are easily prepared from P_4S_{10} and methanol or ethanol, respectively." In a recent paper [12] the reaction of P_4S_{10} with methanol at 160 ℃ produced 2,4-bismethylthio-1,3,2,4-dithiadiphosphetane 2,4-disulfide [13,14] IIa in low yield (25%).

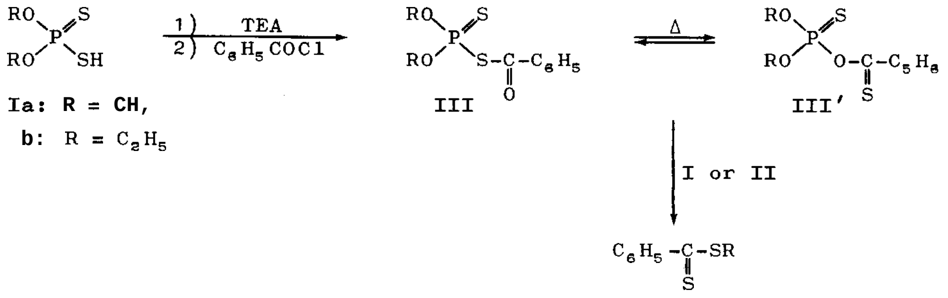


Scheme 3

The low yield is certainly due to the reaction of methanol with IIa to give side products. However, when Ia and P_4S_{10} are heated at 160 ℃ for a short time IIa is isolated in 53% yield. IIb is commercially available and IIc and IId are prepared by reacting P_4S_{10} at 180 ℃ with diphenylether and diphenylsulfide, respectively.

B. Reactions of I

Carboxylic acids react with excess of Ia at 130 ℃ to give the corresponding methyl dithioester in reasonable yields. Also some carboxylic acid (RCOOH, R = C_6H_5, $C_6H_5CH_2$) react with Ib at 200 ℃ to give the corresponding ethyl dithioesters while low-boiling acids (R = CH,, C_2H_7, n-C_3H_7) give mixtures of the corresponding ethyl dithioesters and ethyl carboxylates (Table 1, entries 1-11).



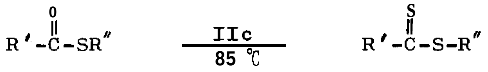
Scheme 4

As to the mechanism for the reaction of I with carboxylic acid it is suggested that at first water is eliminated to give III, incidentally easily prepared by acylation of I.[15] (By heating or standing, III is partly transformed into III'). A 1:1 mixture of III and III' (R = CH,) does not give any dithioester on heating (130 ℃). However, when Ia or IIa is present almost quantitative yields of methyl dithiobenzoate are isolated. Also III (III') (R = C_2H_5) and Ib produce ethyl dithiobenzoate in 77% yield. From these results we do believe that the reaction of I with carboxylic acids can go via III (III').

C. Reactions of II

1) Acid Chlorides. Carboxylic acid chlorides react with IIa in refluxing benzene to give the methyl dithiocarboxylate in reasonable yields (Table 1, entries 15-20). During the reaction also S-methyl thiocarboxylates is isolated. As IIa contains various nucleophilic sites, different mechanisms can account for the formation of dithioesters. 1) Acylation on sulfur (CH_3-S-P) would give the S-methyl thioester, which gives the dithioester after thionation. 2) Acylation on another sulfur would give an acylating reagent (compare III ⇄ III') which rearranges to give the dithioester in one step.

