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Mesogenicity of testosterone and estrone derivatives

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Mesogenicity of 3β, 17β-bis(4-*n*-alkoxybenzoyloxy) androstene homologues (BABA) (carbon No. of alkoxy group, *n*, = 1–10) were studied by use of D.S.C. and a polarized microscopy. It was found that the n = 4–10 compounds of BABA have one cholesteric mesophase with high thermal stability enantiotropically, and that the n = 1–3 compounds decompose just above the melting point. Mesogenicities of BABA and several testosterone and estrone derivatives were also discussed from the perspective of chemical structure and shape. The presence of an intramolecular long-range dipole coupling in two alkoxybenzoyloxy chromophores is found in BABA from CD spectral studies.

1. Introduction

The mesogenicities of cholesteryl derivatives have been extensively investigated to clarify the structure—mesogenicity relationships [1]. However, mesomorphic studies on other steroid derivatives are unexpectedly scant. Hoffmann *et al.* [2–6] have performed elaborative work on mesomorphic properties of steroid hormones such as estrone derivatives. As a result, several derivatives of estrone are found to have a cholesteric mesophase. Moreover, another interest on the steroid hormone–mesogens is drawn towards relationships between the biological activities such as bioregulator (sex hormones, adrenal cortical hormones and so on.) and the mesogenicity, the past work of which is also reviewed by Hoffmann *et al.* [5, 6].

This paper describes mesogenicities of testosterone and estrone mesogens. The compounds conducted here are listed in figure 1.

2. Experimental

2.1. *General syntheses of testosterone and estrone derivatives*

3β, 17β-dihydroxy-4-androstene (DHA) was synthesized by adding dropwise sodium borohydride (0·8 g, 21 mmol)/1NHCL (50 ml) solution to testosterone (5 g, 17 mmol)/absolute ethanol (200 ml) and stirring for 2 h in an ice bath. The crude crystals were obtained by adding 1N HCL (130 ml) to the reaction mixture. The crystals were purified by recrystallizations from methanol/water (3 : 1) solution, giving yield of 2·6 g (52 per cent). ^{1}H-NMR: 5·25 (d, 1H, 4C–H); 4·15 (q, 1H, 3C–H); 3·65 (t, 1H, 17C–H); 2·30–0·60 (androstene skeleton). I.R. (KBr): 3350, 1670, 1440, 1058 cm^{-1}. 3β, 17β-bis(4-*n*-alkoxybenzoyloxy)-4-and ostene (BABA, compound A) were prepared by a conventional dehydrocholoride reaction of DHA (0·2 g, 4·1 mmol) and *n*-alkoxybenzoyloxy chloride (3·5 g, 13 mmol in the octyloxy) in 50 ml dried pyridine. The crude crystals were fully purified by several recrystallizations from

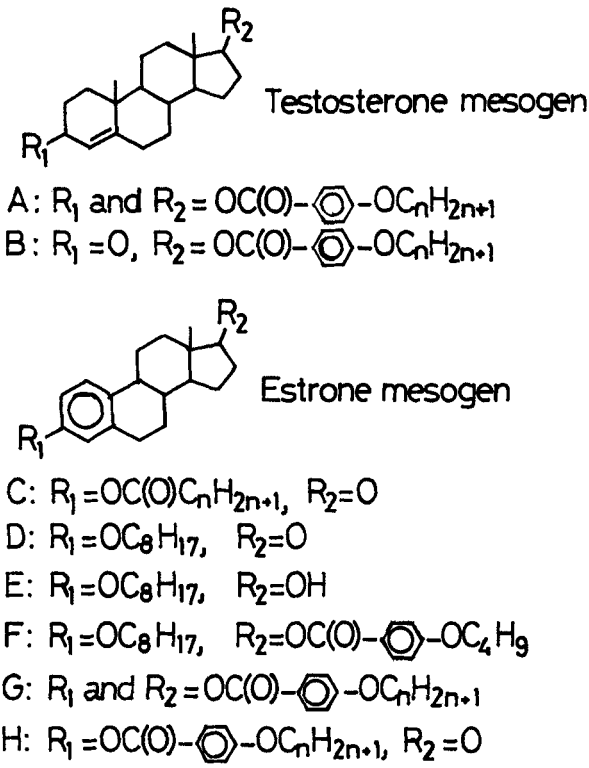

Figure 1. Chemical structures of testosterone and estrone derivatives.

