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The Mesomorphic Behavior of 5α-Cholestan-3β-yl ω-Phenylalkanoates

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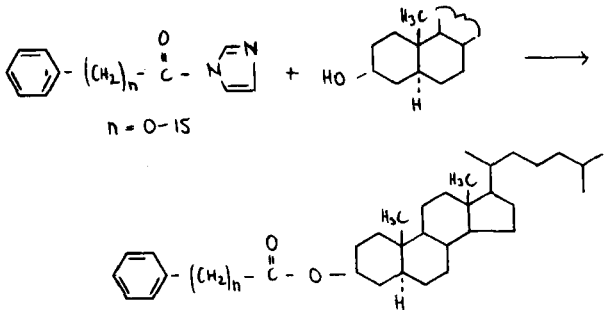
A homologous series of sixteen 5α-cholestan-3β-yl ω-phenylalkanoates was synthesized from 5α-cholestan-3β-ol and the imidazolides of the respective ω-phenylalkanoic acids. Microscopy and scanning calorimetry were used to identify the mesophases and to measure transition temperatures and associated latent heats. All homologs, except the phenylacetate, the 4-phenylbutyrate, and the 6-phenylhexanoate, are cholesteric and selectively reflect light. A smectic mesophase is observed only in the last five members. The values of the cholesteric-isotropic transition temperatures as well as the associated transition entropies fall on two distinct curves: an upper branch for odd acyl chain length and a lower branch for even acyl chain length. The smectic-cholesteric transition temperatures do not exhibit this odd-even effect but increase almost linearly with chain length.

In a short communication we reported[1] that the cholesteric-isotropic transition temperatures of 5α-cholestan-3β-yl ω-phenylalkanoates alternate with the acyl chain length. This odd-even effect, also observed in cholesteryl ω-phenylalkanoates[2,3,4] and in S-cholesteryl ω-phenylalkanethioates,[1] is obviously related to the presence of the phenyl ring in the 3β-substituent, since none of the corresponding homologous series of alkanoates shows this phenomenon to such a pronounced degree. This paper describes the preparation of 5α-cholestan-3β-yl ω-phenylalkanoates and presents their mesomorphic properties.

PREPARATION

The reaction of the imidazolides of ω-phenylalkanoic acids[4] with 5α-cholestan-3β-ol under catalysis with sodium methoxide was found to be the most feasible method:



Yields of analytically pure compounds were on the order of 60–70%, but were much lower without the addition of sodium methoxide. The progress of the transesterification was monitored by thin-layer chromatography on silica gel.

We synthesized the homologous series from the known 5α-cholestan-3β-yl benzoate[5,6] through the 5α-cholestan-3β-yl 16-phenylhexadecanoate. The crude compounds, which contained unreacted 5α-cholestan-3β-ol, cholest-2-ene, and an unindentified side product of the transacylation reaction, were purified by column chromatography on silica gel using mixtures of *n*-hexane and benzene as eluent. They were then recrystallized from ethanol. The physical properties of the synthesized materials and their elemental analyses[7] are listed in Table 1. The yields are expressed in analytically pure material. Transition points were determined microscopically with a Mettler FP-2 hot stage and the temperature readings are corrected. Observations of the selective reflection of light (cholesteric colors) are presented in the experimental part.

MESOMORPHIC BEHAVIOR

We determined the transition temperatures and identified the mesophases microscopically with a temperature programmed Mettler FP-2 hot stage. The heats of fusion and of transitions in the melt were obtained with a modified[8] differential scanning calorimeter. The results of these investigations are graphically demonstrated in Figures 1–3.

The melting point curve shows the typical erratic behavior as observed in other homologous series of 3β-sterol derivatives. In addition, several of the compounds exhibited up to five melting points depending on their thermal history.

