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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 IV.[1]† 17β–Alkyl Substituted Androst–5–en–3β–ols

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—The mesomorphic properties as functions of the length of the 17β-alkyl side chain were investigated on selected alkanoates of androst-5-en-3β-ol, pregn-5-en-3β-ol, 20-methylpregn-5-en-3β-ol, 24-norchol-5-en-3β-ol, chol-5-en-3β-ol, 25-methylchol-5-en-3β-ol and 27-norcholest-5-en-3β-ol. The alkanoates studied were generally the acetates and the octadecanoates. We found that only androst-5-en-3β-ol derivatives are unable to form cholesteric mesophases. Monotropic cholesteric mesophases were found in 3β-octadecanoyloxypregn-5-ene and the next three homologues; their corresponding acetates were not mesomorphic. With increasing chain length, starting with 3β-acetoxy-24-methylchol-5-ene, enantiotropic cholesteric mesophases were obtained. Additional smectic mesophases could not be observed. Thus, we could establish that the 17β-alkyl chain of cholesterol can be shortened considerably without impairing the mesomorphic behavior, since a 17β-ethyl group leads already to a cholesteric mesophase.

As intermediates we obtained the acetates of 24-norchol-5-en-3β-ol-22-one, chol-5-en-3β-ol-22-one, 24-methylchol-5-en-3β-ol-22-one and 27-norcholest-5-en-3β-ol-22-one. Monotropic cholesteric mesophases were observed in the last three 22-ketones.

Introduction

Previous papers of this series were mainly concerned with the influence of both major and minor changes at the 17β-side chain of cholesterol on the mesomorphic behavior. We found that the mesomorphic character is lost if the 17β-side chain is sufficiently abbre-

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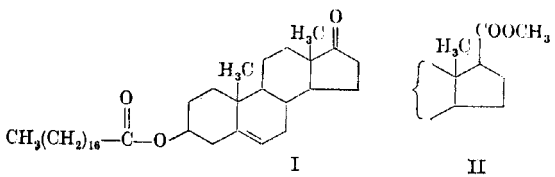
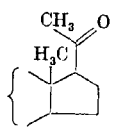
viated as in the case of 3β-octadecanoyloxyandrost-5-en-17-one (I) or 3β-octadecanoyloxy-17β-carbomethoxyandrost-5-ene (II). Even in the case of 3β-octadecanoyloxypregn-5-en-20-one (III) no mesophases were observed. However, when the asymmetric center at C-20 was retained, as exemplified by 3β-octadecanoyloxy-20β-carbomethoxypregn-5-ene (IV), a monotropic cholesteric mesophase was obtained.[2]

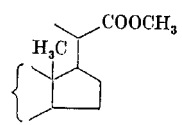


I

II



III



IV

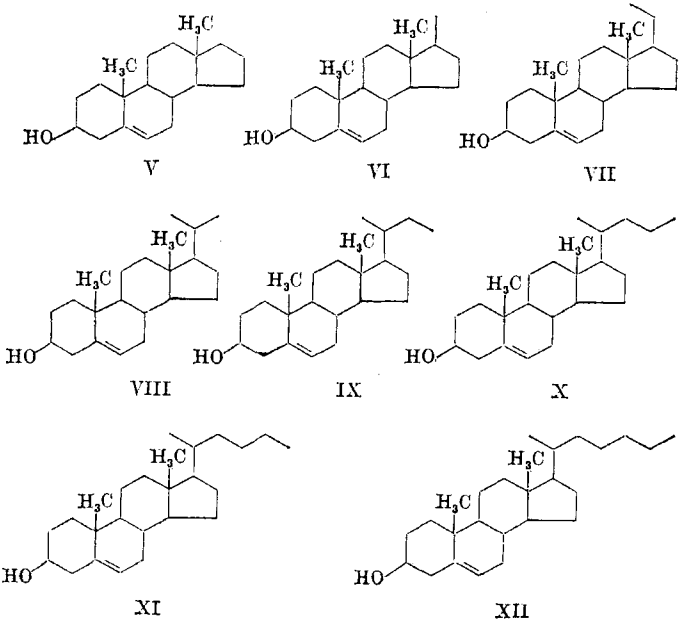
We also reported that replacing the 27-methyl group of cholesterol by an oxo group, a methylene group or by hydrogen only alters the stability of the cholesteric mesophase, while the same modifications at C-20 give rise to either additional mesophases or a complete loss of the mesomorphic properties.[1]

However, it should be pointed out that these investigations had the inherent disadvantage that factors such as dipole moments and polarizability were introduced by the oxo, the carbalkoxy group, and by double bonds. Since very little is known about the interplay of sterane nucleus, 3β-substituent, and 17β-side chain, which is necessary to obtain mesophases, it is difficult to judge which of these parameters contributes the most. The influence of a specific structural feature can only be studied if all other parameters are kept unchanged and if misleading impurity effects are excluded.[3]

