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Catalytic Rearrangement of *O*-Cholesteryl *S*-Alkyl Dithiocarbonates to *S*-Alkyl *S*-Cholesteryl Dithiocarbonates by Phenols

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Phenolysis of *O*-cholesteryl *S*-alkyl dithiocarbonates gave the corresponding *S*-alkyl *S*-cholesteryl dithiocarbonates. The rearrangements obeyed first-order rate laws and the rates were affected by the acidity of the phenols. A plot of the substituent effect of the *S*-alkyl moiety against the Tafts σ^* values was roughly linear. *ortho*-Substituted phenols such as 2-chlorophenol or 2,6-dimethylphenol considerably retarded the rearrangement. The role of phenols and the reaction behavior of *O*-cholesteryl *S*-alkyl dithiocarbonates are discussed on the basis of kinetic and molecular orbital calculation data indicating that the rearrangement may proceed by specific solvation of phenols at the thiocarbonyl sulfur atom.

Keywords——*O*-cholesteryl *S*-alkyl dithiocarbonate; homoallylic participation; phenol-catalyzed rearrangement; *S*-cholesteryl *S*-alkyl dithiocarbonate; hydrogen bonding; phenolysis; frontier molecular orbital; reaction rate

Introduction

In the previous paper,[1] it was reported that various *O*-(2-alkenyl or 2-cycloalkenyl) *S*-alkyl dithiocarbonates (**1**) underwent [3,3]-sigmatropic rearrangement to *S*-(2-alkenyl or 2-cycloalkenyl) *S*-alkyl dithiocarbonates (**3**) through an intramolecular cyclic transition state