isopropanol/THF (8 : 1). The crystals were judged to be fully purified by TLC and DSC. Yield = 0·4 g (13 per cent). ^{1}H-N.M.R. ($CDCl_3$): 8·00 (q, 4H, H_a); 6·89 (q, 4H, H_b); 5·44 (t, 1H, 3C-H); 5·36 (s, 1H, 4C-H); 4·80 (t, 1H, 17C–H); 4·00 (t, 4H, H_c). I.R. (KBr): 1710, 1610, 1260, 1170 cm^{-1}. 17β-4-*n*-heptoxybenzoyloxy testosterone (compound B) was prepared by a conventional dehydrochloride reaction of testosterone (2·0 g, 6·9 mmol) and 4-*n*-heptoxybenzoyloxy cloride (2·3 g, 9·0 mmol) in dried pyridine (40 ml). The crude crystals obtained by adding water to the reaction mixture were purified by several recrystallizations from isopropanol/THF (8 : 1). The crystals were judged to be fully purified by TLC and DSC. ^{1}H-NMR: 7·95 (q, 2H, H_a); 6·90 (q, 2H, H_b); 5·70 (s, 1H, 4C-H); 4·85 (t, 1H, 17C-H); 1·2 (s, 3H, 19C-H); 0·9 (s, 3H, 18C–H). I.R. (KBr): 1710, 1610, 1158, 1520, 1260, 1170 cm^{-1}.

3β-*n*-alkanoyl estrone (compound C) was synthesized by esterification of estrone and anhydrous alkanoic acid in THF. For example, for the propylonyl homologue, it was obtained by adding dropwise anhydrous propionic acid (0·96 g, 7·4 mmol) to estrone (2·0 g, 7·4 mmol) in THF (30 ml). After excluding THF from the reaction mixture, chloroform was added to the residue. The insoluble matter was filtered off and the chloroform solution was washed by 5 per cent $NaHCO_3$ and water. The crystals were purified by column chromatography (Waco gel-200, methanol/chloroform (1 : 9)) and then by recrystallization from methanol. Yield = 45–50 per cent. ^{1}H-NMR ($CDCl_3$): 7·30 (d, 1H, 1C–H); 6·75 (q, 1H, 2C–H); 6·60 (d, 1H, 4C–H); 1·25 (q, 2H, CH_2), 0·9 (s, 3H, 18C–H). I.R. (KBr): 1140, 1765 cm^{-1}. 3β-*n*-octyloxy estrone (compound D) was prepared by refluxing estrone 2·0 g and 7·4 mmol) and *n*-octyl