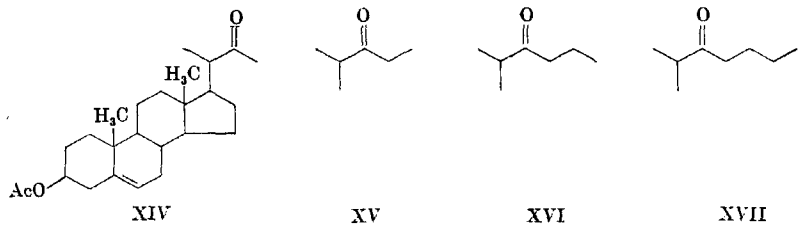
For comparative studies of mesomorphic properties of 3β-sterol derivatives, the investigation of homologous series is still the best approach.[4] The internal consistency of the data obtained by this systematic approach guards against experimental errors and false

conclusions. However, scarcity and high cost of individual 3β-sterols limit the feasibility of this procedure in many cases. The advantages of using the octadecanoates as representatives, whenever the acetates do not exhibit mesophases, has previously been pointed out.[2]

In this paper we report the results of our investigation in which we systematically built up the 17β-side chain, leading step by step toward the structure of cholesterol, as illustrated by the formulas V–XII.



Only a few data on the influence of a keto group in the cholesterol side chain have been reported. 24-Ketocholesteryl acetate[5] was reported to display "unusually vivid colors".[6] A monotropic cholesteric mesophase was observed with a 25-keto group.[1] However, if the keto function is in the 20-position, the mesomorphic character is lost.[1] Since the syntheses of compounds IX–XII afforded the intermediate 22-ketones XIV–XVII, we had an opportunity to investigate the influence of a 22-keto group in conjunction with an increasing chain length on the mesomorphic behavior.

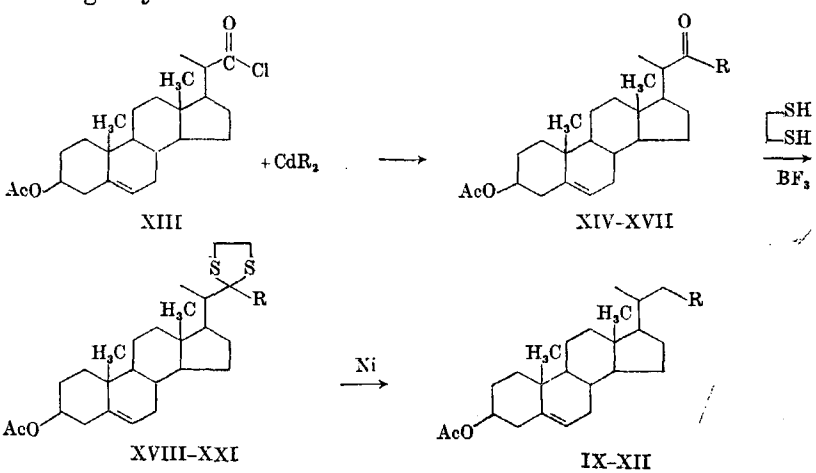


XIV XV XVI XVII

Preparation

Syntheses have been reported for androst-5-en-3β-ol[7] (V), 17β-methylandrost-5-en-3β-ol[8] (VI), pregn-5-en-3β-ol[9] (VII), 20-methylpregn-5-en-3β-ol[10] (VIII), 24-methylchol-5-en-3β-ol[11] (XI), and 27-norcholest-5-en-3β-ol[11] (XII). The acetates of the next two higher homologues of XII have been reported to possess both melting and clearing points.[12]

Starting materials V through VIII were prepared according to literature and compounds IX through XII were synthesized in the following way:



XIII XIV-XVII

XVIII-XXI IX-XII

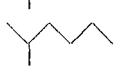
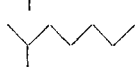
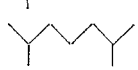
The 22-ketones XIV–XVII, obtained from 3β-acetoxypregn-5-en-20β-carbonyl chloride (XIII)[13] and the corresponding dialkylcadmium compounds, were reacted with an excess of 1, 2-ethanedithiol in the presence of boron trifluoride etherate.[14] The formed ethylenethioketals XVIII–XXI were then desulfurized with Raney nickel[11] to yield compounds IX–XII. Experimental details will be published elsewhere.

Discussion

Transition temperatures were determined and mesophases were identified under the microscope with a temperature programmed Mettler FP-II hot stage.[15] The temperature values are corrected.

Table 1 summarizes the mesomorphic properties as a function of the length of the 17β-alkyl side chain.

