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The Mesomorphic Behavior of Sulfur Containing Steroid Derivatives

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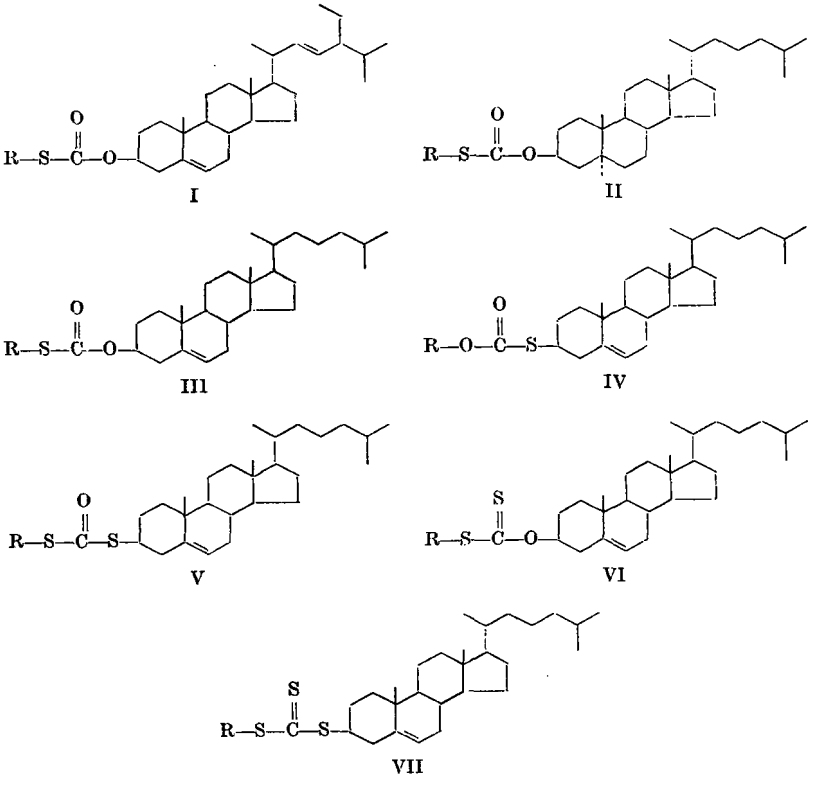
Abstract—Comparative studies have been made on the influence of substitution of oxygen by sulfur in some steroid derivatives. A survey is given on stigmasteryl S-alkyl thiocarbonates, 5α-cholestanyl S-alkyl thiocarbonates, cholesteryl S-alkyl thiocarbonates, S-cholesteryl O-alkyl thiocarbonates, S-cholesteryl S-alkyl dithiocarbonates, cholesteryl xanthates, and cholesteryl trithiocarbonates. Preparation, purification and mesomorphic behavior of the compounds are discussed, and the properties compared with those of the corresponding O-carbonates. Replacement of oxygen by sulfur in the carbonate group leads to an increase of the smectic-cholesteric transition temperature when going from the O-alkyl carbonate to the S-alkyl thiocarbonate. An even larger increase is observed when going from O-cholesteryl S-alkyl to S-cholesteryl O-alkyl thiocarbonate. An increase in the temperature range of the cholesteric mesophase is also found. Stigmasteryl S-alkyl thiocarbonates are only smectic. In the other series an increase in the temperature range of the cholesteric mesophase is observed.