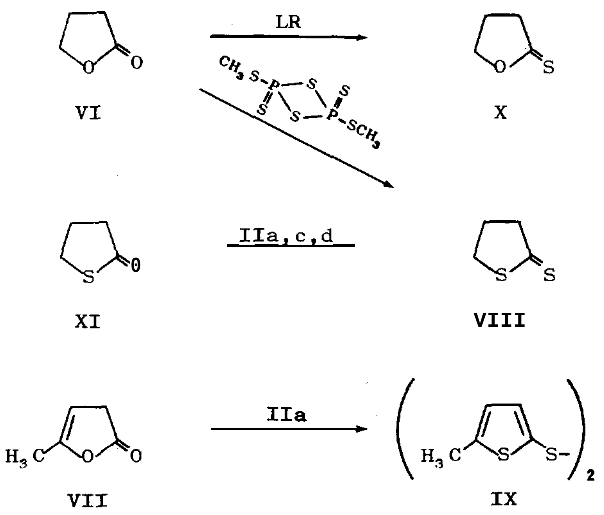
2) Esters and S-substituted thioesters. Methyl benzoate reacts with IIa at 200 ℃ to give methyl dithiobenzoate in reasonable yields (entry 26) and it is obvious that a transesterification has taken place. Ethyl benzoate gives, as expected, mixtures of products. Attempts to transfer S-substituted thioesters to the corresponding dithionoesters by reaction with IIc in refluxing THF did not meet with success. However, in refluxing DME the dithioesters are formed in good yields (entries 21-24).



$$R'-\overset{O}{\overset{\|}{C}}-SR'' \xrightarrow[85\ ℃]{IIc} R'-\overset{S}{\overset{\|}{C}}-S-R''$$

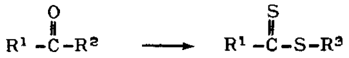
Scheme 5

3) Lactones and thiolactones. It is known [16] that VI reacts smoothly with IIb to give the dihydro-2(3H)-furanthione X. Now it has been found that IIa transforms VI into VIII that means that oxygen in the ring is exchanged with sulfur. During the reaction samples are taken from the reaction mixture but neither X nor dihydro-2(3H)-thiophenone XI were detected (GLC). VII was also reacted with IIa and IX [17] was the final product. The reaction of ethyl 4-oxopentanoate with IIb at elevated temperature gave the same product.[15]



Scheme 6

Table 1. Experimental data for the preparation of dithioesters from acids, III, acid chlorides, thioloesters and esters



$$R^1\text{-}\overset{O}{\overset{\|}{C}}\text{-}R^2 \longrightarrow R^1\text{-}\overset{S}{\overset{\|}{C}}\text{-}S\text{-}R^3$$

Entry	R¹	R²	Reagent	Temp.(℃)	Time (hr)	R³	Yield (%)
1	Me	OH	Ia	130	3	Me	25^{23}
2	Et	OH	Ia	130	3	Me	48^{22}
3	n-Pr	OH	Ia	130	3	Me	56^{5}
4	n-Bu	OH	Ia	130	3	Me	53"
5	$PhCH_2$	OH	Ia	130	3	Me	46^{22}
6	Ph	OH	Ia	130	3	Me	455
7	Me	OH	Ib	200	1	Et	7^{5}, 65^{*}
a	Et	OH	Ib	200	0.8	Et	20^{5}, 54^{*}
9	n-Pr	OH	Ib	200	1.5	Et	32^{17}, 32^{18*}
10	$PhCH_2$	OH	Ib	200	0.5	Et	33^{20}
11	Ph	OH	Ib	200	0.2	Et	505
12	Ph	IIIa	Ia	130	0.5	Me	815
13	Ph	IIIb	Ib	200	0.1	Et	775
14	Ph	IIIa	IIa	130	0.2	Me	895
15	$ClCH_2$	Cl	IIa	80	4	Me	25
16	Et	Cl	IIa	80	4	Me	63^{22}
17	t-Bu	Cl	IIa	80	4	Me	84^{19}
18	$PhCH_2$	Cl	IIa	80	1.5	Me	68^{22}
19	Ph	Cl	IIa	80	4	Me	715
20	4-NO_2Ph	Cl	IIa	80	5	Me	56^{3}
21	Me	$PhCH_2S$	IIc	85	8	$PhCH_2$	827
22	Me	PhS	IIC	85	8	pH	72'
23	Ph	$PhCH_2S$	IIC	85	8	$PhCH_2$	74'
24	Ph	PhS	IIc	85	8	Ph	65'
25	Ph	PhS	IIa	80	8	Me,Ph	40, 23^{5}
26	Ph	MeO	IIa	200	0.5	Me	625
27	Ph	EtO	IIa	140	12	Me,Et	30,10,40^{**}
	Ph	PhO	IIa	140	6	Me	52^{5}

