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PREPARATION OF DITHIOESTERS BY ESTER INTERCHANGE AND THE PMR SPECTRAL PROPERTIES OF THESE COMPOUNDS

N. H. LEON and R. S. ASQUITH
Unilever Research Laboratory, Isleworth, Middlesex, England
and
School of Colour Chemistry, University of Bradford, Bradford, England

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Abstract—Aromatic and aliphatic dithioesters, many of them new, have been easily synthesized in excellent yields by the ester interchange reaction between carboxymethyl dithioesters and mercaptans. PMR spectra of these dithioesters and the corresponding oxygen analogues show that a strong anisotropic deshielding effect is associated with the highly polarized thiocarbonyl group.

DITHIOESTERS have been previously prepared in varying yields by alkylating the salt of a dithioacid[1a, 2–5] and from the nitrile via the thioimidoester by the method of Sakurada[6] or its modification.[7] In the former method, the dithioacid salts are normally obtained by the action of carbon disulphide on phenylmagnesium halide.[1, 3, 8, 9] The preparation via these Grignard compounds is difficult experimentally owing to the instability of the dithioacids and hence low yields are generally obtained, especially

TABLE 1. KNOWN DITHIOESTERS RC(=S)SR'

R	R'	B.p./mm or m.p., °C		PMR,[a]	Formula	Mol.	S, %	
		Found	Lit.	δ SCH		Wt.[b]	Found	Calcd.
Ph	Et	97/0·5	117/0·2[c]	3.35	$C_9H_{10}S_2$	182	35·0	35·18
Ph	i-Pr	88–89/0·2	90/0·2[c]	4·03	$C_{10}H_{12}S_2$	196	33·1	32·66
Ph	Bu	113/0·4	172–173/12[d]	3·35	$C_{11}H_{14}S_2$	210	30·6	30·49
Ph	CH_2Ph	159–160/0·3	179–180/3[e]	4·51	$C_{14}H_{12}S_2$	244	26·2	26·24
Ph	Ph	60–61[f]	60–62[g]	—	$C_{13}H_{10}S_2$	230	27·6	27·84
4-$MeOC_6H_4$	Et	120–121/0·2	143–145/0·2[g]	3·32	$C_{10}H_{12}OS_2$	212	30·0	30·20
Me	Et	61/24	61/23[h]	3·16	$C_4H_8S_2$	120	53·3	53·34
Et	Et	59/9	59/9[i]	3·17	$C_5H_{10}S_2$	134	48·0	47·75
$CH_3(CH_2)_6$	Et	71/0·1	136/9[i]	3·20	$C_{10}H_{20}S_2$	204	31·3	31·38

Compounds with R = aromatic are red and those with R = aliphatic are yellow. Yields are of 85–91%.

[a] Measured in $CDCl_3$ at 100 MHz with TMS as internal standard.

[b] From *m/e* of parent peak in mass spectrum.

[c] R. Mayer, S. Scheithauer and D. Kunz, *Chem. Ber.* **99**, 1393 (1966).

[d] Ref. 22.

[e] J. H. Wood and R. W. Bost, *J. Am. Chem. Soc.* **59**, 1011 (1937).

[f] Red needles, recrystallized from light petroleum (b.p. 60–80°).

[g] Ref. 24.

[h] Ref. 7.

[i] Ref. 13.

TABLE 2. NEW DITHIOESTERS, RC(=S)SR'