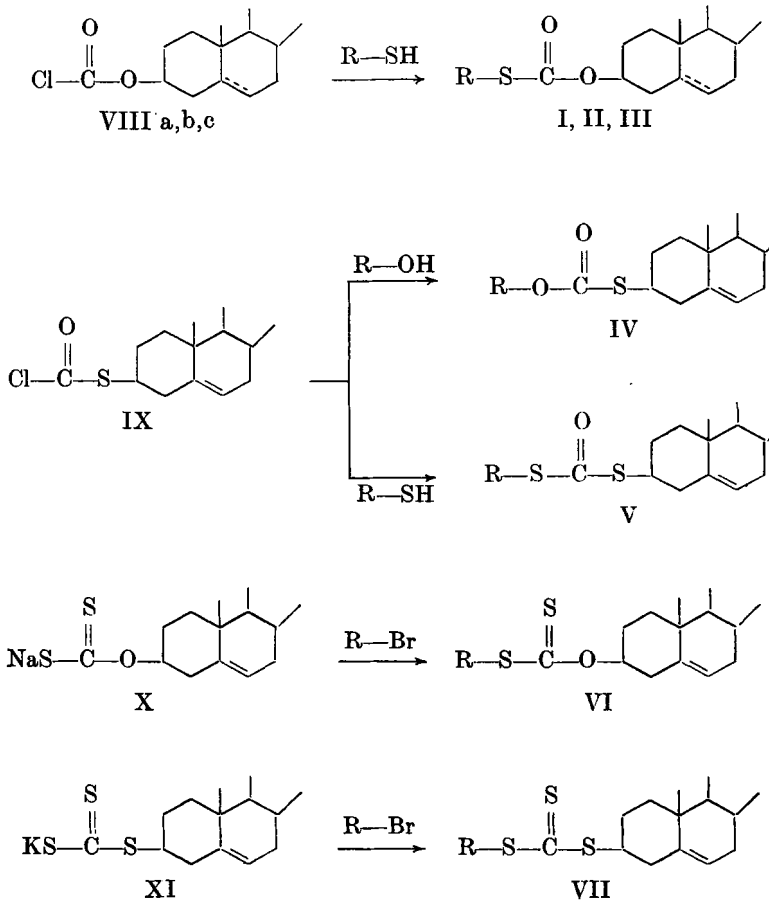
In earlier studies we described the preparation and mesomorphic behavior of cholesteryl alkyl carbonates[1] and stigmasteryl alkyl carbonates.[2] In the series of cholesteryl alkyl carbonates, enantiotropic high-temperature in addition to monotropic low-temperature color bands were observed. None of the stigmasteryl alkyl carbonates exhibited a cholesteric phase, but some of them displayed monotropic smectic phases. To determine whether replacement of oxygen in the carbonate group by sulfur would lead to significant changes in the mesomorphic behavior, representatives or complete homologous series of the following

3β-compounds were synthesized: Stigmasteryl S-alkyl thiocarbonates (I), 5α-cholestanyl S-alkyl thiocarbonates (II), cholesteryl S-alkyl thiocarbonates (III), S-cholesteryl O-alkyl thiocarbonates (IV), S-cholesteryl S-alkyl dithiocarbonates (V), cholesteryl alkyl xanthates (VI), and cholesteryl alkyl trithiocarbonates (VII).



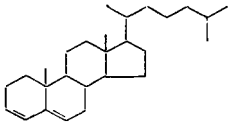
Two of these compounds, cholesteryl methyl xanthate[3–7] and cholesteryl methyl trithiocarbonate,[7] have previously been reported to exhibit colors.

1. Preparation

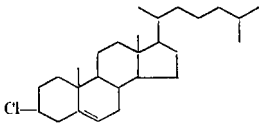


S-cholesteryl chlorothiolcarbonate (IX) was prepared from thiocholesterol[8] and phosgene in the presence of pyridine. The S-alkyl thiocarbonates of stigmasterol (I), 5α-cholestanol (II), and cholesterol (III) were prepared from their corresponding chloroformates (VIII a, b, c,)[9,10,11] and alkanethiols in the presence of triethylamine, which gave higher yields than the weaker

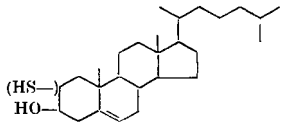
base pyridine. Pyridine was used for the preparation of S-cholesteryl O-alkyl thiocarbonates (IV) and S-cholesteryl S-alkyl dithiocarbonates (V). Cholesteryl alkyl xanthates (VI) and cholesteryl alkyl trithiocarbonates (VII) were prepared from alkyl bromide and the corresponding alkali salt. This, in turn, was obtained by reacting cholesterol with sodium hydride and carbon disulfide (X), or thiocholesterol with potassium tert.-butoxide and carbon disulfide (XI), respectively.