All homologs, except 5α-cholestan-3β-yl phenylacetate, 4-phenylbutyrate, and 6-phenylhexanoate, are cholesteric. Only the 11-phenylundecanoate is enantiotropic cholesteric. The cholesteric-isotropic transition temperatures form two curves. The members of odd acyl chain length, benzoate through 15-phenylpentadecanoate, form the high temperature branch. The even homologs, 8-phenyl-

TABLE I

ω-phenylalkanoate	Transition Temperatures, °C mp	S-Ch[a]	Ch-I[b]	Transition Entropy, ΔS cal/mole °K mp	S-Ch[a]	Ch I[b]	Formula	Mol. Wt.	Analytical Values, % Calculated C	H	O	Found C	H	O	Yield
benzoate	136.0[(c)]	---	156.0[c]	14.74	---	0.37	$C_{34}H_{52}O_2$	492.8	---	---	---	---	---	---	
phenylacetate	92.4	---	---	16.96	---	---	$C_{35}H_{54}O_2$	506.8	82.95	10.74	6.31	83.00	10.83	6.34	
3-phenylpropionate	99.2	---	90.0	17.43	---	0.45	$C_{36}H_{56}O_2$	520.8	83.02	10.84	6.14	83.01	10.79	6.32	
4-phenylbutyrate	55.1	---	---	14.17	---	---	$C_{37}H_{58}O_2$	534.9	83.09	10.93	5.98	83.08	11.08	6.05	
5-phenylpentanoate	74.6	---	67.9	19.75	---	0.60	$C_{38}H_{60}O_2$	548.9	83.15	11.02	5.83	83.12	11.20	5.72	
6-phenylhexanoate	72.5	---	---	27.71	---	---	$C_{39}H_{62}O_2$	562.9	83.21	11.10	5.68	83.37	11.07	5.67	
7-phenylheptanoate	70.5	---	61.7	20.00	---	0.76	$C_{40}H_{64}O_2$	576.9	83.27	11.18	5.55	83.34	11.22	5.47	
8-phenyloctanoate	69.8	---	32.5	30.76	---	0.23	$C_{41}H_{66}O_2$	591.0	83.33	11.26	5.41	83.44	11.33	5.53	
9-phenylnonanoate	58.5	---	58.4	26.44	---	1.03	$C_{42}H_{68}O_2$	605.0	83.38	11.33	5.29	83.46	11.40	5.17	
10-phenyldecanoate	62.4	---	37.9	39.18	---	0.41	$C_{43}H_{70}O_2$	619.0	83.43	11.40	5.17	83.44	11.36	5.19	
11-phenylundecanoate	50.0	---	55.1	34.13	---	1.12	$C_{44}H_{72}O_2$	633.0	83.48	11.46	5.06	83.42	11.40	5.07	
12-phenyldodecanoate	51.8	26.1	42.3	34.77	--[d]	0.62	$C_{45}H_{74}O_2$	647.1	83.53	11.53	4.95	83.48	11.61	4.90	
13-phenyltridecanoate	60.0	28.3	53.2	39.58	--[d]	1.36	$C_{46}H_{76}O_2$	661.1	83.57	11.59	4.84	83.63	11.74	4.62	
14-phenyltetradecanoate	59.4	35.7	46.2	39.72	--[d]	0.94	$C_{47}H_{78}O_2$	675.1	83.62	11.64	4.74	83.73	11.45	4.78	
15-phenylpentadecanoate	66.5	38.4	53.8	44.45	--[d]	1.83	$C_{48}H_{80}O_2$	689.1	83.66	11.70	4.64	83.52	11.71	4.82	
16-phenylhexadecanoate	65.1	41.6	49.6	45.96	--[d]	1.16	$C_{49}H_{82}O_2$	703.2	83.70	11.75	4.55	83.63	11.75	4.69	

[a] Smectic – cholesteric transition; °C.

[b] Cholesteric-isotropic transition, °C.

[c] Reported[5] mp 135°, cp 155°;[6] mp 136.5°, cp 156.0°.

[d] Crystallization of sample prevents determination.

