Some Reactions of Alkoxythiocarbonyl Derivatives with *N,N*-Dimethylhydrazine

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The reaction of xanthate (dithiocarbonate) esters with *N,N*-dimethylhydrazine leads to mixtures of the derived thionocarbamates and thionocarbazates whereas alkoxythiocarbonylimidazoles give cleanly the thionocarbazates. The outcome of these reactions is determined by the nature of the intermediate formed by expulsion of the leaving group.

In connection with a study of the α effect,[1] we wished to prepare several *N,N*-dialkylated alkoxythiocarbonyl derivatives of general structure (**1**). A large variety of such thionocarbazate esters have been prepared,[2] generally by reaction of the appropriately substituted hydrazine either with relatively unstable alkoxythiocarbonyl chlorides or with the mixed anhydride derivatives[3] (**2**) derived by *in situ* rearrangement of the corresponding thioacetic acid salts (**3**). In view of the well known facility for reaction of xanthate esters with primary or secondary amines[4] to give thionocarbamates, we anticipated that an analogous reaction with the powerful nucleophile *N,N*-dimethylhydrazine should give the required thionocarbazates (**1**). Such a reaction has been described with hydrazine itself and with mono-substituted hydrazines.[2]

$RO{\cdot}CS{\cdot}NH{\cdot}NR^1{}_2$
(**1**)

$RO{\cdot}CS{\cdot}O{\cdot}CO{\cdot}CH_2{\cdot}S^-$
(**2**)

$RO{\cdot}CS{\cdot}S{\cdot}CH_2{\cdot}CO{\cdot}O^-$
(**3**)

5α-Cholestan-3β-yl-O·CS·X
(**4**) X = SMe
(**5**) X = $NHNMe_2$
(**6**) X = NMe_2
(**7**) X = Imidazol-1-yl

In the event, reaction of cholestan-3β-yl *S*-methyl xanthate (**4**) proceeded relatively slowly requiring a 40-fold excess of *N,N*-dimethylhydrazine as solvent at 60 °C. Removal of solvent and chromatography gave not only the anticipated thionocarbazate (**5**) (31%) but also a second product (48%) whose analytical and mass spectral data served to establish the molecular formula $C_{30}H_{53}NOS$, clearly demonstrating that only the dimethylamino group of the hydrazine had been incorporated into the product. The identity of this substance as the thionocarbamate (**6**) was supported by the n.m.r. spectrum which displayed the characteristic signals for two magnetically non-equivalent *N*-methyl groups at δ 3.1 and δ 3.3 p.p.m., and was finally confirmed by reaction of the xanthate with dimethylamine. Examination of the Table shows that this is a general reaction of xanthate esters.

We then studied the reaction of the analogous alkoxythiocarbonylimidazole derivatives, which, in contrast to the xanthate esters requires only one equivalent of *N,N*-dimethylhydrazine, proceeds at room temperature, and gives good yields of the thionocarbazates without contamination from thionocarbamates (Table). Clearly, this is the method of choice for smooth incorporation of the hydrazine moiety.

It was therefore of interest to examine the mechanisms of these reactions in more detail. Firstly, in order to establish

RO·CS·X

(**8**) R = Et, X = SMe
(**9**) R = Et, X = SCH_2Ph
(**10**) R = Et, X = Imidazol-1-yl
(**11**) R = Et, X = $NHNMe_2$
(**12**) R = Et, X = NMe_2
(**13**) R = n-$C_{10}H_{21}$, X = SMe
(**14**) R = n-$C_{10}H_{21}$, X = $NHNMe_2$
(**15**) R = n-$C_{10}H_{21}$, X = NMe_2
(**16**) R = n-$C_{18}H_{37}$, X = SMe
(**17**) R = n-$C_{18}H_{37}$, X = Imidazol-1-yl
(**18**) R = n-$C_{18}H_{37}$, X = $NHNMe_2$
(**19**) R = n-$C_{18}H_{37}$, X = NMe_2