*ethyl carboxylate; **O-ethyl-thiobenzoate

Table 2. Experimental data for the preparation of dithiolactones at 80 ℃ from lactones

Lactone	Reagent	Solvent	Time (min)	Yield (%)
VI	IIa	benzene	50	39[18]
XI	IIa	benzene	30	92[18]
XI	IIc	DME	25	85[18]
XI	IId	DME	25	95[18]

EXPERIMENTAL

^1H NMR spectra were recorded at 60 MHz on a Varian A-60 spectrometer in $CDCl_3$. Int.ref. TMS. IR spectra were recorded on a Beckman IR-18 spectrometer. Mass spectra were recorded on a Micromass 7070F spectrometer operating at 70 eV using direct inlet.

Synthesis of IIa

a) from methanol and P_4S_{10}. 111 g (0.25 mole) P_4S_{10} and 150 ml trichlorobenzene are mixedinal ℓ three necked flask with mechanical stirring and reflux condenser. The mixture was heated to 80-90 ℃, then 24 g (0.75 mole) methanol was dropped gradually with stirring (the reaction is exothermic), and then the reaction mixture was kept at 160 ℃ for 20 min, and then cooled to 70-80 ℃ and filtered, The filtrate was then cooled to room temperature and the precipitated compound is filtered and washed with anhydrous pet.ether. Yield 55.5 g(60%), mp 160 ℃ (lit.[13] 112 ℃); M^+ 284 (low intensity); m/e 142 ($M^+/2$); precise MS (Found: M^+ 141.913; Calc. for CH_3PS_3 : M^+ 141.9134) (the low mp mentioned in the literature is due to an impure sample containing elemental sulfur).

b) from compound Ia and P_4S_{10}. 1.58 g (0.01 mole) of Ia, 2.21 g (0.005 mole) P_4S_{10} and 10 ml anhydrous trichlorobenzene are mixed in a 100 ml round flask without condenser. The reaction mixture was kept at 160 ℃ with stirring for 30 min. The reaction was worked up as in a). Yield 0.72 g (53%).

Synthesis of IIc

111 g (0.25 mole) P_4S_{10}, 100 ml 0-dichlorobenzene and 340 g (2 mole) diphenyl ether are mixed in a 1 ℓ two necked flask with mechanical stirring and reflux condenser. The mixture was heated under reflux at 180 ℃ for 25 min and then cooled to 100-120 ℃ and filtered. 200 ml anhydrous ether is addedtuthe filtrate then cooled to room temperature. The precipitated compound is then filtered. Yield 401 g (75%), mp 189 ℃ (lit.[23] 187-189 ℃); MS: M^+ 528.59 low intensity $M^+/2$: 264 base peaks. The precise mass $M^+/2$ is 263.983 (Calc. 263.9832).

Synthesis of IId

111 g (0.25 mole) P_4S_{10}, 100 ml 0-dichlorobenzene and 186 g (1 mole) diphenylsulfide are mixed and completed as in the syntheses of IIc. Yield 182 g (65%), mp 193 ℃. MS: M^+ 560.72 low intensity $M^+/2$: 280 base peak. The precise mass $M^+/2$ 279.960 (Calc. 279.9604).

General procedure for the preparation of dithioesters from carbpxylic acids and Ia or Ib

A mixture of 0.005 mole of carboxylic acid and 5 ml of Ia or Ib are heated (Table 1, entries 1-11). The reaction mixture, which is allowed to obtain room temperature, is extracted with 100 ml ether and washed with $NaHCO_3$. Then it is placed on a silica gel column and the dithioester is eluated by ether/P.E. (1:19). Three carboxylic acids (RCOOH: R=CH_3, C_2H_5, n-C_3H_7) are reacted with Ib as following: 0.6 mole of carboxylic acid and 15 ml of Ib are heated (Table 1) and the esters are isolated by destillation.