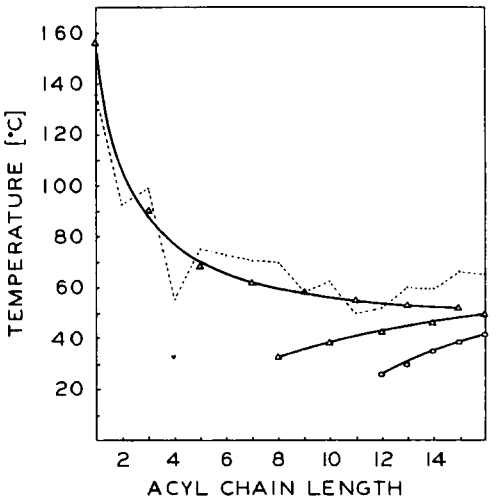
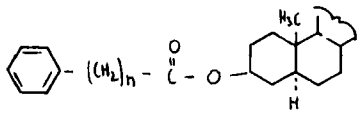


FIGURE 1 Transition temperatures of 5α-cholestan-3β-yl ω-phenylalkanoates – – – –, melting points; –△– cholesteric-isotropic transitions; –O– smectic-cholesteric transitions.

octanoate through 16-phenylhexadecanoate, form the low temperature branch.

Figure 1 presents a close hyperbolic curve fit to these two branches. The difference between the measured and the calculated cholesteric-isotropic transition temperatures amounts to less than ± 3° for the first odd members, and a much closer fit (<0,2°) for the higher members. Mathematically the two branches of the cholesteric-isotropic transition temperatures can be expressed as follows:

$$T_c = \frac{A}{(n+1)+n_0} + B$$



	upper curve	lower curve
A	153.35	−1, 360.16
B	41.80	95.86
n_0	0.33	13.47
SEE[a]	1.21	0.11

[a]SEE = Standard Error of Estimate

$$\sqrt{\frac{\Sigma\,(T_{exp} - T_{calc})^2}{N}}$$

Extrapolation of the two hyperbolic curves results in the intersection of the two hyperbolas in the vicinity of the 17-phenylheptadecanoate, which we could not investigate.

Only the last five members of this series, 5α-cholestan-3β-yl 12-phenyldode-

canoate through 16-phenylhexadecanoate, are monotropic smectic, but no alternation of the smectic-cholesteric transition temperatures is observed.

All the cholesteric members of this series also selectively reflect light. The temperature intervals of the cholesteric colors observed are listed in the experimental part. Some of the homologs exhibit platelets, a texture which has extensively been described[9] in our discussion of cholesteryl alkyl carbonates. A well-defined visible spectrum with a narrow temperature range (~0.15°) is found in the 14-phenyltetradecanoate.

In Figure 2 we plotted the entropies of fusion *versus* acyl chain length. The entropy values show the usual erratic behavior but generally increase with chain length. We notice a rather large deviation from a smooth curve relationship for members of intermediate acyl chain length, which becomes less pronounced for the higher members which are both smectic and cholesteric.

The entropies of the cholesteric-isotropic phase transitions (Figure 3) exhibit a rather smooth curve relationship. Two well-defined curves are obtained. The

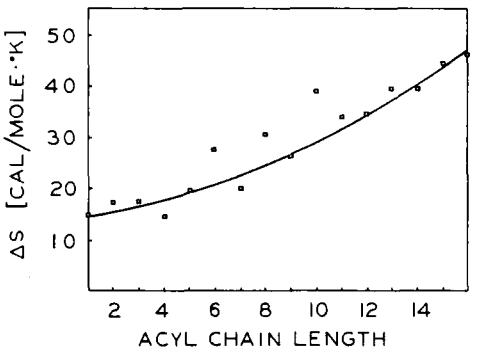


FIGURE 2 Entropy of Fusion

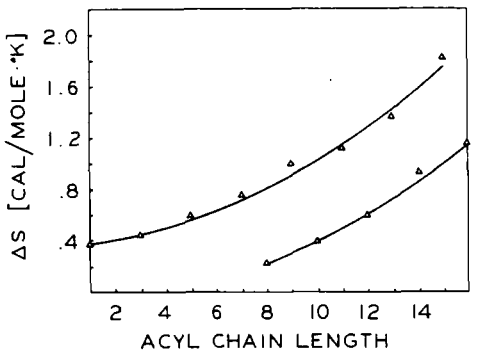


FIGURE 3 Entropy of the cholesteric-isotropic phase transitions.