(**20**) $^-O{\cdot}CH(Me){\cdot}CH_2{\cdot}\overset{+}{N}Me_2{\cdot}NH_2$

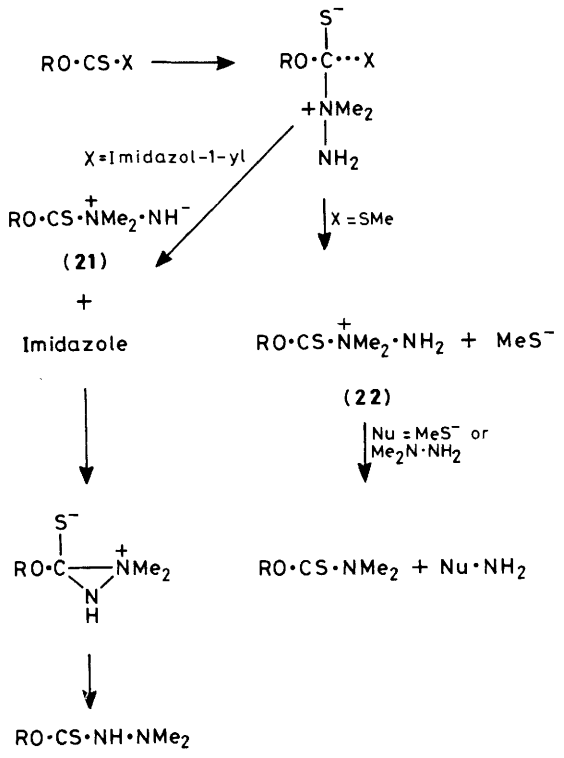
Table. Reaction of alkoxythiocarbonyl derivatives (ROCSX) with *N,N*-dimethylhydrazine

Thiocarbonyl derivative	X	Products (% yield) X = $NHNMe_2$	X = NMe_2
(**4**)	SMe	(**5**) 31	(**6**) 48
(**7**)	Im*	(**5**) 82	
(**8**)	SMe	(**11**) 53	(**12**) 33
(**9**)	SCH_2Ph	(**11**) 55	(**12**) 37
(**10**)	Im*	(**11**) 50	
(**13**)	SMe	(**14**) 36	(**15**) 26
(**16**)	SMe	(**18**) 58	(**19**) 20
(**17**)	Im*	(**18**) 73	

* Im = imidazol-1-yl.

reaction conditions directly comparable with those of xanthate esters, we demonstrated that formation of thionocarbazate (**5**) from the imidazole (**7**) was unaffected by increasing temperature and *N,N*-dimethylhydrazine concentration. A series of simple control experiments showed that the thionocarbazate (**5**) could be recovered unchanged when dissolved in *N,N*-dimethylhydrazine as solvent at 60 °C, either in the presence or absence of added imidazole or 2-methylpropanethiol. Thionocarbamate formation *via* the product thionocarbazate (**5**) is therefore excluded. We have also shown that addition of 2-methylpropanethiol in equimolar amount with the imidazole (**7**) produces no observable change in the reaction with *N,N*-dimethylhydrazine.

The above experiments lend support to the series of possible pathways and intermediates set out in the Scheme. The first step in the sequence is common to both derivatives and involves attack by the dimethylamino group of the hydrazine to form a tetrahedral intermediate. That this is, in fact, the more nucleophilic of the two nitrogen atoms finds precedent in the ring opening of propene oxide[5] to give (**20**) and in the products derived from Michael addition to a variety of unsaturated systems.[6] At this stage a divergence may occur depending on the nature of the leaving group expelled. We therefore consider that reaction of a thiocarbonylimidazole involves expulsion of imidazole and formation of the neutral zwitterionic species (**21**), which can subsequently undergo either inter- or intra-molecular



Scheme.

rearrangement to give the thionocarbazate. On the other hand, reactions of xanthate esters involve thiolate anion as the leaving group and hence lead to the positively charged intermediate (**22**). Since rearrangement of (**22**) to a protonated thionocarbazate will probably require a higher activation energy than for (**21**), a secondary bimolecular attack of thiolate anion or dimethylhydrazine can intervene, thus, leading to the formation of the observed thionocarbamates.

