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Juergen L. W. Pohlmann [a], Wolfgang Elser [a] & Phillip R. Boyd [a]
[a] U.S. Army Electronics Command Night Vision Laboratory, Fort Belvoir, Virginia, 22060
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Structure Dependence of Cholesteric Mesophases II[(1)†]

JUERGEN L. W. POHLMANN, WOLFGANG ELSER and PHILLIP R. BOYD

U.S. Army Electronics Command
Night Vision Laboratory
Fort Belvoir, Virginia 22060

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Abstract—To find a correlation between mesomorphic character and the position of double bonds in ring *A*, we investigated the octadecanoates of 5α-cholest-1-en-3β-ol and cholest-4-en-3β-ol, neither of which was mesomorphic. We attribute this to a change in polarizability. The influence of chain length and substituents at the 17β-position on the mesomorphic behavior was studied with alkanoates of various substituted androst-5-en-3β-ols. Monotropic cholesteric mesophases were exhibited by the octadecanoates of methyl 3β-hydroxychol-5-en-24-oate and 20β-carbomethoxypregn-5-en-3β-ol, and by methyl 3β-acetoxy-24-norchol-5-en-23-oate. This proves that the 17β-side chain of cholesterol can be shortened considerably without destroying mesomorphic characteristics. However, with the introduction of polar substituents in the 17β-position and simultaneous loss of the optically active center at C-20 cholesteric mesophases could no longer be obtained. The octadecanoates of pregn-5-en-3β-ol-20-one, androst-5-en-3β-ol-17-one, 17β-carbomethoxyandrost-5-en-3β-ol, and androst-5-en-3β, 17β-diol were not mesomorphic.

Introduction

Some structural parameters required for the occurrence of mesophases in sterol derivatives have been determined by Wiegand,[(2)] who studied the correlation between the position of double bonds in the sterane skeleton and mesomorphic behavior. These studies, however, did not include the derivatives of 5α-cholest-1-en-3β-ol and cholest-4-en-3β-ol.

Some isolated findings of mesomorphic properties have been reported for 3β-substituted steryl derivatives in which the 17β-side chain is different from that of cholesterol. However, no systematic

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study has yet been made to determine the influence of the 17β-side chain length or the effect of different functional groups, upon the mesomorphic characteristics of such sterol derivatives.

In this paper we present our attempts to prepare a number of 3β-sterols which are not commonly available, and the results of the investigations of the mesomorphic characteristics of selected derivatives. By correlating the obtained data with molecular features of the sterol derivatives, we have obtained a better understanding of structural parameters, and their interplay, necessary for the occurrence of a cholesteric mesophase. In particular, we sought answers to the following questions:

(a) Do 5α-cholest-1-en-3β-ol and cholest-4-en-3β-ol form mesomorphic derivatives?
(b) What is the influence of the chain length of a 17β-substituent, carrying a terminal carbomethoxy group, on the mesomorphic characteristics of comparable (homologous) 3β-substituted sterol derivatives?
(c) What effects have polar substituents in the 17β-position upon the mesomorphic characteristics?

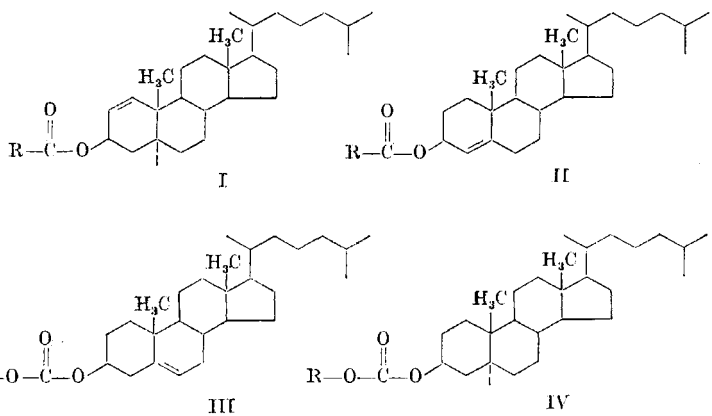
Results and Discussion

Wiegand's[2] investigation of benzoates of 3β-hydroxycholestenes and 3β-hydroxycholestadienes did not include the two sterols with the double bond in allyl position to the 3β-substituent. Therefore, we have prepared 5α-cholest-1-en-3β-ol[3] and cholest-4-en-3β-ol.[4] After column chromatographic purification of the free sterols we synthesized the corresponding octadecanoates. The octadecanoates were selected for the following reasons:

1. Octadecanoates increase the molecular weight of 3β-sterols by about 70%.
2. Octadecanoic acid of 99.5% purity is commercially available.
3. Steryl octadecanoates usually have low melting points, and their isotropic melts do not crystallize easily.
4. We know of no example where the smectic mesophase displaces the cholesteric mesophase[5,6,7] as it does in smectic–nematic systems with long enough chains.

To our surprise, neither the 3β-octadecanoyloxy-5α-cholest-1-ene (I)

nor 3β-octadecanoyloxycholest-4-ene (II) was mesomorphic. This, of course, does not necessarily mean that these two 3β-sterols are not at all suitable for mesomorphic derivatives, but it is still very likely that the octadecanoates are indeed representative. Both materials could be undercooled over a wide range of almost 100° from their melting points at 81.9° and 77° respectively to about −20° without the interference of crystallization and therefore should have had ample opportunity to arrange into mesophases.



It is hard to explain that steric factors are responsible for the lack of mesomorphic behavior. Dreiding stereo models of these two 3β-sterols were compared with those of cholestanol and cholesterol. The angle formed between the direction of the 3β-bonding and the plane of ring *A* showed some deviation due to different distortion of the ring. However, if one compares the angle between the 3β-bond and the resulting plane of the whole ring system, then the distortion is less significant. In our judgment, this alteration in the steric factor could only result in a gradual shift of mesomorphic properties for comparable derivatives of cholest-5-en-3β-ol, cholest-4-en-3β-ol, and 5α-cholest-1-en-3β-ol, approximately in the same manner as we found a shift of mesomorphic characteristics between the homologous series of cholesteryl alkyl carbonates (III)[8] and 5α-cholestanyl alkyl carbonates (IV).[9] If we consider that a change in polarizability is responsible for a different mesomorphic behavior, then it becomes immediately clear that comparable derivatives of cholest-4-en-3β-ol

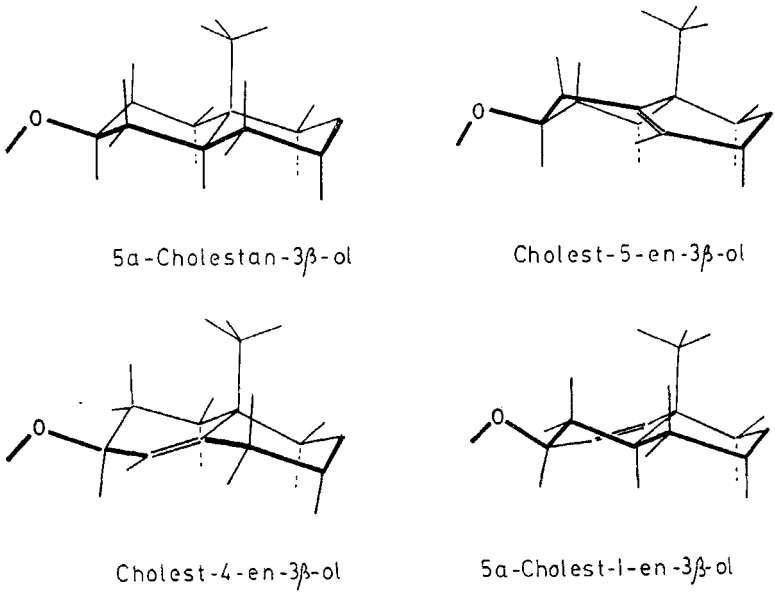


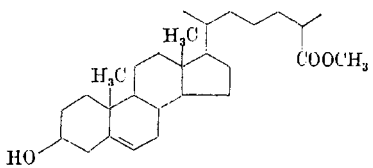
Figure 1. Dreiding stereo models depicting rings *A* and *B*.