bromide (1·43 g, 7·4 mmol) in ethanol (80 ml)/2NKOH (8 ml) for 24 h, and further refluxing for 24 h after adding 2NKOH (8 ml) to the reaction mixture. The crude crystals were precipitated by cooling the mixture in an ice bath. The crystals separated by column chromatography (Waco gel-200, methanol/chloroform (1 : 99)) were fully purified by recrystallizations from ethanol, giving yield of 1·2 g (42 per cent). ^{1}H-N.M.R. ($CDCl_3$): 7·30 (d, 1H, 1C-H); 6·75 (d, 1H, 4C–H); 6·60 d, 1H, 2C–H); 3·93 (t, 2H, CH_2); 0·90 (s, 3H, 18C–H). I.R. (KBr): 1050, 1240 cm^{-1}. 3β-*n*-octyloxy estradiol (compound E) were synthesized by adding dropwise $NaHCO_3$ (0·1 g, 2·7 mol) in 10 ml ethanol to compound E (0·7 g, 1·8 mmol) in ethanol. The crude crystals were precipitated by adding chilled water (100 ml) to the reaction mixture. The product separated by the column chromatography was fully purified by recrystallizations from ethanol, giving yield of 0·4 g (57 per cent). ^{1}H-N.M.R.: 3·75 (t, H, OH) in addition to the peaks of Compound D. I.R. (KBr): 1060, 1260, 3500 cm^{-1}. 3β-*n*-octyloxy-17β-butoxybenzoyloxy estradiol (compound F) were prepared by a conventional dehydrochloride reaction of compound E (2·1 g, 5·4 mmol), 4-*n*-butoxybenzoyloxy chloride (1·2 g, 5·6 mmol) and a small amount of trimethylamine in absolute benzene (30 ml). Yield = 0·5 g (14 per cent). ^{1}H-N.M.R.: 8·00 (d, 2H, H_a); 6·93 (d, 2H, H_b); 4·90 (t, H, 17C–H) in addition to the peaks of Compound D. I.R. (KBr): 1170, 1260, 1520, 1580, 1610, 1710 cm^{-1}. The compounds C–F obtained were judged to be fully purified by TLC and DSC.

2.2. *Experimental method*

Phase transition temperature and the enthalpy change were obtained by use of a differential scanning calorimeter (Perkin Elmer, 1B) at a heating/cooling rate of 5 K min^{-1}. The texture of each mesophase was determined by a polarized microscopy (Nikon, Optiphoto-Pol XTP-11) equipped with a Mettler FP-82 hot stage at a heating/cooling rate of 1 K min^{-1} under crossed polarizer. Ultra-violet and circular dichroism spectra were measured with a Spectro Photometer 330 (Hitachi) and a Spectropolarimeter J-600 (JASCO), respectively.

3. Results and discussion

3.1. *U.V. and CD spectra of BABA*

U.V. spectra showed one peak near 257 nm for BABA homologues, independent of alkoxy length. Apparently this peak is attributable to π-π^* transient of alkoxybenzoyloxy group. CD spectrum of 3β, 17β-dihydroxy-4-androstene in *n*-hexane is shown in figure 2. There is observed one peak near 195 nm, which originates from the π-π^* absorption of –C=C– bond in the androstene skeleton. Since the molecular ellipticity ([θ]) in the CD spectrum is negative, the OH group apparently attaches to the 3-position by β-position. Figure 2 shows a CD spectrum of BABA (n = 3) in *n*-hexane. The CD spectra for other BABA homologues (n = 1–10) were almost the same as that for the n = 3. From higher wave length side, the first Cotton (negative) effect appears near 261 nm and then the second Cotton (positive) effect, near 265 nm. This splitting Cotton effect indicates a presence of an interaction between the two alkoxybenzoyloxy chromophores, which may be explained by an intramolecular long range dipole coupling of the two chromophores [7, 8]. The distance of the two chromophores is estimated to be about 16 Å by use of CPK model. Thus, in BABA homologues, a long-range intramolecular interaction is shown between two chromophores separated by 16 Å over androstene skeleton. Closs and Miller [9] report an

