SYNTHESIS AND MELTING PROPERTIES OF CHOLESTERYL ESTERS OF *ORTHO-n*-ALKOXYBENZOIC ACIDS

By

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The first ten compounds from the homologous series of cholesteryl esters of *ortho-n*-alkoxybenzoic acids have been synthetized, and their melting properties investigated with the aid of polarizing optical microscopy and differential scanning calorimetry (DSC).

In the literature a number of cholesterol benzoic acid esters showing liquid crystalline (mostly cholesteric) properties have been reported. Primarily the *para*-substituted benzoic acid esters have been synthetized, because their substituents are oriented in the direction of the molecular long axis (terminally-positioned substituents) [1, 2]. In the series of homologous *p*-alkoxybenzoic acid cholesteryl esters, the methyl, ethyl, *n*-propyl, *n*-butyl, *n*-pentyl and *n*-hexyl derivatives are enantiotropic cholesteric substances; all the others up to the octadecyl derivative show the enantiotropic C—S—Ch phase-sequence [3].

Little is known about the effects of the *meta*- and *ortho*-substituents. These substituents lie almost in the molecular plane, but not in the direction of the molecular long axis, and therefore they are called lateral substituents. VORA [4] has reported that the cholesterol *ortho*- and *para*-methoxybenzoates are non-mesomorphic, whereas the *ortho*-nitrobenzoate is monotropic smectic and enantiotropic cholesteric.

Recently a number of new series of homologous cholesterol derivatives have been reported, and their mesogenic properties have been studied [5], leading to the conclusion that there is no direct correspondence between the actual structures and the mesogenic properties. That is, from the properties of the first members of the series one cannot extrapolate to the properties of the second ones, etc. Therefore, it seemed reasonable for us to synthetize the title compounds and to study their melting properties.

The route of the preparation, as shown in Fig. 1, follows the sequence: salicylic acid (**I**) — methyl salicylate (**II**) — *ortho*-alkoxybenzoic acid ester (**III**) — *ortho*-alkoxybenzoic acid (**IV**) — *ortho*-alkoxybenzoyl chloride (**V**) — *ortho*-alkoxybenzoic acid cholesteryl ester (**VI**). Since all *ortho*-alkoxybenzoic acids (**IV**) investigated were liquids with high boiling points at atmospheric pressure, the corresponding methyl esters (**III**) and acid chlorides (**V**) were purified and the physical pro-

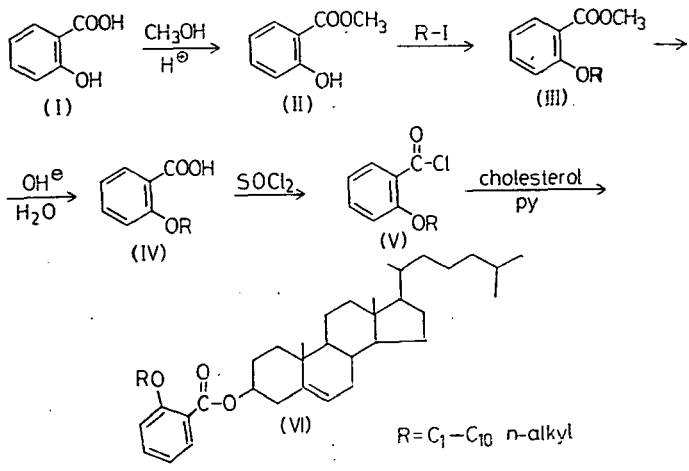

Fig. 1.

perties of the acid chlorides were registered; they are shown in Table I. The physical and analytical data on the cholesteryl esters (**VI**) are shown in Table II.

The melting properties of the compounds are closely similar to each other, with the exception of the methyl derivative. The methyl derivative has two melting points (99° and 120°, respectively), and on cooling a bluish-gray structureless appearance is observed under the microscope. DSC did not reveal any thermodynamic phase transition. With the lengthening of the alkyl chain in the case of the ethyl, *n*-propyl etc. derivatives, on heating only simple melting occured at the temperature values reported (see Table II). On cooling, the isotropic melt remains unchanged to the lowest temperatures investigated (about −20°) and subsequently forms a glass. All these compounds have an extremely low tendency to crystallize from their melts at temperatures down to −10° (several days).

Table I

Boiling points and some IR characteristics of ortho-n-alkoxybenzoyl chlorides

Substituent R	Bp. (°C/mm Hg)	IR $\nu_{C=0}$ (cm^{-1})	$\nu_{as\,COC}$ (cm^{-1})
methyl	105/3	1770	1286
ethyl	118/4	1768	1288
n-propyl	146/10	1770	1292
n-butyl	164/15	1772	1290
n-pentyl	167/11	1770	1288
n-hexyl	158/5	1770	1285
n-heptyl	175/17	1772	1285
n-octyl	179/4	1772	1288
n-nonyl	188/7	1770	1286
n-decyl	199/5	1770	1284

To summarize, in the case the *o*-alkoxybenzoic acid cholesteryl esters the methyl derivative shows a blue texture; the other derivatives were found to be nonmesogenic substances. All compounds investigated exhibited an extremely large temperature hysteresis.