and 5α-cholest-1-en-3β-ol are similar due to their incorporated allyl configuration, and that their mesomorphic characteristics should differ from those of comparable derivatives of 5α-cholestan-3β-ol and cholesterol. These conclusions were confirmed by high resolution NMR. The 3α-proton resonance shifted downfield from about 4.60 ppm in the case of 3β-octadecanoyloxycholest-5-ene, to 5.21 ppm for the corresponding cholest-4-en-3β-yl derivative, and to 5.36 ppm in 3β-octadecanoyloxy-5α-cholest-1-ene. This downfield shift indicates a drift of electrons from the 3α-proton toward ring *A* and thus might explain a decrease of lateral moment. The configuration of ring *A* seems to further enhance this tendency, because in both molecules the allylic double bond is directed almost parallel to the 3β-bond and thereby influences the resulting dipole moment at the 3β-ester group.

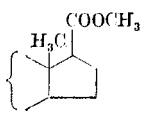
In another effort we investigated the influence of the length of the 17β-side chain carrying a terminal carbomethoxy group upon the mesomorphic properties. Conflicting findings are reported in literature: Šorm[10] observed colors on melting the 4-nitrobenzoate of 27-nor-25-carbomethoxycholest-5-en-3β-ol (V) but not for derivatives of chol-5-en-3β-ol, the latter of which differs from the corres-

ponding cholesteryl derivatives only in that the side chain is shortened by the three C-atoms of the terminal isopropyl group. However, Riegel[11] obtained a " blue fluorescent gel " on melting benzyl or methyl 3β-benzoyloxychol-5-en-24-oate, in which again the original side chain of cholesterol was shortened in the same manner by three C-atoms, but in which a new functional group was introduced in the 24-position.

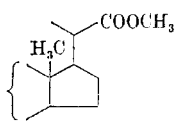
To clarify these discrepancies and to establish the minimum length of the 17β-side chain with a terminal carbomethoxy group, we investigated the octadecanoates of VI through IX.



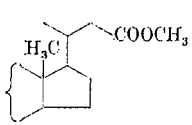
V



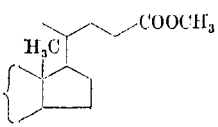
VI



VII



VIII



IX

All these 3β-sterol derivatives retain the identical sterane skeleton as cholesterol. Using systematic nomenclature they are 17β-substituted derivatives of androst-5-en-3β-ol, and in practice they can be obtained by oxidation of cholesterol.

TABLE 1

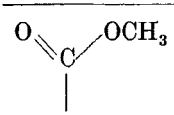
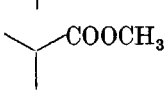
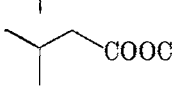
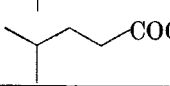
X		R	mp	cp
	VI	octadecanoate	98.3	—
	VII	octadecanoate	92.7	57.0
	VIII	acetate	133.4	97.1
	IX	octadecanoate	92.8	73.4

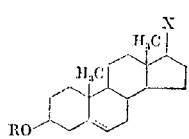
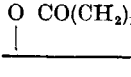
Table 1 shows the results of this study. Only the first member, with the shortest side chain, 3β-octadecanoyloxy-17β-carbomethoxy-androst-5-ene (VI) is not mesomorphic. The remaining compounds are monotropic cholesteric. The acetate of methyl 3β-hydroxy-24-norchol-5-en-23-oate (VIII), which was directly obtained by a modified version of a reported Arndt-Eistert chain elongation[12] of 3β-acetoxypregn-5-en-20β-carboxylic acid, was mesomorphic. Therefore, it was not necessary to convert this mesomorphic derivative into the corresponding 3β-octadecanoate to prove the point.