higher values of entropy, as well as the higher transition temperatures, are exhibited by the homologs of odd acyl chain length. Due to the freezing of the isotropic melt, we were unable to determine the entropies of the smectic-cholesteric phase transitions. However, in the series of cholesteryl ω-phenylalkanoates we found a definite odd-even relationship between the entropy and the acyl chain length, while the associated transition temperatures increased almost linearly with chain length.

DISCUSSION

Alternations of transition temperatures within a homologous series have been linked to the conformation of the alkyl substituent. The alternating nematic-isotropic transition temperatures in 4,4'-di-substituted azobenzenes have been explained by an expression for the free energy in which both dispersion forces and volume effects[10] were taken into account as well as theoretical considerations about the different increments in the polarizabilities on extending the alkyl chain by a methylene group.[11] Unusually large alternations have been reported only for compounds with ω-phenylalkyl substituents, such as the ω-phenylalkanoates of several sterols[1,3] or ω-phenylalkyl 4-(4'-cyanobenzylidene)aminocinnamates.[12]

With the methylene groups in an *all – trans* conformation, Dreiding stereo and Stuart-Briegleb atom models illustrate a *cisoid* conformation of the ω-phenyl group with respect to the ester carbonyl group for even and a *transoid* conformation for odd ω-phenylalkanoates.[1,3,4] The resulting alternation in widths of the molecules might very well result in an alternation of attractive forces between the molecules. The decrease of the odd-even effect with increasing alkyl chain length could then be explained with the greater flexibility of the acyl chain which gradually diminishes the distinction between these two conformations.

Since the ω-phenylalkanoates of both 5α-cholestan-3β-ol and cholesterol show a pronounced odd-even effect, we tried to find differences in their mesomorphic behavior which could be attributed to the precense of the 5,6-double bond of cholesterol. We therefore compared the cholesteric-isotropic and the smectic-cholesteric transitions of the two series (Figure 4). The loss of the double bond results in the lowering of both transition temperatures by essentially equal amounts. This is in agreement with observations of Wiegand[6] for a series of p-substituted benzoates and of recently reported[13] N-[4-methoxyphenyl]carbamates of these two sterols.

We also notice the later appearance of the cholesteric mesophase in the homologs of even acyl chain length. This seems to be related to the 5α-cholestan-

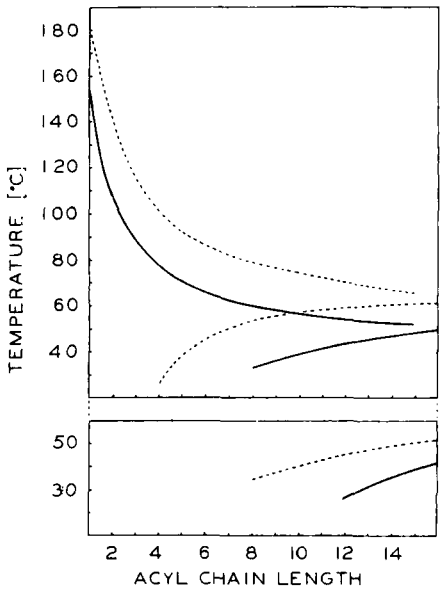


FIGURE 4 Cholesteric-isotropic (upper part) and smectic-cholesteric transitions of ----, cholesteryl ω-phenylalkanoates, ——, 5α-cholestan-3β-yl ω-phenylalkanoater

3β-yl system, since both the 6-phenylhexanoate and 4-phenylbutyrate could be undercooled below room temperature without exhibiting a cholesteric mesophase.

The same argument can be used with respect to the smectic mesophase which could not be obtained by undercooling of the respective homologs of shorter acyl chain length.

