On the Mechanism of the Oxidation of Tropan-3α-ol with Benzoyl Chloride

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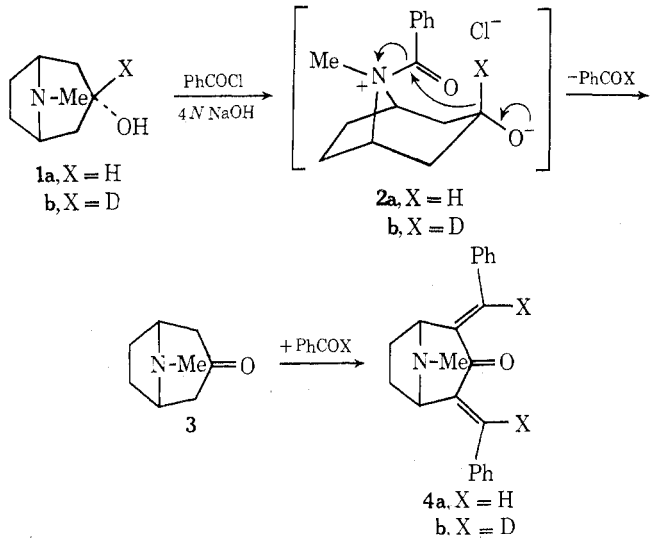
Polycyclic molecules having sterically proximate alcohol and keto functions have been occasionally observed to undergo base-catalyzed redox reactions under mild conditions.[1] However, postulated hydride transfer mechanisms have seldom been verified by isotopic labeling experiments. A case in point is the reaction of tropan-3α-ol[2] (**1a**) with benzoyl chloride under Schotten–Baumann conditions to give *trans,trans*-dibenzylidenetropinone (**4a**), for which Calvert and Hobson[3] proposed the mechanism abbreviated in Scheme I. Although circumstantial evidence is in accord with the proposed mechanism, we have reinvestigated this reaction employing deuterium-labeled precursors and the results of this study fully corroborate the mechanism of Calvert and Hobson.

Scheme I



1a, X = H
b, X = D

2a, X = H
b, X = D

4a, X = H
b, X = D

Reduction of tropinone with $LiAlD_4$ in ether[4] afforded an 89% yield of a 1:1 mixture of the deuterated 3α- and 3β-tropanols which can be separated by fractional crystallization of the picrates.[5] Reaction of a well-stirred solution of 3β-deuteriotropan-3α-ol (**1b**) in 4 *N* NaOH with excess benzoyl chloride at ambient temperature for 15 hr gave the dideuterated dienone **4b** in ca. 80% yield. The presence of the label was readily determined by comparison of the mass spectra of **4b** and its undeuterated counterpart **4a**, which revealed that the molecular ion at *m/e* 315 and the major peaks at *m/e* 287 and 259 in **4a** were shifted two mass units higher in **4b**. Furthermore, the 100-MHz NMR spectra of **4a** and **4b** were superimposable except for the absence of the sharp singlet at δ 7.81 in **4b** corresponding to the benzylidene hydrogens.

These experimental results provide additional conclusive evidence in support of the proposed mechanism the key feature of which is the intramolecular transfer of a 3β-hydride to the strongly electrophilic carbonyl of the *N*-benzoylammonium ion **2** to afford tropinone and benzaldehyde.[6,7] The subsequent stereospecific aldol condensation of **3** with benzaldehyde is well precedented.[8] The fact that cyclohexanol, *N*-benzoylnortropine, and 3α-deuteriotropan-3β-ol are all recovered unchanged under the reaction conditions further implies the intermediacy of **2**.

Experimental Section[9]

Reaction of Tropan-3α-ol with Benzoyl Chloride. To a rapidly stirred solution of 0.426 g (3.38 mmol) of 3β-deuteriotropan-3α-ol in 65 ml of 4 *N* NaOH was added dropwise over a 30-min period 7.10 g (50.7 mmol) of freshly distilled benzoyl chloride. After addition was complete, the mixture was allowed to stir under nitrogen at ambient temperature for 15 hr. The pale yellow precipitate was collected by suction filtration, washed with 25 ml of water, and recrystallized from 10 ml of boiling methanol to afford 0.427 g (1.35 mmol, 80% yield) of the dideuterated *trans*-dibenzylidenetropinone as pale yellow needles: mp 151–153° (lit.[7] mp of undeuterated compound 153°); ir ($CHCl_3$) 1666, 1605, 1495, 1445, 1090, and 1070 cm^{-1}; 100-MHz NMR ($CDCl_3$) δ 7.36 (s, 10 H), 4.40 (m 2 H), 2.60 (m, 2 H), 2.26 (s, 3 H), 2.00 (m, 2 H); MS *m/e* (rel intensity) 317 (M^+, 41), 289 (100), and 261 (29).

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Registry No.—**1b**, 56292-47-8; **4b**, 56290-48-9; benzoyl chloride, 98-88-4.