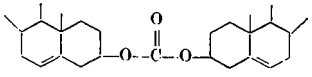
XII



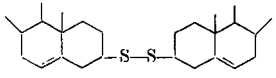
XIII



XIV (XV)



XVI



XVII

In the reaction of cholesteryl chloroformate (VIIIc) and S-cholesteryl chlorothiolcarbonate (IX) with alkanols and alkanethiols in the presence of tertiary amines side products are cholesta-3,5-diene (XII), 3β-chlorocholest-5-ene (XIII), cholesterol (XIV) and thiocholesterol (XV), dicholesteryl carbonate (XVI), and dicholesteryl disulfide (XVII), which can be removed by column chromatography. The corresponding side products of stigmasteryl chloroformate and 5α-cholestanyl chloroformate, and their identification and removal, were reported elsewhere.[2,12] Figure 1 shows a thin-layer chromatogram of some of the synthesized compounds and of their side products. Under the conditions employed the thio compounds migrate faster than their oxygen analogues. Since even minor impurities may have an influence on the mesomorphic behavior,[13,14] special care was taken to have pure starting materials. Alkanethiols were approximately 98% pure, the other starting materials were of better than 99%

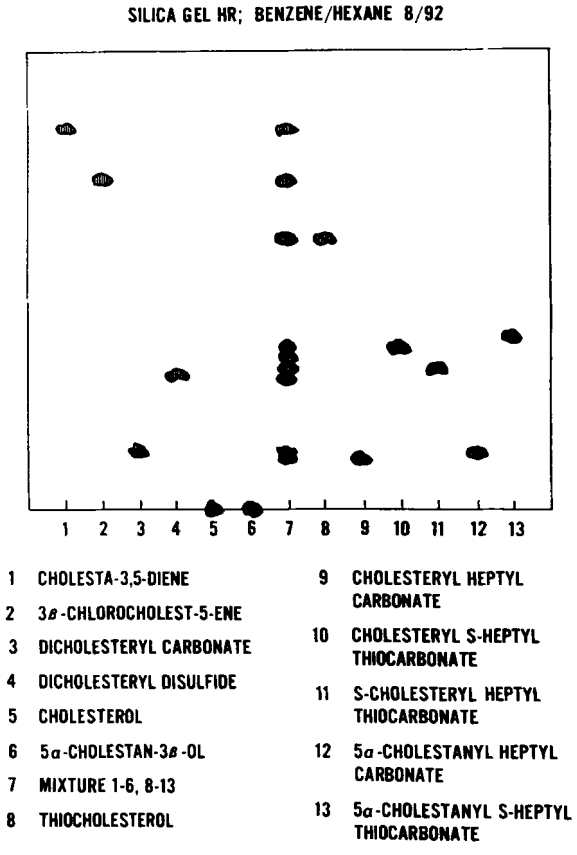


Figure 1

purity as checked by either thin-layer or gas chromatography. All compounds were chromatographed on silica gel with the fractions monitored by thin-layer chromatography for the presence of side products and gave satisfactory elemental analyses.

Figure 2 is a thin-layer chromatogram of the complete homologous series of S-cholesteryl O-alkyl thiocarbonates (IV). It shows clearly the difficulties involved in distinguishing between a particular higher member and its immediate neighbors by thin-layer chromatography.