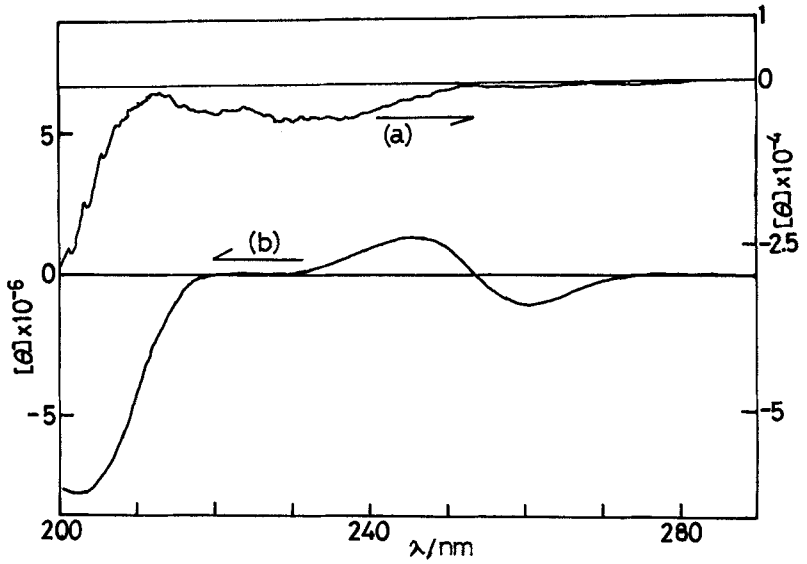

Figure 2. CD spectra of (*a*) 3β, 17β-dihydroxy-4-androstene ($1{\cdot}45 \times 10^{-4}$ mol/l) and (*b*) BABA ($n = 3$) ($8{\cdot}09 \times 10^{-5}$ mol/l) in *n*-hexane. Cell length: 1 mm.

Table 1. CD spectral data of BABA homologues.

n	Ellipticity ([θ]), deg cm^2 decimol^{-1}/ Wavelength (λ), nm min.	max.	Amplitude (*A*)†, deg cm^2 decimol^{-1}
1	−7590/259·4	10732/244·8	18322
2	−6501/260·8	7801/244·2	14302
3	−11013/260·6	13368/245·2	24381
4	−9402/260·8	11390/243·4	20810
5	−10359/260·6	12847/244·8	23206
6	−9712/261·4	9801/246·4	19513
7	−6955/261·6	7820/245·2	14775
8	−8655/261·4	9054/245·0	17709
9	−7360/261·4	12632/244·0	19992
10	−10937/260·8	11299/244·2	22236

†$A = [\theta]_{max} - [\theta]_{min}$.

intramolecular long-distance (17 Å) electron transfer in steroid derivatives. The transient moment in the alkoxybenzoyloxy group is almost parallel in the C–O axis in the 3-position of androstene skeleton. Since the present splitting Cotton effect indicates a negative chilarity, the alkoxybenzoyloxy group is bonded in the β-position to the 3-position. Table 1 shows CD parameters for the Cotton effect of different BABA homologues. The wave lengths at the maximum and minimum value are approximately independent of the length of alkoxy group (carbon No. *n*), although the value of *A* somewhat changes with *n*.

Changes in CD spectra by BABA concentration of $5{\cdot}4 \times 10^{-6}$ to $8{\cdot}5 \times 10^{-5}$ mol/l and that by temperature of 293 to 353 K were measured in *n*-hexane, respectively, and the CD spectra scarcely changed with both BABA concentration and temperature. Therefore the intramolecular interaction in BABA at room temperature may be sustained to 353 K in temperature and to $8{\cdot}5 \times 10^{-5}$ mol/l in the concentration.

3.2. *Mesogenicities of testosterone and estrone derivatives*

Typical DSC curves of BABA homologues are shown in figure 3. In the $n = 3$, one endothermic peak is observed near 434 K, corresponding to the melting point (T_m), and just above T_m, the sample thermally decomposed, this was observed for $n = 1$ and 2 as well. For the $n = 5$, T_m is located at 405 K in the first heating, and then one cholesteric mesophase is observed to 444 K. On the first cooling, the cholesteric mesophase appears at 442 K from the isotropic liquid phase and is sustained even at room temperature, which was also confirmed by polarized microscopy. This phenomenon was also observed for the $n = 4$–7 compounds. In the $n = 8$–10, a cholesteric mesophase is observed enantiotropically and the freezing point is seen as an endothermic peak on DSC curves at a lower temperature below T_m, indicating a presence of a super-cooled state. In the $n = 10$, there is one phase transition in the crystalline state.