It is also interesting to note that a well-defined visible spectrum of selectively reflected light with a narrow temperature range is exhibited in both series only by homologs which are both smectic and cholesteric.

Comparing the transition heats of the two series, we find that the entropies of fusion are approximately the same in both series. The entropies of the cholesteric-isotropic transition of both the homologs of odd and even acyl chain length, however, are greater in the 5α-cholestan-3β-yl ω-phenylalkanoates, while the associated transition temperatures are lower.

We can conclude that the ω-phenyl ring in the 3β-acyl chain leads to a pronounced alternation of the cholesteric-isotropic transition temperatures between members of odd and even acyl chain length. In comparing the mesomorphic properties of the ω-phenylalkanoates of 5α-cholestan-3β-ol with those of cholesterol, we observe that the loss of the 5,6-double bond results in decreased mesophase transition temperatures and decreased smectic stability, while the cholesteric stability is not markedly affected.

EXPERIMENTAL SECTION

(a) Preparation of compounds

The 5α-cholestan-3β-yl ω-phenylalkanoates were synthesized by reacting 5α-cholestan-3β-ol with the imidazolide of the corresponding ω-phenylalkanoic acid in absolute benzene and under nitrogen. The preparation and the purification of the ω-phenylalkanoic acids used in these experiments have been discussed previously.[4] To obtain reasonable yields, small amounts of sodium methoxide had to be added several times in the course of the transacylation, which was monitored by thin-layer chromatography. For purifaction the crude compounds were chromatographed on a 350×50 mm-column of silica gel (Merck, 0.05–0.2 mm). The lower members were eluted with benzene/*n*-hexane 1:1, while the members of longer acyl chain length required a 3:7 mixture of the same eluent. A typical preparation is described in the following:

5α-Cholestan-3β-yl 4-phenylbutyrate: To a stirred slurry of 1.78 g (11 mmol) of 1,1'-carbonyldiimidazole in 50 ml of absolute benzene 1.64 g (10 mmol) of 4-phenylbutyric acid was added which dissolved almost completely with the evolution of CO_2. The last traces were dissolved by gentle warming. After cooling, 3.89 g (10 mmol) of 5α-cholestan-3β-ol was added and the reaction mixture stirred at room temperature for 30 min, then under reflux for 4 hr, with small amounts (~50 mg) of sodium methoxide added every hour. The solvent was evaporated and the residue triturated with benzene-hexane (1:9). The precipitated imidazole was filtered off and the filtrate chromatographed on silica gel using benzene-hexane (1:1) as eluent. The fractions containing the pure compound were combined, the solvent evaporated, and the residue recrystallized from ethanol.

Yield: 3.67 g (69%); mp 55°.

(b) Purity

Thin-layer chromatographic analysis of the crude reaction mixture from the transacylation reaction revealed only two minor side products, one of which could be identified as cholest-2-ene. Another minor impurity was unreacted 5α-cholestan-3β-ol. All three contaminants could be removed by column chromatography on silica gel. Thin-layer chromatographic investigations in several solvent systems, in two dimensions, and on silver nitrate-impregnated layers, did not reveal any other detectable impurity. The 5α-cholestan-3β-ol used in these experiments was analyzed by thin-layer chromatography on silver nitrate-impregnated silica gel and gas-liquid chromatography. No impurities were

detected by either method. Considering these analytical results and the purity of the ω-phenylalkanoic acids used, we can assume a minimum purity of 99% in the synthesized homologous series of 5α-cholestan-3β-yl ω-phenylalkanoates.

(c) Spectroscopy

The infrared spectra were obtained on a Beckman Mdl IR-8 double-beam grating spectrometer. The samples were examined in KBr disks. The NMR spectra were obtained with a Varian HA-100 spectrometer at 100 MHz. The samples, in about 0.2 molar solution in deuterochloroform, were measured at room temperature against tetramethylsilane as internal standard. Selected samples were run without a solvent in the mesomorphic state. Except for line broadening, no changes in the NMR spectra were observed.