These observations prove that the mesomorphic character is not lost if the original 17β-side chain of cholesterol is shortened by even more than three C-atoms. Since only a few derivatives of these esters are known, usually the acetates and benzoates, mesophases could have been easily overlooked by earlier investigators, especially if no cholesteric colors were noticeable.

After we found that the 17β-carbomethoxy group is not sufficient to induce mesomorphic properties for the 3β-octadecanoyloxy-androst-5-ene, we synthesized similar derivatives where only the substituent in the 17β-position was altered (see Table 2).

The keto compounds 3β-octadecanoyloxypregn-5-en-20-one (X) and 3β-octadecanoyloxyandrost-5-en-17-one (XI) were not mesomorphic. This is in agreement with the recently reported finding for 3β-tetradecanoyloxyandrost-5-en-17-one.[13] Also we could not find a mesophase in 3β-octadecanoyloxyandrost-5-en-17β-ol (XII), and even esterification of the 17β-hydroxy group to 3β, 17β-di-(octadecanoyloxy)androst-5-ene (XIII) did not result in a mesomorphic compound.

TABLE 2

X		R	mp	cp	
	X	octadecanoate	99.5	—	
	XI	octadecanoate	79.5	—	
	XII	octadecanoate	87.7	—	
	XIII	octadecanoate	75.5	—	

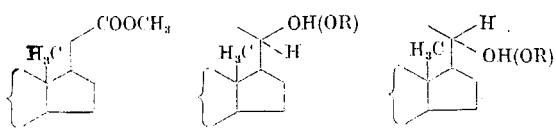
These results indicate that an oxo, acetyl, hydroxyl or carbalkoxy substituent in the 17β-position is not sufficient to induce a mesophase in 3β-substituted androst-5-enes.

Summary and Conclusion

Although this investigation was restricted to 3β-octadecanoyloxy- and 3β-acetoxy-substituted sterol derivatives, which is an arbitrary but reasonable choice for the purpose of our study, we can conclude that there is a very precarious interplay between steric factors and polarizability. In the case of shifted double bonds in ring *A* of derivatives of 5α-cholest-1-en-3β-ol (I) and cholest-4-en-3β-ol (II) the polarizability seems to be the key to different mesomorphic behavior.[14]

In the second group of compounds steric factors apparently outweigh the influence of polarizability as long as the configuration at C-20 is retained. Compounds VII, VIII, and IX have the same configuration at C-20 with the alkyl chain and its terminal ester group oriented along the main axis of the sterane moiety.

In contrast, the optical center at C-20 is lost in the case of compounds VI and X through XIII. Polar substituents at the 17β-position seem to be detrimental to the structural requirements necessary for mesophases. In order to find out which of the two factors is responsible for the suppression of mesophases the following derivatives should be investigated (17β-position):



The first does not have an asymmetric carbon atom in the C-20 position and might not be mesomorphic while the others should, at least in the form of suitable carbalkoxy derivatives, show mesomorphic properties. Unfortunately, these proposed derivatives are not easily accessible in pure form and could not be included in this investigation.

Experimental Part

All reactions were conducted in standard glassware with purified nitrogen as an inert gas. Only modifications of procedures reported in literature are given in detail. Combustion analyses were performed by a commercial laboratory.[15] The purity of starting materials and derivatives was checked by thin-layer chromatography on silica gel and silver nitrate-impregnated silica gel. Transition points were determined with a microscopic Mettler FP-II hot stage; the temperature values are corrected. For analogous preparations only one experiment will be given in detail.

5α-Cholest-1-en-3β-ol was prepared according to a published procedure.[3] Chromatography on silica gel, using chloroform as an eluent, gave a quantitative separation of the two epimers.[16] Mp 131.3° (reported 131.0–131.5°).