Evidence in favour of this rationalisation comes from reaction of *O*-ethyl *S*-benzyl dithiocarbonate (**9**) with *N,N*-dimethylhydrazine in the presence of a five-fold excess of potassium toluene-α-thiolate. Under these conditions, it was possible to suppress completely the formation of the thionocarbazate (**11**) and to obtain a corresponding increase in the 'abnormal' thionocarbamate (**12**) (70%).

Experimental

M.p.s were determined on a Reichert hot-stage and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 141 MC machine, and i.r. spectra taken on a Perkin-Elmer 297 instrument. N.m.r. spectra were determined on Varian T-60 and EM 360 L instruments using [^{2}H]chloroform as solvent and tetramethylsilane as internal standard. Mass spectra were recorded on AEI MS-9 and AEI MS-50 instruments and u.v. spectra by a Jobin-Yvon Duospac 203 spectrometer. T.l.c. was carried out on Kieselgel F 1500 LS 254 silica. All solvents and reagents were purified and dried by standard techniques.

Preparation of O-*Alkyl* S-*Alkyl Dithiocarbonate* (*Xanthate*) *Esters*.—The following compounds were prepared by standard procedures and authenticated by comparisons with literature data: 3β-(methylthio)thiocarbonyloxy-5α-cholestane (**4**), m.p. 84—85 °C (lit.,[7] 87.5—88 °C); *O*-ethyl *S*-methyl dithiocarbonate (**8**);[8] *O*-decyl *S*-methyl dithiocarbonate[9] (**13**); *O*-ethyl *S*-benzyl dithiocarbonate[10] (**9**); *O*-octadecyl *S*-methyl dithiocarbonate (**16**), m.p. 35—36 °C (lit.,[11] 38—39 °C).

Preparation of N-(*Alkoxythiocarbonyl*)*imidazole Derivatives*.—The following compounds were prepared by reaction of the appropriate alcohol with *N,N'*-thiocarbonyldi-imidazole according to literature methods and characterised by comparison of their physical and spectral properties with literature data: 1-ethoxythiocarbonylimidazole (**10**), m.p. 29 °C (lit.,[12] 30 °C); 1-octadecyloxythiocarbonylimidazole (**17**), m.p. 38.5—40 °C (lit.,[13] 39—40 °C); 1-(5α-cholestan-3β-yloxythiocarbonyl)imidazole (**7**), m.p. 151—152 °C (lit.,[13] 151—152 °C); $[\alpha]_D^{20}$ −57.2° (*c*, 0.8).

Preparation of N-*Alkoxythiocarbonyl*-N,N-*dimethylamine Derivatives*.—Reaction of the appropriate xanthate ester with an excess of dimethylamine by literature methods furnished the required derivatives which were characterised either by comparison of their physical and spectral properties with literature data or as indicated below: *N*-ethoxythiocarbonyl-*N,N*-dimethylamine[14] (**12**); N-(5α-*cholestan*-3β-*yloxythiocarbonyl*)-N,N-*dimethylamine* (**6**), m.p. 175 °C (ether–ethanol), $[\alpha]_D^{20}$ +12.3 (*c*, 1.0, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 130 and 1 050 cm^{-1}); $\lambda_{max.}$(EtOH) 251nm (ε 19 900); δ($CDCl_3$) 3.1 (3 H, s, NMe), 3.3 (3 H, s, NMe), and 5.2 (1 H, m, 3αH); *m/z* 476 (M^+), 369, and 106 (Found: C, 76.65; H, 11.1; N, 2.15; O, 3.35; S, 6.83%. $C_{30}H_{53}NOS$ requires C, 75.74; H, 11.23; N, 2.94; O, 3.43; S, 6.74%). N-(*n-decyloxythiocarbonyl*)-N,N-*dimethylamine* (**15**), b.p. 180 °C at 0.05 mmHg, $\nu_{max.}$(film) 1 520, 1 380, 1 290, and 1 190 cm^{-1}; δ($CDCl_3$) 0.86 (3 H, m, CH_3), 1.28 [16 H, s, $(CH_2)_n$], 3.05 (3 H, s, NCH_3), 3.30 (3 H, s, NCH_3), and 4.30 (2 H, t, CH_2O); *m/z* 246 (MH^+), 245, 212, 108, 107, 106, 105, 88, and 72 (Found: C, 63.4; H, 11.1; N, 6.0; S, 12.9%. $C_{13}H_{27}NOS$ requires C, 63.62; H, 11.09; N, 5.71; S, 13.06%). N-*octadecyloxythiocarbonyl*-N,N-*dimethylamine* (**19**), m.p. 43—44 °C (methanol), $\nu_{max.}$(Nujol) 1 520, 1 280, 1 190, and 1 150 cm^{-1}; δ($CDCl_3$) 0.87 (3 H, m, CH_3), 1.22 [16 H, s, $(CH_2)_n$], 3.05 (3 H, s, NCH_3), 3.27 (3 H, s, NCH_3), and 4.33 (2 H, t, CH_2O); *m/z* 357 (M^+), 324, 297, 252, 194, 108, 107, 106, and 105 (Found: C, 70.64; H, 12.05; N, 3.93; S, 8.69%. $C_{21}H_{43}NOS$ requires C, 70.52; H, 12.12; N, 3.92; S, 8.9%).