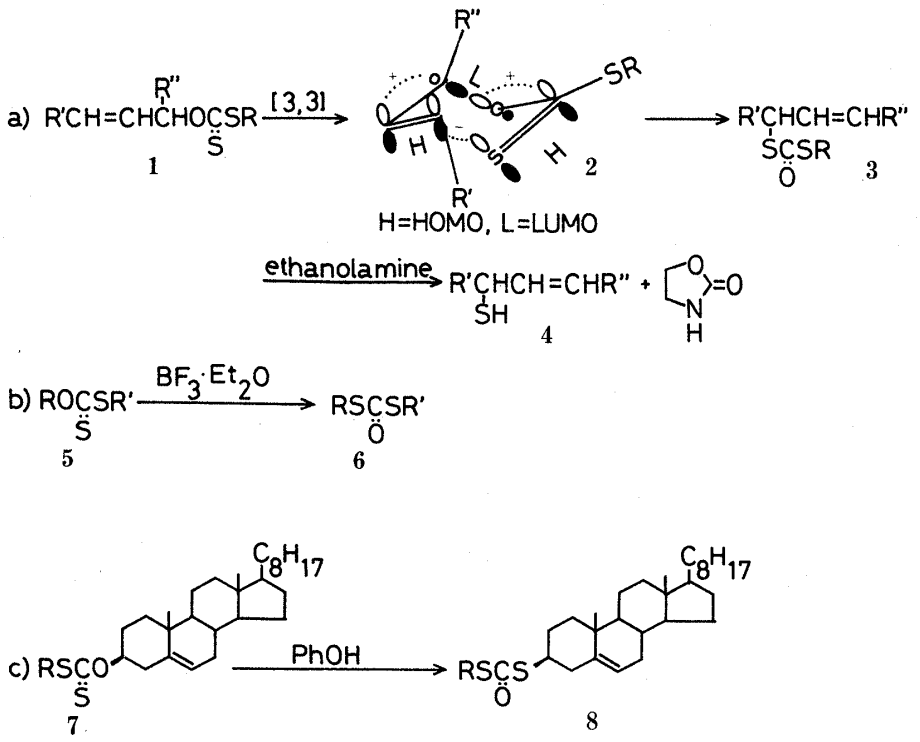


Chart 1

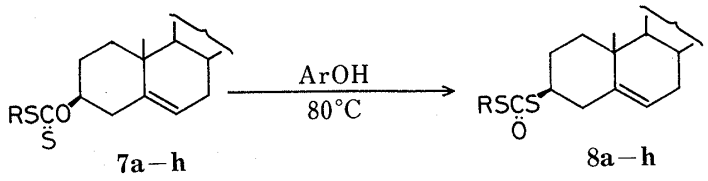
(**2**). Combination of this rearrangement reaction with a procedure[2] in which thiols are easily generated from thiol esters by heating with 2-aminoethanol is of synthetic value for the stereoselective construction of unsaturated systems *via* some allylic thiols (**4**) which might otherwise be difficult to prepare (reaction a in Chart 1).[3]

On the other hand, Lewis acids and more rarely protonic acids have been used to cause catalytic rearrangment of thione esters (**5**) to thiol esters (**6**) (reaction b in Chart 1).[4] In this connection, one of the authors reported that pyrolysis of *O*-cholesteryl *S*-alkyl dithiocarbonates (**7**) in a phenolic solvent such as phenol or cresol caused rearrangement to the corresponding *S*-alkyl *S*-cholesteryl dithiocarbonates (**8**) with retention of configuration[1b] (reaction c in Chart 1). However, in spite of the usefulness of the reaction from a synthetic standpoint, the role of the phenols has remained obscure. Therefore, a study was undertaken to investigate the catalytic activities of phenolic compounds in the thermal rearrangment of *O*-cholesteryl *S*-alkyl dithiocarbonates (**7**).

Results

Preparation of Starting Materials and Phenolysis of *O*-Cholesteryl *S*-Alkyl Dithiocarbonates (7)

A series of *O*-cholesteryl *S*-alkyl dithiocarbonates (**7**) was synthesized according to the reported method.[1c] *O*-Cholesteryl *S*-alkyl dithiocarbonates (**7**) treated in this study include the ethyl (**7a**), methyl (**7b**), benzyl (**7c**), *p*-chlorobenzyl (**7d**), diphenylmethyl (**7e**), *p*-nitrobenzyl (**7f**), methoxycarbonylmethyl (**7g**), and cyanomethyl (**7h**) derivatives.



7—8 **a**: R = C_2H_5, **b**: R = CH_3, **c**: R = $C_6H_5CH_2$, **d**: R = *p*-$ClC_6H_4CH_2$
e: R = $(C_6H_5)_2CH$, **f**: R = *p*-$NO_2C_6H_4CH_2$, **g**: R = CH_3OCOCH_2
h: R = CH_2CN

Chart 2

Heating of these *O*-cholesteryl *S*-alkyl dithiocarbonates (**7**) with phenol at 80—120 °C gave the corresponding *S*-alkyl *S*-cholesteryl dithiocarbonates (**8**). Under more severe reaction conditions, a small amount of 3,5-cholestadiene (**9**) was found in the crude products.