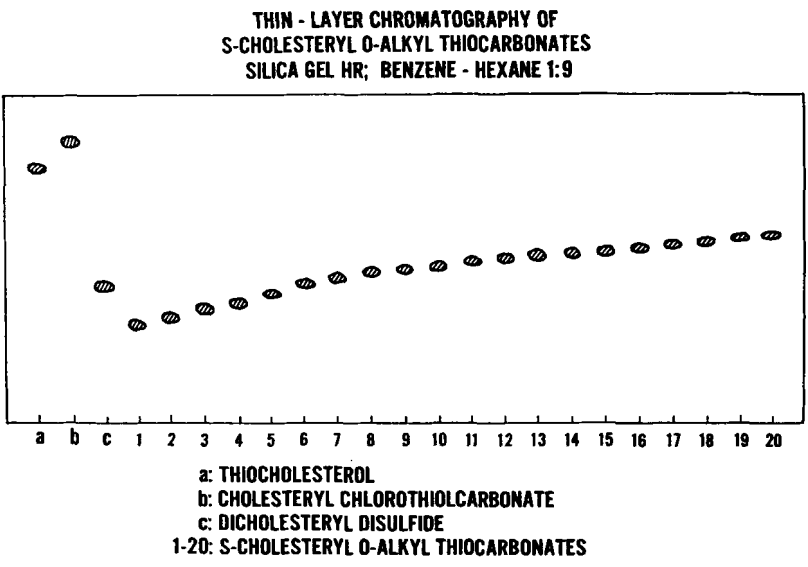


Figure 2

2. Properties

Temperatures of transitions in the melt for all compounds were determined with a modified[15] Perkin-Elmer Differential Scanning Calorimeter, and the respective phases were identified by polarizing microscopy using a Mettler FP-2 hot-stage. Temperature calibration was performed by comparison with zone-refined materials in the appropriate temperature range.

With the exception of cholesteryl S-methyl thiocarbonate none of the investigated materials exhibited enantiotropic cholesteric color bands as was observed in the series of cholesteryl alkyl carbonates.[1]

(1) Stigmasteryl S-Alkyl Thiocarbonates (I)

As in the case of the corresponding stigmasteryl alkyl carbonates[2] no cholesteric mesophases are found. The investigated compounds as well as stigmasteryl alkanoates[16,17] exhibit only smectic mesophases. However, the members C_{13}, C_{15}, C_{17} and C_{19} do exhibit a phenomenon, which we tentatively call " crystal colors ", i.e., regions of intense colors co-existing with crystals over a wide temperature range. Depending on the thermal

history, various "frozen-in" colors can be obtained. In this state the color does not change with temperature until complete crystallization takes place. This is probably a frozen-in plane texture, which occurs during the freezing process, and may explain why differential thermal analysis does not reveal any distinguishable transition other than the freezing point.

(2) 5α-Cholestanyl S-Alkyl Thiocarbonates (II)

A smectic-cholesteric transition could be found in all members but two, where the freezing points are rather high with respect to the temperatures extrapolated from the transition temperature curve.

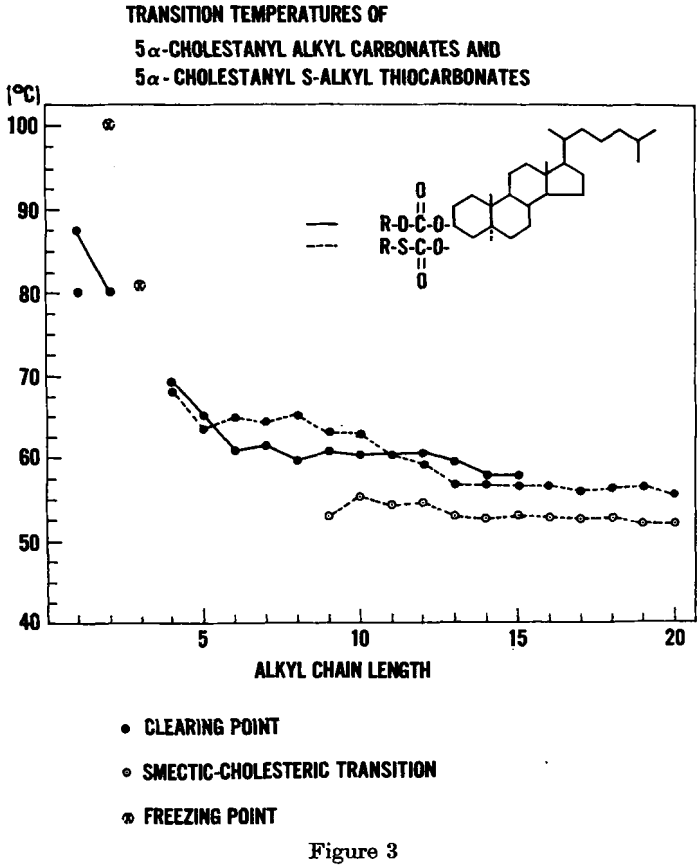


Figure 3

This transition could not be found in the corresponding 5α-cholestanyl alkyl carbonates,[14] probably because of the high freezing points.