R	R'	B.p./mm or m.p., °C	PMR,[a] δ SCH_2	Formula	Mol. Wt.[b]	Found, % C	H	S	Required, % C	H	S
Ph	Pr	119/1·4	3·31	$C_{10}H_{12}S_2$	196	61·2	6·2	32·4	61·18	6·16	32·66
Ph	$CH_2CH{=}CH_2$	96–97/0·6	3·97	$C_{10}H_{10}S_2$	194	61·7	5·2	33·1	61·81	5·19	33·00
Ph	CH_2COOMe	118–119/0·2	4.30	$C_{10}H_{10}O_2S_2$	226	53·1	4·4	28·0	53·07	4·45	28·34
Ph	CH_2CHCH_2OH | OH	140/0·15	[c]	$C_{10}H_{12}O_2S_2$	228	52·7	5·3	27·9	52·60	5·30	28·09
Ph	CH_2CH_2 | NHCSPh	108·5–109[d]	[c]	$C_{16}H_{15}NS_3$[e]	317	60·4	4·8	30·4	60·51	4·76	30·30
4-$MeOC_6H_4$	Pr	128–129/0·2	3·32	$C_{11}H_{14}OS_2$	226	58·4	6·3	28·2	58·37	6·23	28·33
4-$MeOC_6H_4$	$CH_2CH{=}CH_2$	141–142/0·5	4·03	$C_{11}H_{12}OS_2$	224	59·0	5·4	28·7	58·89	5·39	28·58
4-$AcNHC_6H_4$	Et	127–128[f]	3·36	$C_{11}H_{13}NOS_2$[g]	239	55·1	5·5	26·7	55·20	5·47	26·79
4-$AcNHC_6H_4$	$CH_2CH{=}CH_2$	[h]	4·04	$C_{12}H_{13}NOS_2$[i]	251	57·5	5·3	25·4	57·34	5·21	25·51
4-ClC_6H_4	Et	102–104/0·1 31–32[j]	3·35	$C_9H_9ClS_2$	216	49·7	4·2	29·5	49·87	4·18	29·59
4-ClC_6H_4	Pr	113–115/0·1	3·31	$C_{10}H_{11}ClS_2$	230	52·2	4·8	27·9	52·05	4·81	27·79
3-$NO_2C_6H_4$	Et	140/0·2 52·5–53·5[j]	3·38	$C_9H_9NO_2S_2$[k]	227	47·7	4·0	28·0	47·56	3·99	28·21
3-$NO_2C_6H_4$	$CH_2CH{=}CH_2$	137–138/0·2	4·03	$C_{10}H_9NO_2S_2$[l]	239	50·0	3·8	26·8	50·18	3·79	26·80
1-Naphthyl	Et	37–38·5[m]	3·38	$C_{13}H_{12}S_2$	232	67·3	5·2	27·7	67·20	5·21	27·60
1-Naphthyl	CH_2Ph	180–184/0·1	4·64	$C_{18}H_{14}S_2$	294	73·5	4·8	21·8	73·43	4·79	21·78

1-Naphthyl	$CH_2CH{=}CH_2$	141–142/0·2	4·05	$C_{14}H_{12}S_2$	244	68·7	4·9	26·4	68·81	4·95	26·24
2-Furyl	Et	72–73/0·1	3·30	$C_7H_8OS_2$	172	48·9	4·7	37·3	48·81	4·68	37·23
2-Furyl	Pr	78–79/0·1	3·25	$C_8H_{10}OS_2$	186	51·6	5·4	34·5	51·58	5·41	34·42
2-Furyl	$CH_2CH{=}CH_2$	81–82/0·2	4·03	$C_8H_8OS_2$	184	52.1	4·4	34·7	52·14	4·37	34·80
4-Phenylazophenyl	Et	58–59[j]	3·40	$C_{15}H_{14}N_2S_2$[n]	286	62·8	4·9	22·5	62·90	4·93	22·39
Me	$CH_2CH{=}CH_2$	104/45	3·90	$C_5H_8S_2$	132	45·3	6·1	48·4	45·41	6·10	48·49
$CH_3(CH_2)_{12}$	Et	148/0·7	3·21	$C_{16}H_{32}S_2$	288	66·7	11·1	22·1	66·60	11·18	22·22
$EtSSC(CH_2)_8$	Et	[o]	3·20	$C_{14}H_{26}S_4$	322	52·2	8·2	39·5	52·12	8·12	39·75
$3\text{-}EtSSCC_6H_4$	Et	174–175/0·1	3·34	$C_{12}H_{14}S_4$	286	50·4	4·8	44·9	50·31	4·92	44·77

Compounds with R = aromatic are red to orange and those with R = aliphatic are yellow. Yields are of 82–91%.

[a] Measured in $CDCl_3$ at 100 MHz with TMS as internal standard.

[b] From *m/e* of parent peak in mass spectrum.

[c] Cannot be determined due to signal overlap.

[d] Orange-red needles, recrystallized from chloroform–light petroleum (b.p. 40–60°).

[e] Anal. N, Found: 4·4, requires: 4·41%.

[f] Red needles, recrystallized from chloroform–light petroleum (b.p. 60–80°).

[g] Anal. N, Found: 5·7, requires: 5·85%.

[h] Red oil, dec. on distillation.

[i] Anal. N, Found: 5·5, requires: 5·57%.

[j] Red needles.

[k] Anal. N, Found: 6·0, requires: 6·17%.

[l] Anal. N, Found: 5·8, requires: 5·85%.

[m] Orange prisms.

[n] Anal. N, Found: 9·7, requires: 9·78%.