Procedure for the preparation of dithioesters from III, III' and Ia, Ib or IIa

0.005 mole of III are heated with 0.01 mole of compound Ia, Ib or IIa (Table 1, entries 12-14). The reaction mixture, which is allowed to obtain room temperature, is placed on a silica gel column, and the dithioester is eluated with ether/P.E. (1:19).

General procedure for the preparation of dithioesters from acid chlorides and IIa

0.005 mole of acid chloride and 1.42 g (0.005 mole) of IIa are refluxed in anhydrous benzene (Table 1, entries 15-20). The solvent is stripped off and the residue is placed on a silica gel column, The dithioester is eluted with ether/

P.E. (1:19).

General procedure for the preparation of dithioesters from thioloesters and IIa or IIc

0.005 mole of thioloester and 0.005 mole of IIa or IIc in 10 ml anhydrous DME are heated at 80 ℃ (Table 1, entries 21-25). The solvent is stripped off and the residue is placed on a silica gel column. The dithioester is eluted with ether/P.E. (1:19).

Procedure for the preparation of methyl dithiobenzoate from methyl benzoate and IIa

0.68 g (0.005 mole) methyl benzoate and 1.42 g (0.005 mole) IIa are heated at 200 ℃ in 10 ml anhydrous 1,2,4-trichlorobenzene (Table 1, entries 26-28). The reaction mixture, which is allowed to obtain room temperature, is placed on a silica gel column. Methyl dithiobenzoate is eluted with ether/P.E. (1:19).

Preparation of dithioesters from IIa and ethyl benzoate or phenyl benzate

0.005 mole of the ester and 1.42 g (0.005 mole) IIa are refluxed in 10 ml anhydrous xylene (Table 1). The reaction mixture, which is allowed to obtain room temperature, is placed on a silica gel column and the dithioester is eluted with ether/P.E. (1:19). Transesterification is obtained for phenyl dithiobenzoate.

Preparation of dihydro-2(3H)-thiophenethione, VIII. from dihydro-2(3H)-furanone, VI. and IIa

0.43 g (0.005 mole) of VI and 1.42 g (0.01 mole) of IIa in 10 ml anhydrous benzene are heated for 50 min. The solvent is stripped off and the residue is placed on a silica gel column. VIII is eluted with ether/P.E. (1:19).

Preparation of dihydro-2(3H)-thiophenthione, VIII, from dihydro-2(3H)-thiophenone, XI, and IIa

0.51 g (0.005 mole) of XI and 1.42 g (0.01 mole) of IIa in 10 ml anhydrous benzene are heated for 30 min. The solvent is stripped off and the residue is placed on a silica gel column. VIII is eluted with ether/P.E. (1:19).

Preparation of dihydro-2(3H)-thiophenthione, VIII. from dihydro-2(3H)-thiophenone, XI. and IIc or IId

0.51 g (0.005 mole) of XI and 0.01 mole of IIc or IId in 10 ml anhydrous DME are heated at 80 ℃ for 25 min. The solvent is stripped off and the residue is placed on a silica gel column. VIII is eluted with ether/P.E. (1:19).

Preparation of 2,2'-dithiobis(5-methyl-thiophene), IX; from 5-methyl-Z(3H)-furanone, VII, and IIa

0.49 g (0.005 mole) of VII and 1.42 g (0.01 mole) of IIa in 10 ml anhydrous benzene are heated at 80 ℃ for 60 min. The reaction mixture, which is allowed to obtain room temperature, is placed on a silica gel column and IX is eluted with ether/P.E. (1:10) and 0.2 g (31%) is obtained. ^{1}H NMR ($CDCl_3$): 2.25 (6H,s), 6.75-6.85 (2H,d), 7.05-7.15 (2H,d). MS: 258 (M+), 226 (M+-S), 129 (M+/2) base peak, 97 (M+/2-S), 85 (M+/2-CS).

The known compounds are identified by IR, ^{1}H NMR and MS spectroscopy. The following data for the unknown compound methyldithiochloroacetate is found: ^{1}H NMR ($CDCl_3$): 2.6 (3H,s), 4.55 (2H,s). MS: M+ 140 and precise mass M+ 139.9521 (Calc. 139.95212).

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