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Structure Dependence of Cholesteric Mesophases

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Abstract—Cholesteric mesophases are mainly found in derivatives of cholesterol. Corresponding derivatives of other sterols do not necessarily show mesomorphic properties. Some of the known structural requirements for the occurrence of mesophases are a planar arrangement of the ring system and substituents extending the long axis of the sterane skeleton.

An attempt is made to determine the structural elements in the side chain of sterols which enable a properly substituted sterol to form cholesteric mesophases. A survey of available data pertaining to the mesomorphic properties of a selected group of 3β-sterols is given. It includes data for homologous series as well as for some individual compounds. In the case of the homologous series, the data are very reliable due to internal consistency. For individual compounds, which were carefully selected so that they were representative of their class, existing discrepancies can be explained in terms of impurity effects.

From the information presently available the structure dependence of the cholesteric mesophase cannot be explained. However, the derivatives of brassicasterol, 22.23-dihydrobrassicasterol and 22.23-dehydrocholesterol will indicate the dependence of mesomorphic properties upon elements of the molecular structure in the 17β-side chain of 3β-sterols.

Background

Most compounds exhibiting cholesteric mesophases are derivatives of cholesterol.[1] Attempts to obtain the same mesomorphic characteristics for derivatives of different sterols were only successful for those very similar in their structure to cholesterol. Wiegand[2] studied the influence of stereoconfiguration in the ring system and the conformation of the substient upon the mesomorphic properties. He prepared and investigated the corresponding benzoates of cholestanol, epi-cholestanol, coprostanol and epi-coprostanol and found

that only the derivatives of cholestanol have cholesteric properties. The benzoates of the other stereoisomers were not even mesomorphic.

Wiegand also investigated the benzoates of 3β-hydroxy-cholestenes and 3β-hydroxy-cholestadienes, which had been previously prepared. He found that the position of double bonds in the ring system does not affect the type of mesophase exhibited by the benzoates, with one unexplainable exception: whenever a double bond is between the C-atoms 14 and 15, the mesomorphic properties are lost.

Based upon his experimental evidence Wiegand inferred that mesomorphic properties are possible only for derivatives of sterols whose rings A and B are in trans-configuration, and where the substituent is in 3β-position. In his explanation, the structural requirement for the occurrence of mesophases is a planar arrangement of the ring system of the sterol and a substituent capable of extending the long axis of the sterane moiety.[3] This structural requirement is fulfilled by 3β-sterols, of which many are found in biological systems. In the following study only mesomorphic compounds of 3β-sterols are considered.

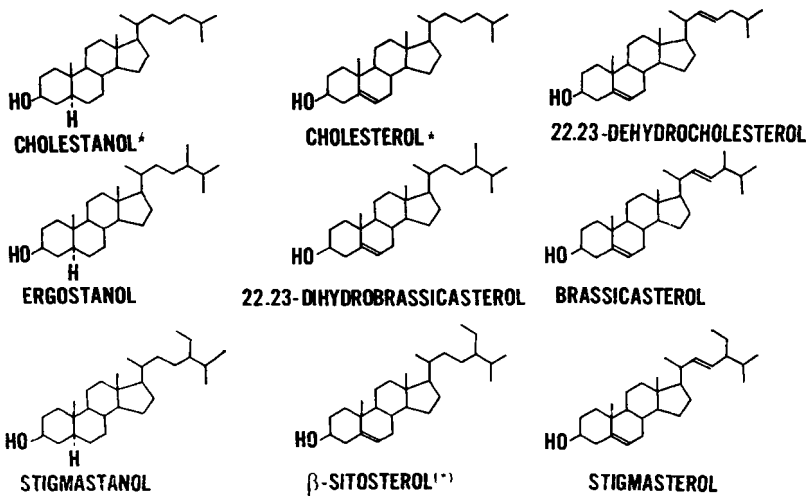


Figure 1

Mesomorphic Derivatives of 3β-Sterols

A number of 3β-sterols is given in the following list (Fig. 1). A systematic change of structural elements from cholestanol to stigmasterol is the guiding principle for this arrangement. Starting from cholestanol in each line, first the double bond in 5.6-position and then the one in 22.23-position is introduced. In each column one H-atom at C-atom 24 is replaced first by the methyl group and then by the ethyl group. The asterisk behind the name of the sterol indicates that cholesteric properties are observed for at least one derivative. In the following survey the available data for the derivatives of the listed 3β-sterols are presented.

5α-Cholestanol

The homologous series of 5α-cholestanyl *n*-alkyl carbonates[4] and 5α-cholestanyl S-alkyl thiocarbonates[5] prepared in our laboratory showed cholesteric phases for most of the investigated members. This is in agreement with Wiegand's finding for benzoates.

Cholesterol

Most homologous esters of cholesterol and thiocholesterol,[6] and also the homologous series of cholesteryl *n*-alkyl carbonates,[7] cholesteryl S-alkyl thiocarbonates[5] and S-cholesteryl O-alkyl thiocarbonates[5] exhibit cholesteric mesophases.