[o] Yellow oil, dec. on distillation.

in the preparation of aliphatic dithioacids.[1c] Another drawback is the limitation of the Grignard synthesis itself—the halide molecule may not contain groups that are reactive towards the reagent. The latter method seemed to be more general. However, unsatisfactory yields were often encountered and in some cases no desired products could be produced. Moreover, this method is restricted by the availability of the starting material.

Carboxymethyl dithioesters are excellent reagents for thioacylation of amines, amino acids, amino acid derivatives, and hydrazines.[10-12] These readily preparable compounds are crystalline solids, stable at ordinary temperatures, and may be stored for long periods. Being acids, most of them are readily soluble in dilute aqueous alkaline solutions. During the studies of the reaction of these dithioesters with amino acids and their derivatives, it was observed that rapid and nearly quantitative interchange occurred between sulphydryl groups and carboxymethyl dithioesters leading to S-thioacylation of the free sulphydryl groups. This type of ester interchange, therefore, seemed a feasible method for the preparation in good yield of aliphatic and aromatic dithioesters.

It has now been found that many carboxymethyl dithioesters react readily with a variety of mercaptans to form the corresponding dithioesters in aqueous solutions or organic solvents at room temperature. The reaction is rapid, simple to conduct, and affords the dithioesters in high yields. This reaction may be considered as an example of nucleophilic displacement at thiocarbonyl carbon involving sulphur nucleophiles.

$$R{-}\overset{\overset{S}{\|}}{C}{-}SCH_2COOH + R'SH \rightleftharpoons R{-}\overset{\overset{S}{\|}}{C}{-}SR' + HSCH_2COOH$$

Because the reaction occurs in aqueous solution, in which the desired dithioester separates out, the equilibrium is moved to the product side resulting in a complete transesterification. When the reaction is carried out in organic solvents, however, treatment of the reaction mixture with aqueous alkaline solution preferentially removes the by-product thioglycollic acid, and near quantitative yields of the desired dithioesters are usually obtained.

The reaction was first tested for the preparation of known dithioesters. Without any experimental difficulty, this simple one-step preparation in all cases gave the dithioesters in excellent yields. The results are summarized in Table 1. Unreported dithioesters, many of them difficult to obtain by the standard methods, were prepared in good yields by these ester interchange reactions. The physical properties of these new dithioesters are tabulated in Table 2. From the number and variety of compounds synthesized, it can be concluded that this method of preparation is of general application.

The IR absorption spectra of the dithioesters show that the C=S stretching vibration appears at a position varying from 1225–1170 cm^{-1}, in agreement with the literature.[7, 13-15] Mass spectrometric fragmentation behaviour of all the dithioesters prepared has been studied and the details will be reported elsewhere.

The PMR spectra of dithioesters described in this paper present some points of interest. A strong anisotropic deshielding effect associated with the highly polarized thiocarbonyl group has been shown in thioamides,[16] thioaldehydes[17] and anions of the cyclic amine N-carbodithioic acid salts.[18] In dithioesters and their oxygen

analogues, the chemical shift of the proton(s) in $-C(=X)YCH-$ (X = O or S and Y = O or S) is readily determined. In the present studies, it has been found that the deshielding of the proton(s) in $-C(=X)YCH-$ decreases in the following order:

$$-C(=S)OCH- > -C(=O)OCH- > -C(=S)SCH- > -C(=O)SCH-$$

This observation is useful for identifying dithioesters and their oxygen analogues.

The downfield shift (ca. 0·3 ppm) for the methylene or methine proton(s) when changing from $-C(=O)OCH-$ to $-C(=S)OCH-$ or from $-C(=O)SCH-$ to $-C(=S)SCH-$ clearly indicates that the thiocarbonyl group causes greater deshielding than does the carbonyl group. The upfield shift (ca. 0·9 ppm) for the methylene or methine proton(s) when changing from $-C(=O)OCH-$ to $-C(=S)SCH-$ is apparently due to the relative magnitudes of two opposing effects—namely, (a) the stronger anisotropic deshielding effect of C=S as compared to C=O and (b) the weaker deshielding by —S— than —O—, the contribution due to (b) being more important than that due to (a).

TABLE 3. CHEMICAL SHIFT (δ VALUES) OF THE METHYLENE PROTONS IN $Ph-\overset{\overset{X}{\|}}{C}-YCH_2R$*; APPROXIMATE J VALUES (Hz) IN PARENTHESIS

R	X = S, Y = O	X = Y = O	X = Y = S	X = O, Y = S
CH_3	4·60	4·40	3·35	3·00
	(7·1)	(7·1)	(7·1)	(7·1)
$CH_2CH_2CH_3$	4·60	4·30	3·35	3·06
	(6·2)	(6·2)	(6·2)	(6·2)
$CH=CH_2$	5·03	4·75	3·97	3·63
	(6·2)	(6·2)	(6·2)	(6·2)

* Measured in $CDCl_3$ at 60 MHz with TMS as internal standard.