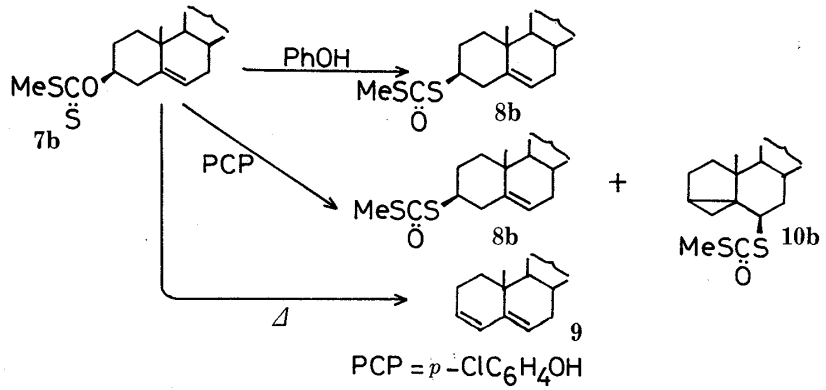


Chart 3

When *O*-cholesteryl *S*-alkyl dithiocarbonates (**7**) were heated under similar conditions without any phenols, no detectable change was observed. In a more acidic phenol, *e.g.*, *p*-chlorophenol, a small amount of 6-substituted 3,5-cyclosteroid (*i*-steroid) (**10b**) was isolated. Inspection of the nuclear magnetic resonance (NMR) spectrum of the product formed by the phenolysis of *O*-cholesteryl *S*-methyl dithiocarbonate (**7b**) by *p*-chlorophenol at 80 °C showed the characteristic cyclopropane ring protons near the tetramethylsilane (TMS) signal.

The axial or equatorial nature of protons adjacent to the alkyldithiocarbonyl moiety can be determined based on observation of the half-band width ($W_{1/2}$) of the proton signal compared with the data for similarly constituted steroids bearing an acetoxy group.[5a)]

Phenolysis Rates for *O*-Cholesteryl *S*-Alkyl Dithiocarbonates (7)

The rates of phenolysis for *O*-cholesteryl *S*-alkyl dithiocarbonates (**7**) were determined spectroscopically at several temperatures between 60 and 75 °C by measuring the decrease of the thione chromophore at 350 nm. Good first-order behavior was observed for each run. The energies and entropies of activation were calculated from these data. The results are summarized in Tables I and II.

As can be seen in Table II, phenols bearing an electron-attracting substituent at the *para*-position accelerate the reaction, whereas phenols with an electron-donating substituent retard the rearrangement. The rate constants in *ortho*-substituted phenols are smaller than those in the corresponding *para*-substituted phenols as evidenced by the data for chloro- and methyl-

Table I. Reaction Rates and Activation Parameters for Phenolysis of *O*-Cholesteryl *S*-Methyl Dithiocarbonate (**7b**) in Some Phenols

Solvent	Temp. (°C)	$k \times 10^6$ (s^{-1})	ΔE (kcal·mol^{-1})	$\Delta S^{\neq}$ (e.u.)
Phenol	57.1	8.51		
	61.7	12.80	23.6	−12.7
	66.4	21.06		
	71.0	36.37		
p-Cresol	57.1	3.67		
	61.7	5.19	23.2	−15.7
	66.4	10.70		
	71.0	14.07		
p-Chlorophenol	57.1	42.59		
	61.7	48.79	22.4	−13.9
	66.4	83.04		
	71.0	127.1		

e.u., entropy unit.

Table II. Rearrangement Rate for *O*-Cholesteryl *S*-Methyl Dithiocarbonate (**7b**) in Various Phenols (Ar-OH) at 71 °C

Ar	pK_a[a)]	$k \times 10^6$ (s^{-1})
4-Methylphenyl	10.3	14.1
Phenyl	10.0	36.4
4-Bromophenyl	9.81	95.6
4-Chlorophenyl	9.38	127
2-Methylphenyl	10.4	3.04
2-Chlorophenyl	8.48	2.62
2,6-Dimethylphenyl	10.6	1.15

a) Reported values: G. Kortum, W. Vogel and K. Andrussov, *Pure Appl. Chem.*, **1**, 190 (1961).

substituted phenols: the rate retardation in going from a *para*-substituted phenol to an *ortho*-substituted phenol is larger with the chloro substituent than with the methyl one (ratios of k_{para}/k_{ortho} for chloro and methyl substituents are 48 and 3, respectively). Among the *mono*-substituted phenols examined, the rate for *o*-chlorophenol in which the hydroxy group is intramolecularly fixed by a hydrogen bridge[5b] is the smallest, while that of *p*-chlorophenol is the largest. It should be noted that the rate may also be reduced by the steric interference of *ortho*-substituents. *ortho*-Disubstituted phenols, *e.g.*, 2,6-dimethylphenol, showed the smallest catalytic capacity in the rearrangement reaction. The methyl groups might prevent the thiocarbonyl group from forming an intermolecular hydrogen bond with the hydroxy group of the phenol.