Infrared spectra: The C=O streching frequency was observed at 1726–1732 cm^{-1}, the skeletal in-plane vibrations of the phenyl ring at 1605 cm^{-1} and 1495–1500 cm^{-1}, the C-O stretching frequency at 1170 cm^{-1}, the out-of-plane deformations of the monosubstituted benzene ring at 738–740 cm^{-1} and 698–700 cm^{-1}, and the $(CH_2)_4$ rocking vibration of the higher members at 718–720 cm^{-1}. A comparison with the IR spectra of the corresponding cholesteryl ω-phenylalkanoates reveals no differences in the respective infrared modes within the limit of this study.

Nuclear magnetic resonance spectra: A comparison of the spectra, with the exception of those of the benzoate and the phenylacetate, indicates no gross changes in the chemical shifts of certain protons as the chain length increases, and no difference between ω-phenylalkanoates of odd and even acyl chain length. The spectra consist of a 5H multiplet at 7.18 ppm (benzenoid protons), a very broad 1H resonance centered at 4.65 ppm (3α-proton), and a 2H triplet at 2.24 ppm of the α-methylene protons of the acyl chain. The latter is shifted, as a singlet, to 3.5 ppm in the phenylacetate, and can not be observed in the benzoate.

The only difference between these resonant lines and those of the corresponding cholesteryl ω-phenylalkanoates is a small downfield shift of the 3α-proton resonance, which appears at 4.56 ppm in the cholesteryl series.

(d) Cholesteric properties

The following observations were obtained microscopically. The temperature readings are corrected but the readings for fast cooling were not adjusted for the thermal lag due to varying cooling rates. These rates were chosen to facilitate observation rather than to obtain temperature equilibrium. Only those 5α-cholestan-3β-yl ω-phenylalkanoates that exhibit cholesteric colors are listed.

3-Phenylpropionate exhibits the complete visible spectrum of platelets just below the clearing point of 90.0°.

5-Phenylpentanoate: Green platelets appear below the clearing point. On mechanical disturbance the regular cholesteric colors appear: yellow at 67°, gold at 65°, orange at 62°, red at 45°, followed by crystallization at 23°.

7-Phenylheptanoate exhibits cholesteric colors on cooling: green at 60°, gold at 54°, orange at 44°, and red at 32°.

8-Phenyloctanoate exhibits faint blue and green platelets below the clearing point and no other colors.

9-Phenylnonanoate: Blue at 58.4°, green at 50°, with orange and red appearing on further cooling; crystallization at 30°.

10-Phenyldecanoate: A violet color appears below the clearing point (37.9°) which remains unchanged to ~24° where crystallization occurs.

11-Phenylundecanoate is enantiotropic cholesteric. A blue color appears at 53.5°, which changes to the focal-conic texture at 55°, followed by clearing at 55.05°. On cooling, an aqua color is observed at 53°, which changes to green at 47°, with crystallization starting at 36°.

12-Phenyldodecanoate forms blue platelets at 42.2° on cooling, followed by aqua platelets at 42.0° and green platelets at 41.8°. On further cooling the platelets disappear and are followed by regular cholesteric colors: 39° indigo, 26.6° aqua, 26.5° green, 26.3° yellow, 26.2° red. The red color disappears at 26.1°, followed by the cholesteric-smectic phase transition.

13-Phenyltridecanoate exhibits the visible spectrum: 52° blue, 34° green, 30.8° yellow, 30.6° orange, 30.4° red, 30.0° deep red, which disappears at 29.7°.

14-Phenyltetradecanoate is completely homeotropic until mechanically disturbed, where the entire visible spectrum is exhibited at 35.85–35.7°.

15-Phenylpentadecanoate: 53.9° blue, 52.0° aqua, 45.0° green, 39.7° red, and the color disappears at 39.5°.

16-Phenylhexadecanoate: 44° violet, 42.2° blue, 41.8° orange, 41.75° red, the color disappears at 41.7°.

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