As examples, the chemical shifts of the methylene protons in ethyl, n-butyl, and allyl benzoates and their sulphur analogues are presented in Table 3.

EXPERIMENTAL

M.ps were taken in open capillaries with an electrothermal m.p. apparatus and are uncorrected. PMR spectra were recorded in $CDCl_3$ soln and integrated with a Perkin–Elmer R 10 (60 MHz) and a Perkin–Elmer R 14 (100 MHz) spectrometer with TMS as internal standard and all chemical shifts are in ppm. Mass spectra were obtained with an AEI MS-12 mass spectrometer at an ionizing energy of 70 eV. Mol. wt. values correspond to parent peaks, which are prominent in all cases. IR spectra of solids were determined in KBr discs, and liquids in pressed out films on NaCl discs with a Perkin–Elmer 257 grating infrared spectrophotometer.

Carboxymethyl dithiobenzoate was prepared by the method of Kurzer and Lawson.[19] Other known carboxymethyl dithioesters were prepared by the methods of Jensen and Pedersen.[20] *Carboxymethyl 4-phenylazodithiobenzoate, carboxymethyl dithiooctanoate, carboxymethyl dithiotetradecanoate, dicarboxymethyl octane-1,8-dicarbodithioate,* and *dicarboxymethyl benzene-1,3-dicarbodithioate* were prepared similarly to method III of Jensen and Pedersen[20] starting from the corresponding piperidides. The detailed procedure will be reported elsewhere.

Ethyl thionbenzoate,[21] n-butyl thiolbenzoate,[22] n-butyl thionbenzoate,[22] allyl thiolbenzoate,[23] and allyl thionbenzoate[23] were obtained according to the literature. Ethyl thiolbenzoate, b.p. 101°/4 mm (lit.[24] b.p. 135°/15 mm) was prepared by benzoylation of ethyl mercaptan with benzoyl chloride in benzene and pyridine.

General procedure of ester interchange. Carboxymethyl dithioesters usually react so readily with mercaptans that the thioacylation is effected by the simplest experimental procedure.

For a carboxymethyl dithioester, soluble in dilute alkaline soln, an equal molar quantity of mercaptan is mixed at room temp with a carboxymethyl dithioester, dissolved in two equivs of NaOH. Reaction is usually complete within minutes; the colour of the aq soln is discharged, and the desired dithioester separates out either as an oil or a crystalline solid.

When the carboxymethyl dithioester is sparingly soluble in dilute alkaline soln, the reaction can be carried out in organic solvents. In this case, an excess of mercaptan is mixed with a carboxymethyl dithioester in ether or benzene and the reaction mixture washed with dil NaOH aq to remove the thioglycollic acid formed during the reaction.

Allyl 4-methoxydithiobenzoate. A soln of carboxymethyl 4-methoxydithiobenzoate (4·8 g) in 0·1 N NaOH (40 ml) was mixed with allyl mercaptan (1·5 g); a red oil separated out immediately and the colour of the aq soln was discharged. After 0·5 hr, the red oil was extracted with benzene or ether and the extracts were washed with 1 N NaOH and then with water, and dried (Na_2SO_4). After removing the solvent under reduced pressure, the residue was distilled *in vacuo* to give 4·1 g (91·5%) *allyl 4-methoxydithiobenzoate* as a mobile red liquid, b.p. 96–97°/0·6 mm.

Other known dithioesters and the new dithioesters listed in Table 2, except *ethyl 4-phenylazodithiobenzoate, ethyl dithiotetradecanoate, ethyl* and *allyl 4-acetamidodithiobenzoates*, were prepared in the same way.

Ethyl dithiotetradecanoate. To a soln of carboxymethyl dithiotetradecanoate (3·2 g) in ether was added ethyl mercaptan (1·9 g) and the reaction mixture was well mixed. After 0·5 hr, the reaction mixture was washed with 1 N NaOH. To the ether layer ethyl mercaptan (1·9 g) was again added and the procedure repeated. The ether layer was then washed with water or, if emulsification occurred, with 10% NaCl and then dried (Na_2SO_4). Evaporation of the solvent under reduced pressure yielded 2·4 g (83%) of *ethyl dithiotetradecanoate* as yellow mobile liquid, b.p. 148°/0·7 mm.

Ethyl 4-phenylazodithiobenzoate, ethyl and allyl 4-acetamidodithiobenzoates were prepared in the same way.

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