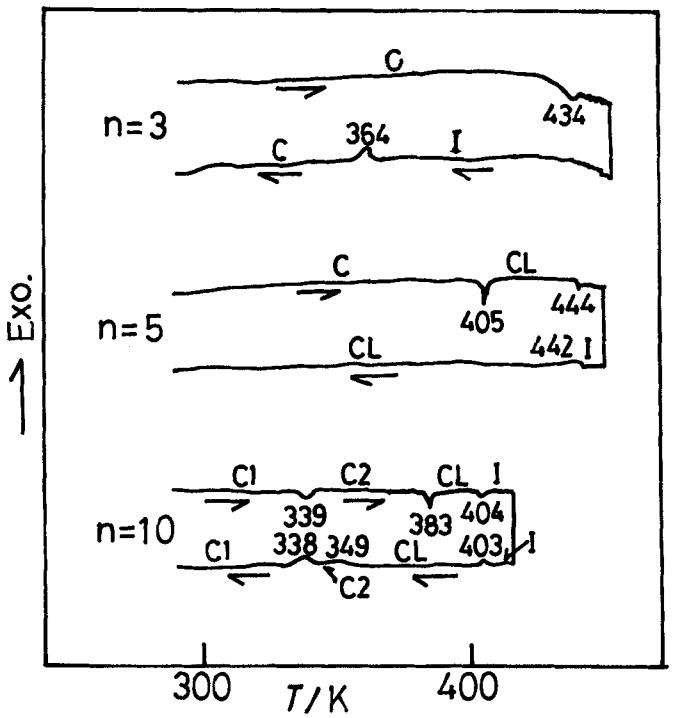

Figure. 3. Typical DSC curves of BABA homologues.

Table 2 lists thermodynamical parameters of the phase transition in BABA homologues. Figure 4 shows plots of phase transition temperature versus the alkoxy length (n) in BABA with those in 3β, 17β-bis(4-*n*-alkoxybenzoyloxy)-1,3,5,(10)-estratriene (BABE) (Compound G in figure 1) by Hoffmann *et al.* [2]. A cholesteric mesophase exists in the $n = 4$–10 of BABA and in the $n = 1$–10 of BABE. The values of the cholesteric-isotropic liquid phase temperatures ($T_{Ch\text{-}I}$) gradually decrease indicating an odd–even effect for both homologous series. The thermal stability of the mesophase is, however, apparently higher in BABA than in BABE. The sizes of a molecule for both homologues were estimated by use of CPK model, where it is assumed that the molecule is fully extended and that 3-alkoxybenzoyloxy group is in

Table 2. Phase transition parameters†.

Compound	n	T_m (K)/ ΔH_m(kJ mol^{-1})	$T_{Ch\text{-}I}$ (K)/ $\Delta H_{Ch\text{-}I}$(kJ mol^{-1})
A	1	433/	
	2	451/	
	3	434/	
	4	416/37	458/2
	5	405/43	444/1
	6	397/45	435/2
	7	390/23	417/2
	8	393/29	418/2
	9	374/8	408/1
	10	383/19	404/2
B		373/22	
C	1	399/15	
	2	409/23	
	3	381/22	
	4	398/25	
	5	370/23	
	6	338/21	
	7	348/24	
	8	337/24	
	9	344/29	
	10	345/34	
	11	342/31	
D		331/19	
E		338/21	
F		332/27	

†T_m and ΔH_m, melting point and its enthalpy change, $T_{Ch\text{-}I}$ and $\Delta H_{Ch\text{-}I}$, cholesteric–isotropic phase transition temperature and its enthalpy change.

Table 3. Molecular sizes in Angstrom unit of BABA (n = 4) and BABA (n = 4).