These observations suggest that the hydrogen bonding to the thione sulfur contributes to the driving force for the rearrangement reaction.

Discussion

In previous studies on the phenolysis rates for alkyl halides such as *tert*-butyl chloride, it has been demonstrated that phenol is an unusual solvolytic solvent, which can provide marked electrophilic assistance (by hydrogen bonding) to the ionization of the substrate.[6a]

Recently, Okamoto *et al.* have made a quantitative assessment of the ionizing power of phenolic solvents by the use of 1-adamantyl bromide and *p*-toluenesulfonate. They observed significant deviations in the correlation of the solvolysis rates of 1-adamantyl derivatives with *Y*-values, and suggested that these deviations may be attributed to electrophilic assistance by hydrogen bonding of the phenolic solvents to the leaving group.[6b]

Thus, attention has been focused on the phenolysis behavior of typical substrates (*e.g.* those cited above) from a theoretical viewpoint. To our knowledge, few reports dealing with the phenolysis of thione esters have appeared.

Pocker showed that phenols catalyzed the solvolysis reaction of *tert*-butyl halide in the presence of pyridine in nitromethane, and the rates could be expressed in the form: $10^5 \times k_1 = 0.367 + k_2 \times [\mathrm{ArOH}]$. The values of $10^5 \times k_2$ have been used as a measure of the hydrogen bonding capacity to assist the ionization of *tert*-butyl halide.[7] As shown in Fig. 1, a plot of the rearrangement rate against the values of the catalytic coefficient, $10^5 k_2$, is roughly linear for our data, suggesting that hydrogen bonding plays an important role in the rearrangement.

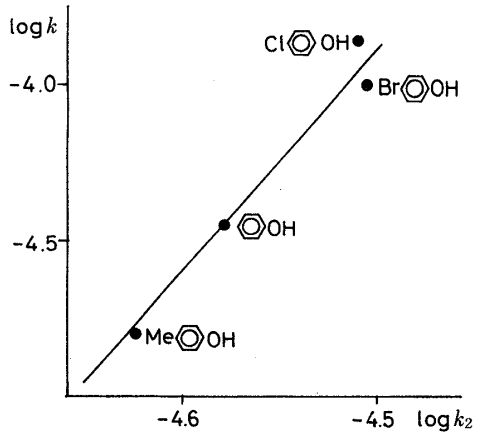


Fig. 1. Plot of Phenolysis Rates against Catalytic Coefficients ($10^5 k_2$)[8] of Some Phenols

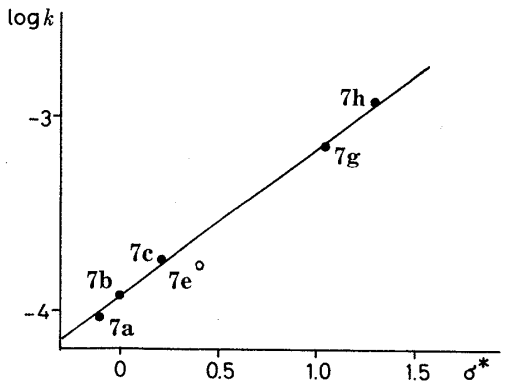


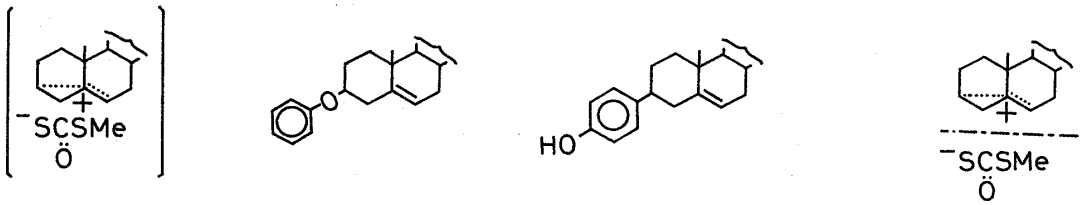
Fig. 2. Plot of log *k* against σ^* for Phenolysis of *O*-Cholesteryl *S*-Alkyl Dithiocarbonates with *p*-Chlorophenol

The least-squares slope (ρ) of the line (neglecting the point for **7e**) is 0.747 ($r = 0.997$).