Reaction of Xanthate Esters with N,N-*Dimethylhydrazine: General Procedure*.—A solution of the xanthate ester (5 mmol) in 1,1-dimethylhydrazine (15 ml, 252 mmol) as solvent was heated at 60 °C until reaction was complete as judged by t.l.c. (2.5—3 h). Excess of dimethylhydrazine was then evaporated under reduced pressure and the residue thus obtained purified by silica gel column chromatography. Progressive elution using a pentane–ether gradient gave firstly the derived thiocarbamate and then the analogous thiocarbazate. 3β-(Methylthio)thiocarbonyloxy-5α-cholestane (**4**) with 1,1-dimethylhydrazine gave *N*-(5α-cholestan-3β-yloxythiocarbonyl)-*N,N*-dimethylamine (**6**) (48%) whose physical and spectral properties were identical with the above prepared sample and N-(5α-*cholestan*-3β-*yloxythiocarbonyl*)-N',N'-*dimethylhydrazine* (**5**) (31%), m.p. 182—184 °C (ether–methanol), $[\alpha]_D^{20}$ +8.0° ($CHCl_3$, *c* 1.0), $\nu_{max.}$(Nujol) 3 160, 1 540, 1 200, 1 150, and 1 040 cm^{-1}; δ($CDCl_3$), 2.55 (6 H, s, NMe_2), 5.20 (1 H, m, H-3), 7.20 (1 H, s, exch. with D_2O, NH); *m/z* 490 (M^+), 388, 371, and 370; $\lambda_{max.}$(EtOH) 248nm (ε 11 800) (Found: C, 72.25; H, 11.15; N, 6.1. $C_{30}H_{54}N_2OS$ requires C, 73.42; H, 11.09; N, 5.71%).

O-Ethyl *S*-methyl dithiocarbonate (**8**) with 1,1-dimethylhydrazine gave *N*-ethoxythiocarbonyl-*N,N*-dimethylamine (**12**) (33%) identical with the sample prepared above and *N*-ethoxythiocarbonyl-*N',N'*-dimethylhydrazine (**11**) (53%), m.p. 81 °C (ether–hexane) (lit.,[2] 82—83 °C), $\nu_{max.}$($CHCl_3$), 3 300, 1 440, 1 370, 1 150, and 1 130 cm^{-1}; δ($CDCl_3$) 1.3 (3 H, t,