The members C_1, C_7 through C_{15} and C_{17} show the typical temperature-dependent cholesteric colors. The complete solar spectrum is exhibited in C_7 through C_{10} and C_{12}, and the already mentioned " crystal colors " are observed in the members C_{13}, C_{15} and C_{17}.

(3) CHOLESTERYL S-ALKYL THIOCARBONATES (III)

All members are cholesteric but some do not show cholesteric

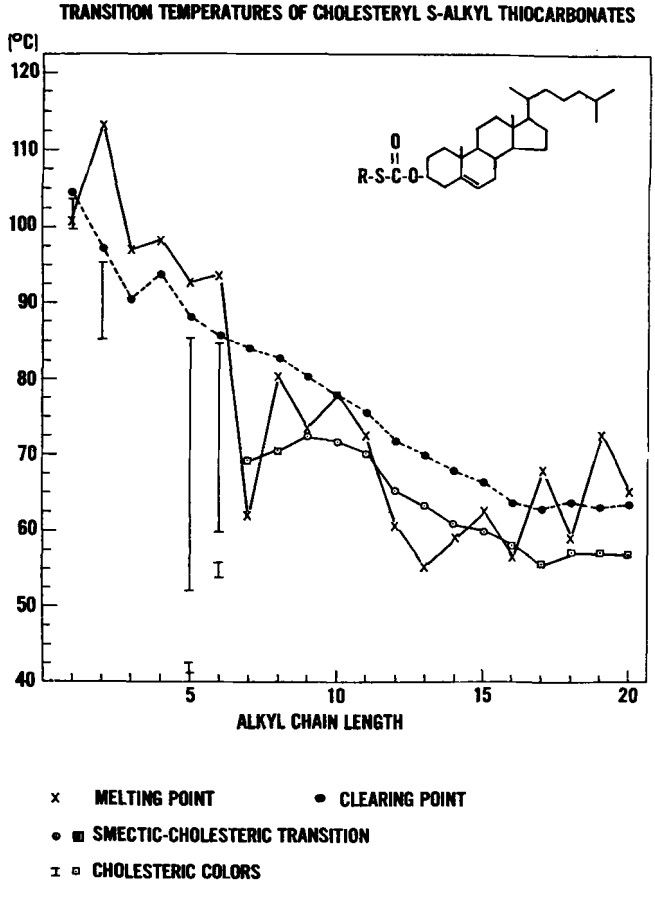


Figure 4

colors. Only the first member, cholesteryl S-methyl thiocarbonate, exhibits an enantiotropic color band. C_2 exhibits colors, C_3 and C_7 do not, and C_5 and C_6 give a blue color on cooling, which disappears on further cooling and then is followed by the solar spectrum. Only the solar spectrum as a narrow band is exhibited by C_7 and C_8, no colors are shown by C_9 through C_{14}, and again the solar spectrum as a narrow band is given by C_{15} through C_{20}.

(4) S-Cholesteryl O-Alkyl Thiocarbonates (IV)