Compound	Breadth (D)	Length (L)	L/D	Length of skeleton
BABA	5·92	32·4	5·5	9·2
BABE	5·83	32·7	5·6	9·1

β-position on the steroid skeleton, which is determined by BABA from the CD spectral results described already. The data are listed in table 3. Since this value of L/D for BABA is almost the same as that for BABE, the difference in the thermal stability can not be explained by the molecular size. The chemical structure of BABA differs only in A-ring of the steroid skeleton from that of BABE; A-ring is in triene structure in BABE, and contains only one double bond in BABA. This difference is believed to influence the thermal stability.

17β-heptyloxybenzoyloxy testostrone (compound B) show no mesophase as shown in table 2. This suggests that testosterone skeleton is not so good in the ability for formation of mesophase.

Hoffmann *et al.* [2] found that BABE (compound G) shows enantiotropic cholestric mesophases as described already. In the present work, we studied mesogenicities

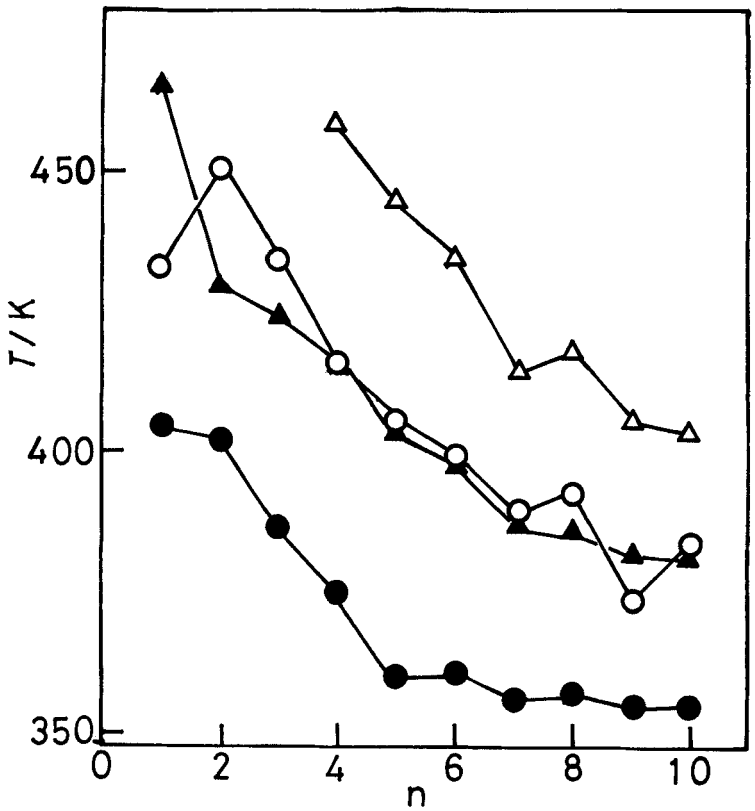

Figure 4. Phase transition temperatures versus alkoxy length (n) in BABA and BABE homologues. BABA, opened symbol; BABE, closed symbol; ○, T_m; △, $T_{Ch\text{-}I}$.

of compound D, E, F and G to clarify the ability of estron skeleton on formation of mesophase. As the results, these compounds apparently don't form any mesophase as shown in table 2. 3β-*n*-alkoxybenzoyloxy estrone (compound H) shows cholesteric mesophase monotropically only in the cooling process, which is reported by Hoffmann *et al.* [2], while compound D, 3β-*n*-alkanoyl estrone shows no mesophase. Apparently the elongated rigid core by the benzoate group is responsible for the appearance of the mesophase. Consequently the estrone skeleton is not as good a mesogen as the testosterone skeleton.

4. Conclusion

Testosterone and estrone skeletons are not so good as a rigid core of a mesogen. However, BABA homologues elongated by the two alkoxybenzoyloxy groups have a cholesteric mesophase with good thermal stability. The mesogenicities of BABA homologues were discussed on the basis of both the chemical structure and the conformation which was investigated by the CD spectra. The relationships between the mesogenicity of steroid hormone and the biological activity will be one of the important problems in the future.

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