CH_3), 2.6 [6 H, s, $N(CH_3)_2$], 4.6 (2 H, q, CH_2), and 7.3 (1 H, s, exch. with D_2O, NH); *m/z* 149 ($MH^{+\cdot}$), 148 ($M^{+\cdot}$), 107, 106, 60, and 59. The spectral properties of a sample of (**11**) prepared by the literature method were identical with those reported above. Use of *O*-ethyl *S*-benzyl dithiocarbonate (**9**) also gave (**12**) (37%) and (**11**) (55%). *O*-Decyl *S*-methyl dithiocarbonate (**13**) with 1,1-dimethylhydrazine gave *N*-decyloxythiocarbonyl-*N*,*N*-dimethylamine (**15**) (26%) identical with the previously prepared sample and N-*decyloxythiocarbonyl*-N′,N′-*dimethylhydrazine* (**14**) (36%), m.p. 54—55 °C (pentane), $\nu_{max.}$(Nujol) 3 170, 1 220, 1 190, 1 150, and 1 000 cm^{-1}; $\delta(CDCl_3)$ 0.86 (3 H, t, CH_3), 1.26 [16 H, s, $(CH_2)_n$], 2.58 [6 H, s, $N(CH_3)_2$], and 4.46 (2 H, m, CH_2O); *m/z* 261 ($MH^{+\cdot}$), 260 ($M^{+\cdot}$), 246, 218, 120, 78, and 59 (Found: C, 59.85; H, 10.65; N, 10.9; S, 12.25. $C_{13}H_{28}N_2OS$ requires C, 59.95; H, 10.84; N, 10.76; S, 12.31%).

O-n-Octadecyl *S*-methyl dithiocarbonate (**16**) with 1,1-dimethylhydrazine gave *N*-(n-octadecyloxythiocarbonyl)-*N*,*N*-dimethylamine (**19**) (20%) whose physical and spectral properties were identical with the sample described above and N-(*n-octadecyloxythiocarbonyl*)-N′,N′-*dimethylhydrazine* (**18**) (58%), m.p. 78—80 °C (dichloromethane–hexane), $\nu_{max.}$(Nujol) 3 150, 1 520, 1 220, 1 200, 1 160, and 1 050 cm^{-1}; $\delta(CDCl_3)$ 0.90 (3 H, t, CH_3), 1.25 [32 H, s, $(CH_2)_n$], and 2.55 [6 H, s, $N(CH_3)_2$]; $\lambda_{max.}$(EtOH) 246 nm (ε 9 700); *m/z* 372 (M^+), 252, 121, 120, and 97 (Found: C, 67.2; H, 11.9; N, 7.6; S, 8.45. $C_{21}H_{44}N_2OS$ requires C, 67.70; H, 11.90; N, 7.52; S, 8.55%).

Reaction of 1-*Alkoxythiocarbonylimidazole Derivatives with* N,N-*Dimethylhydrazine: General Procedure.*—1,1-Dimethylhydrazine (0.76 ml, 10 mmol) was added to a solution of the appropriate 1-alkoxythiocarbonylimidazole derivative (10 mmol) in dry benzene (16 ml) and the reaction mixture was stirred at room temperature until complete as judged by t.l.c. (5.5—6 h). The reaction mixture was then diluted with a large volume (≃ 100 ml) of dichloromethane and the organic phase washed successively with water and brine and then dried over sodium sulphate. Removal of solvent under reduced pressure gave a residue which was recrystallised. The yield of thiocarbazate for each compound prepared by this procedure is given in parentheses. In each case the physical and spectroscopic properties were identical with those of samples prepared above: *N*-ethoxythiocarbonyl-*N*′,*N*′-dimethylhydrazine (**11**) (50%); *N*-(n-octadecyloxythiocarbonyl)-*N*′,*N*′-dimethylhydrazine (**18**) (73%); *N*-(5α-cholestan-3β-yloxythiocarbonyl)-*N*′,*N*′-dimethylhydrazine (**5**) (82%).

Reaction of N-(5α-*Cholestan*-3β-*yloxythiocarbonyl*)-N′,N′-*dimethylhydrazine* (**5**) *with an Excess of* 1,1-*Dimethylhydrazine.*—A solution of the thionocarbazate (**5**) (120 mg, 0.24 mmol) in 1,1-dimethylhydrazine (0.7 ml, 0.91 mmol) was heated at 60 °C for 6 h. Removal of excess of 1,1-dimethylhydrazine under reduced pressure gave essentially unchanged starting material. Similar experiments in the presence of imidazole (1 mmol equiv.) or 2-methylpropanethiol (1 mmol equiv.) gave the same result.