TABLE 1

Nr	17β-substituent	3β-derivative	mp	S–Ch	Ch–I
V	H	acetate	98.8	—	—
		octadecanoate	71.0	—	—
VI	CH_3	—	—	—	—
		—	—	—	—
VII		acetate	—	—	—
		octadecanoate	81.3	—	51.7
VIII		acetate	125.6	—	—
		nonanoate	71.2	28.5	43.7
		octadecanoate	88.1	—	—
IX		acetate	138.3	—	72.9
X		acetate	130.5	—	115.7
XI		acetate	115.3	—	126.8
XII		acetate	112.7	—	118.8
—		acetate	114.2	—	95.4

S–Ch: smectic-cholesteric transition, °C; Ch–I: cholesteric-isotropic transition, °C.

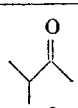
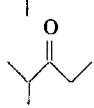
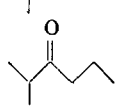
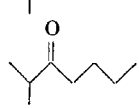
Monotropic cholesteric mesophases were observed in 3β-acetoxy-24-norchol-5-ene (IX) and 3β-acetoxychol-5-ene (X). Chain elongation to 3β-acetoxy-24-methylchol-5-ene (XI) and 3β-acetoxy-27-norcholest-5-ene (XII) gave rise to enantiotropic cholesteric mesophases. Smectic mesophases could not be observed in either one of these compounds.

Since the acetates of compounds V–VIII did not exhibit mesophases, we prepared the corresponding octadecanoates. Even that

modification did not lead to a mesophase in 3β-octadecanoyloxy-androst-5-ene (V). The mesomorphic properties of 17β-methyl-androst-5-en-3β-ol derivatives (VI) could not be included in this table because we were unable to prepare pure starting material. However, a monotropic cholesteric mesophase was observed in the next homologue, 3β-octadecanoyloxypregn-5-ene (VII). But we were unable to detect a mesophase in 3β-octadecanoyloxy-20-methylpregn-5-ene (VIII). It melted at 88.1° and the isotropic melt crystallized at 59°. This might explain why a mesophase could not be observed, because the isotropic melt could only be undercooled by about 30°. Nevertheless, in the capillary a bluish tint was observed just before the isotropic melt crystallized. But, because of the unstable state it was not possible to determine whether this optical effect was the result of light scattering by little crystallites or the result of a mesomorphic texture close to the clearing point. Since we know that the temperatures of both the smectic-cholesteric and cholesteric-isotropic transitions of homologous series generally have a maximum in the vicinity of the tenth homologue,[4] we prepared the nonanoate. And indeed, 3β-nonanoyloxy-20-methyl-pregn-5-ene (VIII) not only exhibited a monotropic cholesteric, but also a monotropic smectic mesophase.

The intermediate ketones XIV–XVII were investigated under the microscope for the occurrence of mesophases with the following results (Table 2):

TABLE 2

Nr	17β-side chain	3β-derivative	mp	Ch–I
XIV		acetate	169.3	—
XV		acetate	172.1	99.0
XVI		acetate	174.2	128.7
XVII		acetate	167.8	123.8

Ch–I: cholesteric-isotropic transition, °C.

No mesophase was observed in 3β-acetoxy-24-norchol-5-en-22-one[13] (XIV). The following three ketones, 3β-acetoxychol-5-en-22-one[13] (XV), 3β-acetoxy-24-methylchol-5-en-22-one[16] (XVI) and 3β-acetoxy-27-norcholest-5-en-22-one[11] (XVII) were monotropic cholesteric. Cholesteric colors or smectic mesophases could not be observed. Since the monotropic cholesteric mesophase of XV occurs just above the freezing point, a mesophase in XIV might not be observable due to the high freezing point of 117°.

Conclusion

The results of this investigation establish the contribution of the 17β-side chain to the formation of mesophases. We can conclude that the 17β-linked 2-(6-methylheptyl) group of cholesterol can be shortened considerably without impairing the occurrence of cholesteric mesophases. An ethyl substituent in the 17β-position already enables the molecules to arrange themselves in an order necessary for the cholesteric mesophase. The fact that 3β-octadecanoyloxy-pregn-5-en-20-one[2] and 3β-acetoxy-21-norcholest-5-en-20-one[1] did not exhibit a cholesteric mesophase may be ascribed to the 20-keto group and to the loss of the asymmetric center at C-20. But apparently the loss of the asymmetric carbon atom C-20 can still lead to the appearance of a cholesteric mesophase if there are no polar substituents at the C-20 position of the 17β-side chain. While we do not know yet whether a 17β-methyl group has the same effect, we are certain that the omission of an alkyl substituent at the 17β-position prevents the occurrence of mesophases in pure compounds.[17]

Acknowledgements

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