3β-Octadecanoyloxy-5α-cholest-1-ene (I) was prepared according to Staab[17,18] using octadecanoic acid and 1, 1′-carbonyldiimidazole. The advantages of this method for the preparation of steryl esters have previously been pointed out.[1,9] Chromatography on silica gel using benzene/*n*-hexane 3/7 (v/v) and recrystallization from ethanol gave long needles melting at 81.9°. Not mesomorphic.

Calc'd for $C_{45}H_{81}O_2$ (652.4)	C, 82.83; H, 12.26; O, 4.90
Found	C, 82.80; H, 12.34; O, 5.02

Cholest-4-en-3β-ol. No complete reduction could be obtained at lower temperatures as reported,[4] and no temperature dependence of the ration of 3α- and 3β-epimers was found. Therefore the following method was used: 3.84 g (10 mmol) of cholest-4-en-3-one was dissolved in 100 ml of absolute benzene and dried by azeotropic distillation. The remaining solution, about 25 ml, was diluted with 50 ml of absolute tetrahydrofuran. To this was added over a period of 15 min a slurry of 3.82 g (15 mmol) of lithium tri-*tert.*-butoxyaluminum hydride in 25 ml of absolute tetrahydrofuran with stirring at 0–5°. The ice bath was then removed, stirring continued, and after 3 hr the yellow solution was poured into 500 ml of 10% acetic acid. After extraction with hexane and ethyl acetate and evaporation of the solvent, the crude material was chromatographed on silica gel using ethyl acetate/*n*-hexane 3/7 (v/v) as eluent. The

fractions containing cholest-4-en-3β-ol were combined, the solvent evaporated, and the residue recrystallized from methanol. Yield 2.2 g (57%).

3β-*Octadecanoyloxycholest*-4-*ene* (II) was obtained by the above method with octadecanoic acid and 1, 1'-carbonyldiimidazole. After chromatography on silica gel using benzene/*n*-hexane 3/7 (v/v) as eluent and recrystallization from ethanol it melted at 77.0°. Not mesomorphic.

Calc'd for $C_{45}H_{81}O_2$ (652.4)	C, 82.83; H, 12.26; O, 4.90
Found	C, 83.01; H, 12.38; O, 4.88

3β-*Octadecanoyloxy*-17β-*carbomethoxyandrost*-5-*ene* (VI) was obtained from 17β-carbomethoxyandrost-5-en-3β-ol[19] in the prescribed manner. The yield was 67% after chromatography on silica gel using ethyl acetate/*n*-hexane 1/9 (v/v) as eluent and recrystallization from acetonitrile/butanone. It melted at 98.3° and was not mesomorphic.

Calc'd for $C_{39}H_{66}O_4$ (589.9)	C, 78.21; H, 11.11; O, 10.69
Found	C, 78.16; H, 11.26; O, 10.50

3β-*Octadecanoyloxy*-20β-*carbomethoxypregn*-5-*ene* (VII) was synthesized correspondingly from 20β-carbomethoxypregn-5-en-3β-ol.[20] The crude material was chromatographed on silica gel with ethyl acetate/*n*-hexane 1/9 as an eluent and then recrystallized from acetonitrile/butanone; yield: 52%. It melted at 92.7° and cleared at 57.0°. Monotropic cholesteric.

Calc'd for $C_{41}H_{70}O_4$ (627.0)	C, 78.54; H, 11.25; O, 10.21
Found	C, 78.58; H, 11.34; O, 10.22

Methyl 3β-*acetoxy*-24-*norchol*-5-*en*-23-*oate* (VIII). Over a period of 2 hr, silver oxide, prepared from 25 g of silver nitrate, was added to a boiling slurry of 31.8 g (77 mmol) of 3β-acetoxy-23-diazo-24-norchol-5-en-22-one[12] in 500 ml of absolute methanol with vigorous stirring. After an additional hour of reflux, activated carbon (Darco) and Celite filter aid was added, and the mixture filtered. The solvent was removed, and the residue chromatographed on silica gel. The material was eluted with benzene and was recrystallized from ethanol. Yield: 25.0 g (78%) of needles, melting at 134–135° (reported[21] mp 133.5–135.5°). By microscopic investiga-

tion we observed melting at 133.4° and clearing at 97.1°. Monotropic cholesteric.