Reaction of 1-(5α-*Cholestan*-3β-*yloxythiocarbonyl*)*imidazole* (**7**) *with an Excess of* 1,1-*Dimethylhydrazine in the Presence of* 2-*Methylpropanethiol.*—The imidazolide (**7**) (305 mg, 0.61 mmol) was added portionwise to a solution of 2-methylpropanethiol (55 mg, 0.61 mmol) in 1,1-dimethylhydrazine (1.85 ml, 24 mmol) maintained in an oil-bath at 60 °C, and heating was continued for 1 h. Removal of excess of 1,1-dimethylhydrazine under reduced pressure followed by dilution with dichloromethane and successive partitioning between water and then brine gave an organic extract which was dried over sodium sulphate. Removal of solvent and chromatography gave the thionocarbazate (**5**) (260 mg, 87%) described above.

Reaction of O-*Ethyl* S-*Methyl Dithiocarbonate* (**8**) *with* 1,1-*Dimethylhydrazine in the Presence of an Excess of* 2-*Methylpropanethiol.*—A solution of the xanthate (**8**) (820 mg, 6 mmol) in a mixture of 1,1-dimethylhydrazine (24 ml, 316 mmol) and 2-methylpropanethiol (10 ml, 92 mmol) was heated for 3 h at 60 °C, and excess of reagents were then removed by careful distillation under reduced pressure. N.m.r. analysis of the residue indicated that the thionocarbamate (**12**) and the thionocarbazate (**11**) were formed in the same proportions as in the absence of the thiol (**12**)/(**11**) = 38/62.

Reaction of O-*Ethyl* S-*Benzyl Dithiocarbonate* (**9**) *with* 1,1-*Dimethylhydrazine in the Presence of Potassium Toluene-α-thiolate.*—To a suspension of potassium toluene-α-thiolate, prepared from potassium hydride (523 mg, 13 mmol) and toluene-α-thiol (1.54 ml, 13.1 mmol) in 1,1-dimethylhydrazine (8.1 ml, 106 mmol) was added portionwise with stirring the xanthate (**9**) (554 mg, 2.61 mmol); the reaction mixture was then heated at 60 °C for 3 h. Excess of reagents were removed under reduced pressure and the residue was diluted with water and thoroughly extracted with ether. The combined ethereal extracts were washed with brine and dried over sodium sulphate. Removal of solvent gave a residue containing the thionocarbamate (**12**) (70%) by n.m.r. analysis. The thionocarbazate (**11**) was not detected in the reaction mixture.

References

1 For leading references see: R. F. Hudson, *Angew. Chem., Int. Ed. Engl.*, 1973, **12**, 36; J. Hine and P. Dalsin, *J. Am. Chem. Soc.*, 1972, **94**, 6998; F. Fillipini and R. F. Hudson, *J. Chem. Soc., Chem. Commun.*, 1972, 522.
2 K. A. Jensen, V. Anthoni, and A. Holm, *Acta Chem. Scand.*, 1969, **23**, 1916.
3 D. H. R. Barton, C. Chavis, M. K. Kaloustian, P. D. Magnus, G. A. Poulton, and P. J. West, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1571.
4 A. G. M. Barrett, P. A. Prokopiou, and D. H. R. Barton, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1510 and references therein.
5 R. C. Slagel, *J. Org. Chem.*, 1968, **33**, 1374.
6 A. Le Berre and C. Porte, *Bull. Soc. Chim. Fr.*, 1978, 602.
7 G. L. O'Connor and H. R. Nace, *J. Am. Chem. Soc.*, 1952, **74**, 5454.
8 H. S. Fry, *J. Am. Chem. Soc.*, 1906, **28**, 796.
9 T. Kawata, K. Harano, and T. Taguchi, *Chem. Pharm. Bull.*, 1973, **21**, 604.
10 I. B. Douglass and T. B. Johnson, *J. Am. Chem. Soc.*, 1938, **60**, 1486; W. H. Dietsche, *Tetrahedron*, 1967, **23**, 3049.
11 D. L. Vincent and C. B. Purves, *Can. J. Chem.*, 1956, **34**, 1302.
12 H. A. Staab and G. Walter, *Liebigs Ann. Chem.*, 1962, **657**, 98.
13 D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1574.
14 Y. Kinoshita, M. Misaka, S. Kubota, and H. Ishikawa, *Agric. Biol. Chem.*, 1972, **36**, 1975.

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