Stigmasterol

A few homologous series of stigmasterol have been investigated including the esters,[8] the carbonates[9] and thiocarbonates.[5] Not a single compound was found to be cholesteric; most derivatives exhibited monotropic smectic properties.

Stigmastanol

Although a number of esters have been prepared and investigated, no data for their mesomorphic properties are recorded.[10]

β-Sitosterol

Some esters of this 3β-sterol are known. Although monotropic cholesteric phases are specifically mentioned,[11] more recent papers report only smectic mesophases for the same derivatives.[10]

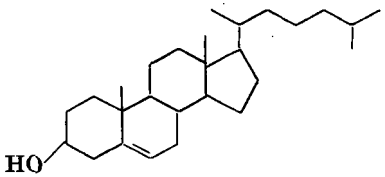
The other 3β-sterols listed have not been isolated in preparative quantities, and therefore data pertaining to their mesomorphism are not available.

From these data it is evident that not all 3β-sterols are capable of forming cholesteric mesophases; however, there seems to be no doubt that their structure is suitable for the formation of mesophases.

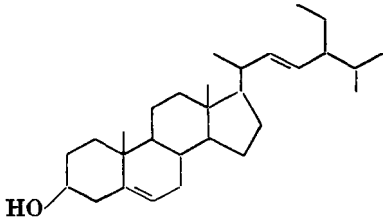
Molecular Structure and Cholesteric Mesophases of 3β-Sterols

Studies of structural changes in the side chain and their effect upon the mesomorphic properties should lead to a better understanding of the cholesteric mesophase. From the investigation of new mesomorphic materials, it might be established which structural elements are still compatible with the molecular arrangement for cholesteric mesophases, or which changes in the side chain of the sterol induce only smectic mesophases.

Stigmasterol and cholesterol, the two counterparts for this investigation, have an identical sterane skeleton. They differ only in structural elements of the side chain in 17β-position. Stigmasterol has a double bond in 22-position and an ethyl group on C-atom 24.



cholesterol



stigmasterol

In pure form stigmasteryl *n*-alkyl carbonates exhibit only monotropic smectic phases. However, in mixtures with distigmasteryl carbonate they display cholesteric mesophases associated with color bands.[9] On freezing, a few pure stigmasteryl derivatives show intensive colors which strongly resemble those exhibited by cholesteric mesophases. Most likely they are " frozen in " plane textures and are tentatively called " crystal colors ".[12]

These two observations indicate that stigmasteryl derivatives might have the chance of forming a cholesteric phase, or that the hindrance is a very small one. Since stigmasterol differs from cholesterol by two structural elements, it is not possible to determine which one is responsible for the difference of the mesomorphic properties. The influence of the double bond is presumably due to its polarizability, while the ethyl substituent may primarily affect the mesomorphism through increased molecular volume. These two effects may be in opposition as far as cholesteric properties are concerned. Furthermore both structural elements restrict the flexibility of the 17β-side chain.

β-Sitosterol carries only the ethyl group on C-atom 24 and a study of suitable derivatives offers a means of separating the effect of the ethyl group from that of the double bond in stigmasterol systems.

Investigations of β-Sitosteryl Derivatives

The available β-sitosterol is only of technical grade and contains an appreciable amount of other sterols. As Ennulat[13,14] has pointed out, it is of questionable value to investigate contaminated materials. Also, for the same reason, many mesomorphic systems reported in literature have to be regarded with extreme caution. Commercial β-sitosterol was purified by way of the acetate; saponification of the chromatographed ester fraction gave a sterol, which is pure as judged by TLC. Since only a limited amount of β-sitosterol was available, it was not possible to prepare an extended series of homologous esters or *n*-alkyl carbonates.

From previous experience, the members seven to nine inclusive were chosen for study.

n-Heptyl, *n*-octyl and *n*-nonyl β-sitosteryl carbonate were synthesized and investigated. They exhibit only smectic mesophases. Because of contradicting data reported for β-sitosteryl octanoate[10,11], we prepared this ester. It exhibits monotropic smectic properties. The discrepancy in the literature[11] most likely originates from investigations which were carried out on a mixture of steryl octanoates obtained from contaminated β-sitosterol. It is possible that the suppression of cholesteric properties in both stigmasteryl and β-sitosteryl derivatives is caused by the ethyl substituent at C-atom 24. However, it also must be verified first, whether the synthesized and investigated compounds are the typical representatives.

Future Approach

The influence of the alkyl substituent in the 17β-side chain can be investigated further on derivatives of brassicasterol, 22.23-dihydrobrassicasterol and 22.23-dehydrocholesterol, which offer different combinations of structural elements. From the mesomorphic data of their esters and of their *n*-alkyl carbonates, it should be possible to determine in which way the cholesteric mesophase depends upon alkyl substituents and/or double bonds in the 17β-side chain.