TABLE III. Substituent Effect of *O*-Cholesteryl *S*-Alkyl Dithiocarbonates (7) and Comparison of the Rates with the Pyrolysis Rates[a]

R	Phenolysis $k \times 10^{6}$ [b]	Phenolysis ΔE [c]	Phenolysis ΔS^{*} (e.u.)	Pyrolysis[a] $k \times 10^{4}$ [d]
Ethyl (**7a**)	93	22.4	−14	120
Methyl (**7b**)	127	22.4	−14	143
Benzyl (**7c**)	197	24.3	−7.0	214
4-Chlorobenzyl (**7d**)	218	23.7	−8.4	295
Diphenylmethyl (**7e**)	168	13.9	−38	495
4-Nitrobenzyl (**7f**)	232	26.3	−1.1	623
Methoxycarbonylmethyl (**7g**)	707			
Cyanomethyl (**7h**)	1168			

a) See ref. 13. *b*) Values at 71.0 °C, s^{-1}. *c*) kcal·mol^{-1}. *d*) Values at 176 °C, min^{-1}.



11 12 13 14

Fig. 3. Possible Intermediates and Phenolysis Products

It should be noted that there is a trend in the reactivity of the thione esters (**7**), namely, the more electronegative the *S*-alkyl group, the more reactive is the thione ester. The substituent effect is shown in Fig. 2, in which the rate constants for the rearrangement of the various thione esters are plotted against the Tafts σ^{*} values. The plot is approximately linear.[8]

As can be seen in Table III, the rearrangement rate was not appreciably affected by change of the *S*-alkyl group in comparison with the corresponding pyrolysis rate (Chugaev reaction). The influence of the alkylthio group is presumably due to an inductive electron-attracting effect, which assists the ionization of the C–O bond of **7**. However, the value for the diphenylmethyl compound (**7e**) deviates considerably from that expected for an inductive effect.

The interpretation of substituent effects in rearrangement reactions is complicated by the difficulty encountered in separating electronic from steric effects. In a fairly rigid system, such as the present case, steric effects may be predominant. Their influence on the reactivity of the rearrangement must be due to a combination of inductive and steric effects which nearly cancel. In fact, the activation entropy of **7e** is considered to depend on the steric effects[9] (see Fig. 2).

In the present investigation, the rate increases with increasing ionizing power of the phenol used, indicating that the rearrangement might proceed *via* an ionic intermediate, *e.g.* an intimate ion-pair (**11**) (Fig. 3), in which the cation and anion lie in a common solvent shell. In the case of nonsubstituted phenol, the force of attraction is not great enough to produce the free carbonium ion. Therefore, the observed product at C-3 seems likely to arise by the formation and rapid collapse of an ion-pair, which retains the stereochemistry of the parent compound. In contrast, *p*-chlorophenol is far more reactive and, therefore, the ion-pair may have a loose structure. Thus, owing to its longer lifetime, it survives long enough to permit attack at C-6, resulting in the formation of the *i*-steroid product (**10b**). However, the phenol