The complete monotropic solar spectrum is exhibited by the

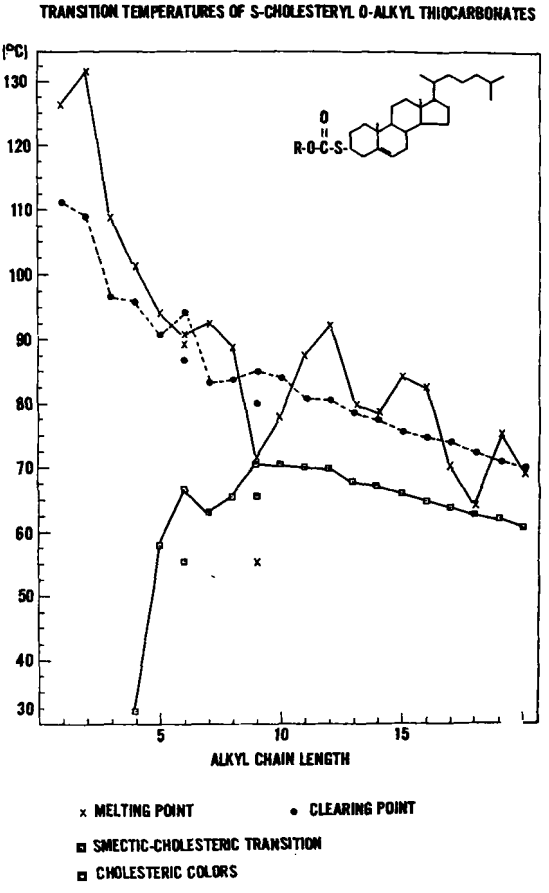


Figure 5

members C_4 through C_{20}, followed immediately by the cholesteric-smectic transition on further cooling.

Other examples of the effect of impurities on the mesomorphic behavior are the two marked members C_7 and C_9, which were erroneously prepared from 93% 1-heptanol and 93% 1-nonanol. Both compounds gave only one spot on thin-layer chromatography and correct combusion analyses, but the transition points were off the relatively smooth curves. Gas chromatography revealed the impurities and using 99% pure alkanols raised both the smectic-cholesteric transition and the clearing point several degrees.

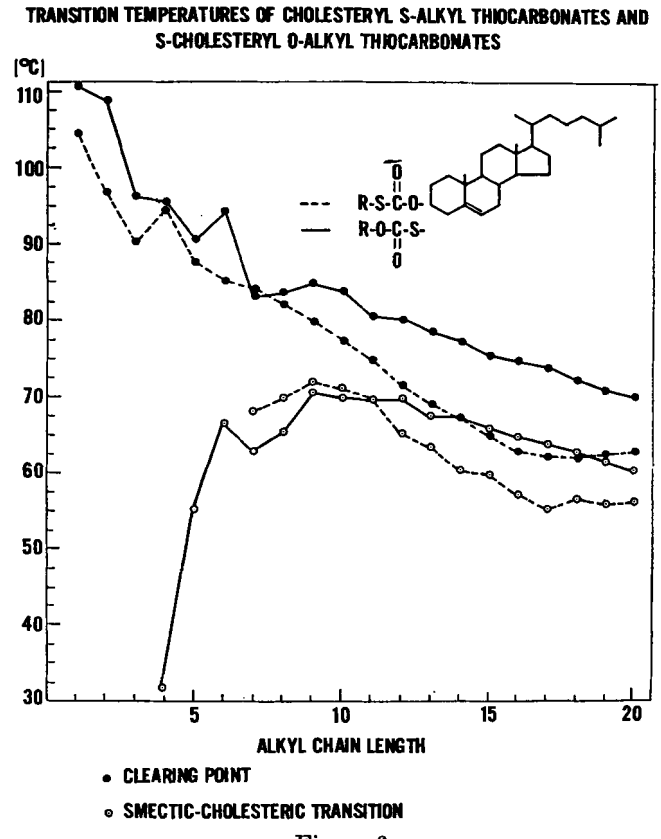


Figure 6

Figure 6 is a comparison of the 2 series, cholesteryl S-alkyl thiocarbonates (III) and S-cholesteryl O-alkyl thiocarbonates (IV). By moving the sulfur from the alkyl side to the steroid side in the thiocarbonate group an increase in both clearing point and smectic-cholesteric transition is obtained.

(5) S-Cholesteryl S-Alkyl Dithiocarbonates (V), Cholesteryl Alkyl Xanthes (VI), and Cholesteryl Alkyl Trithiocarbonates (VII).

Only a few representatives of each of the three series have been synthesized. They all exhibited cholesteric mesophases and cholesteric colors.

3. Summary and Conclusion

Figure 7 depicts the overall effect of substitution of oxygen by sulfur in the carbonate group for the cholesteric mesophase.