Methyl 3β-*octadecanoyloxychol*-5-*en*-24-*oate* (IX) was obtained from methyl 3β-hydroxychol-5-en-24-oate.[11] After chromatography on silica gel with ethyl acetate/*n*-hexane 5/95 (v/v) as eluent and recrystallization from acetonitrile the crystals (72% yield) melted at 92.8° and cleared at 73.4°. Monotropic cholesteric and cholesteric colors.

Calc'd for $C_{43}H_{74}O_4$ (655.1)	C, 78.84; H, 11.39; O, 9.77
Found	C, 79.02; H, 11.45; O, 9.70

3β-*Octadecanoyloxypregn*-5-*en*-20-*one* (X). The esterification was performed in absolute tetrahydrofuran on a 10-mmol scale under conditions outlined above. Recrystallization from acetonitrile afforded leaflets in a yield of 78%, which melted at 98.1°. Not mesomorphic.

Calc'd for $C_{33}H_{66}O_3$ (583.0)	C, 80.35; H, 11.41; O, 8.23
Found	C, 80.17; H, 11.32; O, 8.34

3β-*Octadecanoyloxyandrost*-5-*en*-17-*one* (XI). A mixture of 2.85 g (10 mmol) of octadecanoic acid, 1.78 g (11 mmol) of 1, 1′-carbonyldiimidazole, 2.88 g (10 mmol) of androst-5-en-3β-ol-17-one, and 50 mg of sodium methoxide in 50 ml of absolute benzene was boiled under reflux for 3 hr. The solvent was removed *in vacuo* and the crude product chromatographed on silica gel. After elution with cyclohexane/ethyl acetate 8/2 (v/v), evaporation of the solvent, and recrystallization from acetonitrile 4.5 g (81%) of fine needles were obtained which melted at 79.1°. Not mesomorphic.

Calc'd for $C_{37}H_{62}O_3$ (554.9)	C, 80.09; H, 11.26; O, 8.65
Found	C, 79.97; H, 11.12; O, 8.84

3β-*Octadecanoyloxyandrost*-5-*en*-17β-*ol* (XII). A solution of 5.55 g (10 mmol) of 3β-octadecanoyloxyandrost-5-en-17-one (XI) in 60 ml of absolute tetrahydrofuran was added to a boiling solution of 5.59 g (22 mmol) of lithium tri-*tert*.-butoxyaluminum hydride in 70 ml of absolute tetrahydrofuran over a period of 30 min. After one additional hour of reflux, the mixture was cooled and poured into 420 ml of 5% acetic acid which had been cooled to 5°. The material obtained by this almost stereospecific reduction[22] was extracted into chloroform and, after washings with water, 5%

sodium bicarbonate, and water, the solvent was removed *in vacuo*. Recrystallization from acetonitrile/butanone yielded 4.7 g (84.5%) of small needles, which melted at 87.0°. Not mesomorphic.

Calc'd for $C_{37}H_{64}O_3$ (556.9)	C, 79.80; H, 11.58; O, 8.62
Found	C, 79.71; H, 11.72; O, 8.66

3β, 17β-*Di(octadecanoyloxy)androst-5-ene* (XIII). This di-ester was prepared by esterification of 2.78 g (5 mmol) of XII with 0.9 g (5.5 mmol) of 1, 1′-carbonyldiimidazole and 1.43 g (5 mmol) of octadecanoic acid in the presence of a small amount of sodium methoxide as outlined above. The crude material was chromatographed on silica gel. Elution was performed with ethyl acetate/*n*-hexane 1/9 (v/v). Recrystallization from ethyl acetate gave fine needles in a yield of 66% (2.7 g), which melted at 74.5–75.5° and were not mesomorphic.

Calc'd for $C_{55}H_{98}O_4$ (823.4)	C, 80.23; H, 12.00; O, 7.77
Found	C, 80.24; H, 12.12; O, 7.67

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