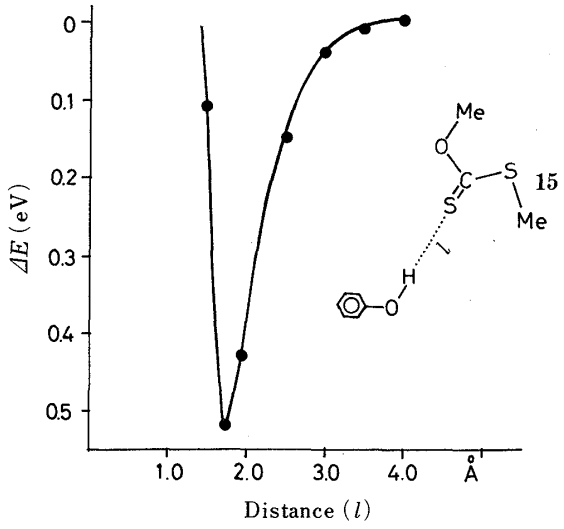


Fig. 4. Change of the Total Energy Due to the Hydrogen Bonding between *O,S*-Dimethyl Dithiocarbonate and Phenol

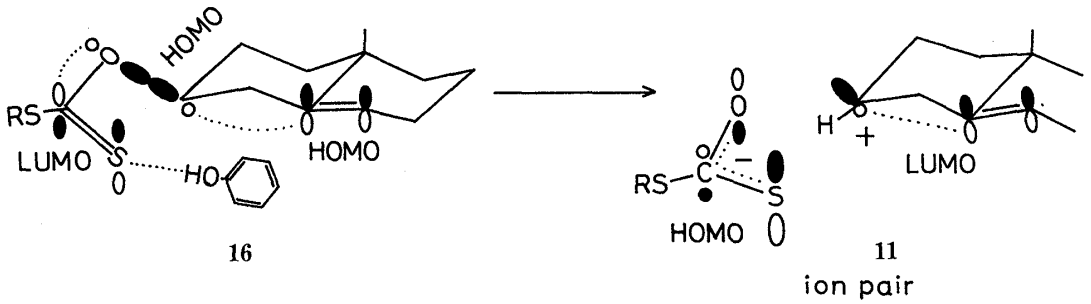


Fig. 5. The Proposed Transition State for the Phenolysis of *O*-Cholesteryl *S*-Alkyl Dithiocarbonates

ether (**12**) or alkylated phenol (**13**), which might be formed intermolecularly from the solvent-separated ion-pair intermediate (**14**) or free carbonium ion, could not be detected. From the above results, it is concluded that intermolecular hydrogen bonding to the thiocarbonyl group does play a leading role in the rearrangement.

In order to confirm this assumption, molecular orbital (MO) calculations were carried out using the CNDO/2 method.[10] For simplicity, *O,S*-dimethyl dithiocarbonate (**15**) was selected as the model compound. In the calculation, phenol was considered to approach the sulfur atom of C=S along the axis[11] through the C=S bond, which is varied from 4.0 to 1.5 Å. The net charge on the sulfur atom increases with decreasing distance of the hydrogen bridge, resulting in polarization of the C=S double bond. The total energy (E_{total}) for the interaction of phenol and thione ester decreases with decrease of the distance between the hydrogen and sulfur atoms to stabilize the reaction system, and has the minimum value at 1.75 Å, which is more stable by 12.5 kcal/mol than that at 4.0 Å. The ultraviolet (UV) spectral data qualitatively supports the calculation data, *i.e.*, there is a large blue shift [λ_{max}(benzene) − λ_{max}(*p*-chlorophenol) = 19.5 nm] of the absorption band (n–σ^*) at 335.5 nm in *p*-chlorophenol.

In conclusion, the catalytic activity of phenol is probably a consequence of the formation of a complex of the type RO(RS)C=S···HOAr between the catalyst and substrate. Such a complex should dissociate much more readily than the thione ester itself.

The rearrangement can be understood in terms of the acyclic three-system interaction (**16**)[12] as depicted in Fig. 5. In this case, a hydrogen-bonded thiocarbonyl group works as a strong acceptor[12] and the homoallylic system as a strong donor to allow the through-space

interaction to be effective, and consequently the C–O bond releases to produce an ion-pair (**11**) through which the rearrangement takes place intramolecularly.