There is an increase in the cholesteric range on going from O-alkyl to S-alkyl in the 5α-cholestanyl series, and from O-cholesteryl S-alkyl to S-cholesteryl O-alkyl in the cholesteryl series. Too little is known on the molecular arrangement and the molecular interaction of the molecules in the cholesteric mesophase for an explanation of this increase.

An increase is also observed in the smectic-cholesteric transition temperatures from O-alkyl carbonate to the S-alkyl thiocarbonate in all series. By moving the sulfur from the alkyl side to the steroid side, i.e., comparing O-cholesteryl S-alkyl thiocarbonate (III) and S-cholesteryl O-alkyl thiocarbonate (IV), the increase is larger yet. The different orbital hybridization of sulfur must be responsible for this marked effect. On substitution of oxygen by sulfur, the bond angle decreases from approximately 110° to 104° and the bond length increases from approximately 1.3 Å to 1.7 Å. Inspecting a Stewart-Briegleb or a Dreiding stereo model this substitution does not appear to change the geometry appreciably. In particular, there is no difference in lateral dimensions of the molecule, which could effect smectic thermal

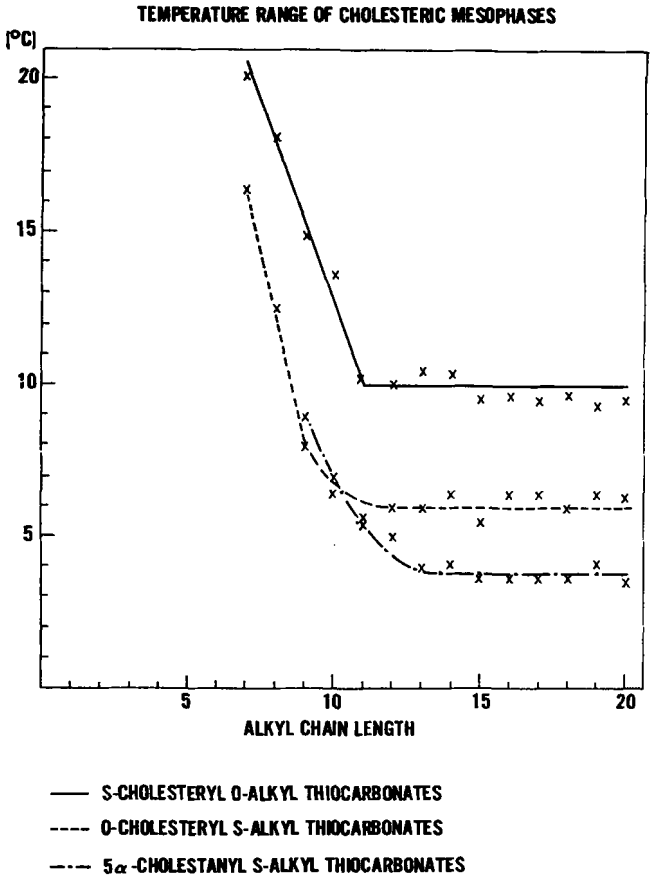


Figure 7

stability.[18] Making the customary assumption[18] that lateral forces are mainly responsible for the smectic state, only a stronger dipole moment or higher polarizability of the thiolcarbonate group would lead to an increase in smectic stability.

From chemical and spectroscopic[19] evidence, like reduced carbonyl basicity,[20] 10-electron sulfur in resonance,[21,22] smaller electron-donating (+ M) effect of sulfide sulfur,[23] etc., one assumes[20] that the group molecular orbital is set up by a $p\pi$–$d\pi$ orbital overlap. This allows a certain amount of electron drift

from the carbonyl bond into the sulfur orbitals thus decreasing the force constant of C=O, but increasing that of C—S. With this data one would expect a decrease in the smectic thermal stability, i.e., exactly the opposite of the results of sulfur substitution. Without more data from the other series, i.e., cholesteryl dithiocarbonates (V), xanthates (VI), and trithiocarbonates (VII), where only spot-checks for the occurrence of mesophases have been made, a conclusive picture and an explanation for this phenomenon cannot be drawn. This problem is under further investigation and the results will be reported in a separate communication.

4. Acknowledgments

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