Summary

The occurrence of a cholesteric mesophase for derivatives of 3β-sterols is influenced by structural elements, such as double bonds or alkyl substituents in positions remote from the functional group in 3β-position of the sterane skeleton, and this despite the fact that their influence does not touch the stereoconfiguration of the ring system. Since the exact structural model for the cholesteric mesophase is not known, one can only estimate the general direction in which the molecular structure affects the mesomorphic

behavior. It is reasonable to assume that the forces associated with the double bond increase the molecular interaction. An alkyl substituent, on the other hand, might decrease the molecular interaction due to its widening of the volume and thus cut the molecular interaction below a level which is required for the cholesteric mesophase. Unless more compounds are prepared and investigated this question remains open.

Acknowledgments

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Experimental Part

All experiments were run in standard glassware using nitrogen as an inert purge gas. One typical example for preparations pertaining to this work is given in detail.

1. PURIFICATION OF β-SITOSTEROL

(a) *β-Sitosteryl acetate.* In 100 ml of benzene 41.5 g (0.1 mole) crude β-sitosterol (mp 75–90°) was dried by azeotropic distillation; about 1 ml water was carried out with 65 ml of the solvent. The remaining syrup was dissolved in 80.5 ml (1 mole) pyridine. While cooling 18.9 ml (0.2 mole) acetic anhydride was added. The mixture was heated under reflux for 2 hours; then the main portion of the solvents was distilled off. The viscous residue was filtered off, washed, redissolved in ethyl ether and dried over sodium sulfate. The crude β-sitosteryl acetate contained seven side products all of which could be removed by column chromatography using silica gel as adsorbent and a 15/85-mixture of benzene/ligroin for elution. The main fractions yielded 28.5 g (62.5%) β-sitosteryl acetate, mp. 122–124°.

(b) *β-Sitosterol.* For saponification of 22.83 g (50 mmoles),

β-sitosteryl acetate was heated under reflux in 200 ml ethanol which contained 0.2 mole potassium hydroxide. When all material had dissolved, the main portion of the solvent was distilled off and the remaining solution poured into water. After neutralization with 2N hydrochloric acid, the precipitated β-sitosterol was filtered off, washed, dried, and recrystallized from ethanol; yield 19.7 g (95%), mp 137–139°.

2. β-Sitosteryl *n*-Heptyl Carbonate

In 100 ml of benzene was dissolved 2.45 g (6 mmoles) β-sitosterol. About 50 ml of benzene was distilled off, thereby removing the last traces of water. The remaining solution was stirred with 1.42 g (8 mmoles) *n*-heptyl chloroformate while 0.65 ml (8 mmoles) pyridine was added. After two hours heating under reflux the precipitated pyridinium chloride was filtered off. Purification of the carbonate was achieved by column chromatography using silica gel as adsorbent and a 15/85 mixture of benzene and ligroin for elution. The purified carbonate was recrystalized from acetone.

Analytical data for β-sitosteryl *n*-heptyl carbonate and two of its homologues are given:

					C		H		O	
carbonate	yield	mp	formula	mol wt	calcd	found	calcd	found	calcd	found
n-heptyl	74	69–71	$C_{37}H_{64}O_3$	556.9	79.80	79.61	11.58	11.52	8.62	8.68
n-octyl	90	69–70	$C_{38}H_{66}O_3$	570.9	79.94	79.67	11.65	11.51	8.41	8.38
n-nonyl	69	71–73	$C_{39}H_{68}O_3$	585.0	80.08	79.88	11.72	11.59	8.21	8.10

3. β-Sitosteryl Octanoate

To a suspension of 1.20 g (7.5 mmoles) N.N′-carbonyldiimidazole in 60 ml dry benzene was added 1.01 g (7 mmoles) octanoic acid. When the generation of gas had ceased 2.45 g (6 mmoles) β-sitosterol was added. After 4 hours heating under reflux the solvent was distilled off and replaced by *n*-hexane, whereby the formed imidazole precipitated. The ester was purified by column chromatography with silica gel as adsorbent and a 3/7-mixture of

benzene/*n*-hexane as eluent. The purified β-sitosteryl octanoate was recrystallized from ethanol; yield 2.05 g (63%), mp 72–74°.

4. Investigation of mesomorphic Properties

Melting and clearing points were determined both by normal capillary methods and with a polarizing microscope equipped with a temperature programmed heating stage (Mettler FP 2). An asterisk indicates that a positive optical sign was measured verifying that the material exhibited monotropic smectic properties.

derivative	mp °C cap.	mp °C FP 2	cp °C cap.	cp °C FP 2
acetate	122–124	122.5		
octanoate	72–74	72.6	64	63.2*
n-heptyl carbonate	69–70	68.5	28	28.7*
n-octyl carbonate	69–70	69.0	34	33.1*
n-nonyl carbonate	71–73	71.1	38	37.7*

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