Experimental

The melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. The UV spectra were determined with a Hitachi EPS-3T and a JASCO UVIDEC-220B digital spectrophotometer. The NMR spectra were taken with a JEOL PS-100 spectrophotometer with tetramethylsilane as an internal standard and the chemical shifts are expressed in δ values. The infrared (IR) spectra were taken with JASCO IRA-1 and DS-301 grating spectrophotometers. All the calculations were performed on FACOM M-200 and 382 computers at the computer center of Kyushu University.

Phenols——Phenols were obtained from commercial suppliers and were purified by distillation or by recrystallization.

Materials——*O*-Cholesteryl *S*-alkyl dithiocarbonates were prepared according to the reported method and were purified by column chromatography on silica gel.[1,13]

Kinetics——The phenolysis rates were followed at a given temperature by measuring the decrease of the thione absorption at 350 nm, using a 10×10 mm quartz cell which was thermostated with flowing water at constant temperature. The first-order rate constants were calculated from a plot of $\ln(A_t - A_\infty)$ *vs.* time by a least-squares method, where A_t is the absorbance at time t and A_∞ is the absorbance after about 10 half-lives. The absorption data were collected automatically. The results are listed in Tables I, II and III. All spectra were calculated by means of a nonweighted least-squares program written in FORTRAN.

Rearrangement of *O*-Cholesteryl *S*-Alkyl Dithiocarbonates (7) to the Corresponding *S*-Alkyl *S*-Cholesteryl Dithiocarbonates (8) in *p*-Chlorophenol. *S*-Cholesteryl *S*-Methyl Dithiocarbonate (8b)——A mixture of **7b** (1000 mg) and *p*-chlorophenol (3.0 ml) was heated at 80—90 °C on a water bath until the completion of the reaction had been confirmed by thin-layer chromatography (TLC). The product was extracted repeatedly (*ca.* five times) with *n*-hexane and the combined *n*-hexane extract was passed through a short column of silica-gel to remove a small amount of *p*-chlorophenol and unchanged starting material. The eluent was evaporated to leave a colorless solid. Several recrystallizations from ethyl acetate gave colorless needles, 565 mg. A further crystallization of the residue afforded an additional 128 mg, mp 158 °C for a total of 693 mg (69%); the product was identical with an authentic sample obtained by thermolysis in hydroquinone or phenol.[1b] The product was allowed to react with 2-aminoethanol at 120 °C to give cholesteryl disulfide, mp 145—146 °C.[1b]

The filtrate was subjected to chromatography on silica gel to give a colorless glass, 192 mg (19%). The elemental and proton nuclear magnetic resonance (^{1}H-NMR) analyses of this material indicated the presence of a small amount of the epimer.

The structure **10b** was assigned to the principal product on the basis of its ^{1}H-NMR spectrum. In addition to a singlet as δ 2.38 (S–Me) and a distorted triplet at δ 3.48, the spectrum showed a well-resolved multiplet at δ 0.25—0.60 ($J = 5$ Hz, two hydrogens) whose chemical shift and splitting corresponds to that expected for protons on the cyclopropane ring bearing the methylene group.[5a] The data obtained in a double-resonance experiment are as follows; NMR (in $CDCl_3$): 0.35 (1H, dd, $J_{gem} = 5$ Hz, $J_{H3,H4} = 5.6$ Hz, $>CH_2$ of cyclopropane ring), 0.55 (1H, t, $J_{gem} = 5$ Hz, $J_{H3,H4} = 4$ Hz, $>CH_2$ of cyclopropane ring), 2.38 (3H, s, S–Me), 3.48 (1H, br s, C_6-H (eq.)).

***S*-Cholesteryl *S*-Ethyl Dithiocarbonate (8a)**——Prepared from **7a** in 88% yield with work-up just as in the case of **7b**, mp 114—115.5 °C (ethanol–benzene). *Anal.* Calcd for $C_{30}H_{50}OS_2$: C, 73.43; H, 10.27. Found: C, 73.72; H, 10.21. IR (KBr): 1646 (C=O), 860 (C–S) cm^{-1}. NMR (in $CDCl_3$): 0.67 (3H, s, C_{19}-Me), 3.2—3.8 (1H, br, >CH–S), 1.28 (2H, t, $J = 7.8$ Hz, $-SCH_2-$), 2.98 (3H, d, –S–C–Me), 5.41 (1H, br d, =CH–).