Experimental

The melting points were determined with a PHMK (VEB Analytik, Dresden) hot stage. The thermal properties were studied with a Perkin—Elmer DSC 2 differential scanning calorimeter under nitrogen flushing, at 10°/min heating or cooling rates. The NMR and IR spectra were registered with JEOL 60 HL and Unicam SP 1000 spectrometers, respectively.

The preparation of 2-alkoxybenzoic acids (or its methyl esters)

To 35 ml 0.1 M methanolic sodium methylate solution, 0.1 mole (15.2 g) methyl salicylate and 0.12 mole of the corresponding alkyl iodide were added. The mixture was boiled under nitrogen, till TLC showed reaction to be complete (8—12 hours). After filtration of the inorganic substance the liquid was evaporated to one-half volume and the sodium iodide separating on cooling filtered on pump again.

(A) To the above filtrate, 10 ml water was edded and the mixture was extracted twice with 30 ml ethyl ether. The extracts were evaporated and hydrolyzed by boiling with aqueous methanolic KOH (about 1.5—8 hours). The solution was acidi-

Table II

Analytical and physical data of ortho-n-alkoxybenzoic acid cholesteryl esters (VI)

Substituent R	Formula	M. W.	Anal. calcd. C	Anal. calcd. H	Anal. found C	Anal. found H	M. p. °C	DSC C→I transition *(°C)
methyl	$C_{35}H_{52}O_3$	520.801	80.71	10.06	80.62	10.31	120.5—121**	99.0 and 120**
ethyl	$C_{36}H_{54}O_3$	534.828	80.85	10.18	81.05	10.26	120.2—121	119
n-propyl	$C_{37}H_{56}O_3$	548.855	80.97	10.28	80.93	10.17	91.5—92.8	93.5
n-butyl	$C_{38}H_{58}O_3$	562.882	81.09	10.39	80.96	10.46	73.8—75.1	74.0
n-pentyl	$C_{39}H_{60}O_3$	576.909	81.20	10.48	81.12	10.47	96.0—96.2	96.0
n-hexyl	$C_{40}H_{62}O_3$	590.336	81.30	10.58	81.15	10.75	91.7—92.8	92.0
n-heptyl	$C_{41}H_{64}O_3$	604.963	81.40	10.66	81.22	10.69	84.3—86	86.0
n-octyl	$C_{42}H_{66}O_3$	618.990	81.50	10.76	81.32	10.59	85.0—87.5	87.0
n-nonyl	$C_{43}H_{68}O_3$	633.017	81.59	10.83	81.42	10.80	79.0—81.0	80.0
n-decyl	$C_{44}H_{70}O_3$	647.044	81.68	10.90	81.41	10.72	44.0—46.0	45.5

* The temperatures of the C→I transition were extrapolated from the thermograms according to the linear slope method.

** At 98,5—99° melting to the isotropic melt was observed, and then at 103—6° the sample crystallized. On the thermogram two endothermic peaks appeared centered at about 101° and 122°, with a protracted exothermic peak at 103—115°

fied with aqueous HCl and extracted with ethyl ether. The extracts were shaked with lime-water and the calcium salicylate filtered off. To the filtrate conc. HCl was added and the mixture was extracted with benzene. Upon evaporation, the benzene solution yielded the crude *n*-alkoxybenzoic acids in sufficiently pure form to prepare the corresponding acid chlorides.

(B) The filtrate was evaporated completely and extracted with benzene. The extracts were distilled *in vacuo* and the methyl ester fraction collected. The methyl ester was hydrolyzed as above. This process was more convenient to prepare the alkoxybenzoic acids from the *n*-pentyl derivative up.

Preparation of ortho-alkoxybenzoic chlorides

At ambient temperatures 0.12 mole thionyl chloride was added to 0.1 mole alkoxybenzoic acids and the solution allowed to stand one day. The hydrogen chloride and the unreacted thionyl chloride were removed under moderate vacuum, and the acid chloride distilled as given in Table I.

Preparation of ortho-alkoxybenzoic acid cholesteryl esters

0.005 mole cholesterol was dissolved in 3.5 ml dry pyridine at ambient temperature, and then 0.006 mole *ortho*-alkoxybenzoic acid chloride dissolved in 5 ml dry benzene was added. The mixture was allowed to stand at room temperature for two (or more) days until no cholesterol spot was observed on TLC. Then the reaction mixture was poured into dilute HCl solution and extracted with benzene. The benzene extracts were washed in turn with water, with saturated aqueous $NaHCO_3$ solution and with water. After drying on anhydrous $CaCl_2$, the extracts were concentrated and purified on a silica column by eluting with benzene: chloroform (1:1) mixture. The pure fractions were collected, evaporated to dryness and crystallized from ethyl alcohol. The physical and analytical properties of esters prepared are given in Table II.

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СИНТЕЗ И ТЕРМИЧЕСКИЕ ПРЕВРАЩЕНИЯ ЭФИРОВ ХОЛЕСТЕРИНА И *орто-н*-АЛКОКСИ БЕНЗОЙНЫХ КИСЛОТ

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Синтетизированы первые десять членов гомологического ряда эфиров холестерина и *орто-н*-алкокси бензойных кислот и изучены их термические превращения методом поляризованной оптической микроскопии и дифференциально-сканирующей калориметрии (ДСК).