***S*-Cholesteryl *S*-(*p*-Chlorobenzyl) Dithiocarbonate (8d)**——Prepared from **7d** in 89% yield with work-up as in the case of **7b**, mp 134—137.5 °C (ethanol–benzene). *Anal.* Calcd for $C_{35}H_{51}ClOS_2$: C, 71.57; H, 8.75. Found: C, 71.68; H, 8.79. IR (KBr): 1641 (C=O), 860 (C–S) cm^{-1}. NMR (in $CDCl_3$): 0.67 (3H, s, C_{19}-Me), 3.24—3.68 (1H, br, >CH–S), 4.15 (2H, S–CH_2–Ar), 5.4 (1H, br d, =CH–), 7.25 (4H, $-C_6H_4-$).

***S*-Cholesteryl *S*-Diphenylmethyl Dithiocarbonate (8e)**——Prepared from **7e** in 82% yield with work-up as in the case of **7b**, mp 115.5—117.5 °C (ethanol–acetone). *Anal.* Calcd for $C_{41}H_{56}OS_2$: C, 78.29; H, 8.97. Found: C, 78.46; H, 9.01. IR (KBr): 1642 (C=O), 860 (C–S) cm^{-1}. NMR (in $CDCl_3$): 0.66 (3H, s, C_{19}-Me), 3.24—3.66 (1H, br, >CH–S), 5.36 (1H, br d, =CH–), 6.05 (1H, s, –CH–Ph_2), 7.29 (10H, m, $2C_6H_5$).

***S*-Cholesteryl *S*-Cyanomethyl Dithiocarbonate (8h)**——Prepared from **7h** in 63% yield with work-up just as in the case of **7b**, mp 152—153 °C (ethanol–benzene). *Anal.* Calcd for $C_{30}H_{47}NOS_2$: C, 71.80; H, 9.44; N, 2.79. Found: C, 71.58; H, 9.35; N, 2.58. IR (KBr): 1648 (C=O), 843 (C–S), 2240 (CN) cm^{-1}. NMR (in $CDCl_3$): 0.67 (3H, s, C_{19}-Me), 3.2—4.0 (1H, br, >CHS–), 3.72 (2H, s, $-CH_2-CN$), 5.45 (1H, br d, =CH–).

***S*-Cholesteryl *S*-(Methoxycarbonylmethyl) Dithiocarbonate (8g)**——Prepared from **7g** in 94% yield with work-up as in the case of **7b**, mp 89—90 °C (ethanol–benzene). The rearrangement product was contaminated with a trace of impurity and was identified by conversion to cholesteryl disulfide. IR (KBr): 1643 (C=O), 860 (C–S), 1746 (C=O–

OMe) cm^{-1}. NMR (in $CDCl_3$): 0.67 (3H, s, C_{19}-Me), 3.20—3.90 (1H, br, >CH–S), 3.75 (2H, s, –S–CH_2–COO–), 5.36 (1H, br d, =CH–).

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11) M. R. Crampton, "The Chemistry of the Thiol Group: Acidity and Hydrogen-Bonding," ed. by S. Patai, John Wiley and Sons, Inc., New York, 1974, Chapter VIII.
12) S. Inagaki, H. Fujimoto and K. Fukui, *J. Am. Chem. Soc.*, **98**, 4693 (1976). In the acyclic D (donor)–D (donor)–A (acceptor) system, the HOMO–HOMO interaction between D's appreciably contributes to the stabilization in the presence of the third entity (A) interacting with one of them.
13) G. L. O'Connor and H. R. Nace, *J. Am. Chem. Soc.*, **75**, 2118 (1953).