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(6) Deuterated benzaldehyde can be isolated by extraction after 3 hr reaction time.

(7) The *N*-benzoyl group must be situated syn relative to the 3β-hydride in order for the intramolecular transfer of hydride to occur as shown in structure **2**. However, Fodor has recently reviewed a body of evidence which indicates that irreversible N-quaternization and N-oxidation reactions of tropines occur preferentially anti. These data suggest that formation of the *N*-benzoylammonium ion is reversible, leading to both the syn and anti isomers, but only the syn isomer is reduced. See G. Fodor in "The Alkaloids", Vol. XIII, R. H. F. Manske, Ed., Academic Press, New York, N.Y., 1971, pp 359–365, for a discussion of the configuration of quaternary tropanium salts.

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(9) The tropan-3α-ol, tropinone, and lithium aluminum deuteride were obtained from Sigma Chemical Co., Aldrich Chemical Co., and Merck Sharp and Dohme, Inc., respectively. The NMR spectra were recorded on a Varian HA-100 spectrometer, the ir spectra on a Perkin-Elmer 457 spectrometer, and mass spectra on a Du Pont 21-497B spectrometer.

Low-Melting Nematic Phenyl 4-Benzoyloxybenzoate Liquid Crystals[1]

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The preparation of nematic liquid crystals with specific physical properties for use in electrooptical applications has been the subject of many recent investigations.[2-5] The initial work on materials for use in these applications emphasized the preparation of liquid crystals that were either

Table I
Transition Temperatures[a] for Some Phenyl 4-Benzoyloxybenzoate Liquid Crystals (2)

R[b]	R' 3	4	5	6	7	8
5, X = Y = H	K78N188I	K75N179I	K78N180I	K74S78N169I	K76S104N169I	K79S117N161I
5, X = Cl; Y = H	K57N130I	K41N118I	K40N122I	K40N113I	K46N114I	K42N109I
5, X = H; Y = Cl	K75N133I	K76N123I	K67N130I	K58N119I	K58N119I	K63N112I
6, X = Cl; Y = H	K48N120I	K48N110I	K35N114I	K40N106I	K47N107I	K41S45N102I
7, X = Cl; Y = H	K46N119I	K45N109I	K34N115I	K40N107I	K46N109I	K41N104I
8, X = Cl; Y = H	K45N108I	K51N102I	K40N109I	K55N101I	K41N104I	K43S49N100I
8, X = H; Y = Cl	K60N117I	K64N109I	K65N112I	K64N105I	K72N106I	K73N101I

[a] Reference 25. [b] R equals number of carbon atoms in n-alkyl chain.

mesomorphic at room temperature or were sufficiently low melting to provide room temperature materials when two or more components were mixed. The preparation of compounds to meet the room temperature requirement has not been easy. The number of single-component room temperature nematic materials is fairly limited and these materials have relatively narrow nematic ranges. More success has been obtained by preparing low-melting materials that can be mixed to provide room temperature nematic compositions.[6,7] However, some of the currently available materials are unstable. For example, the commonly used Schiff base materials are readily hydrolyzed to the starting aldehyde and amine.[8] Mixtures of Schiff bases undergo exchange reactions under various conditions to give additional liquid crystals, which results in a new liquid crystal mixture with different physical properties.[9] Other examples are the α-chloro-*trans*-stilbenes prepared by Young,[3] which were found to be photochemically unstable, and thus not so generally useful.[6]

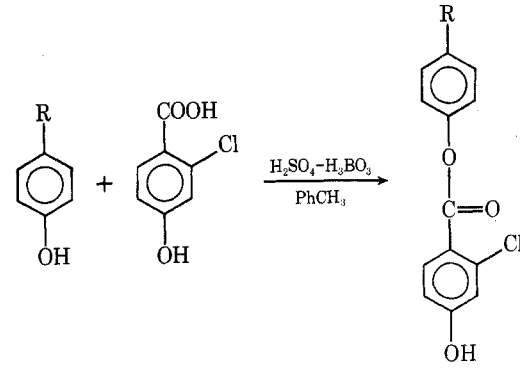
In addition to the mesomorphic transition temperatures, the dielectric anisotropy of the liquid crystal is of critical importance in that it governs the specific type of electrooptical effects for which a given material is suitable and also determines the type of molecular reorientations the liquid crystal molecules make with respect to the direction of an applied electric field.[10] Recent studies in relating the dielectric anisotropy to molecular structure have increased our understanding of this characteristic.[11-13] Although we now know the type of molecular modifications necessary to change the dielectric anisotropy, we are still confronted with the problem of preparing compounds that are both low melting and also have the desired dielectric properties. Thus there remains a considerable synthetic challenge to balance these physical properties into usable materials with high stability.

The recent work on the preparation of liquid crystalline aromatic esters may provide materials that are useful in electrooptical as well as other applications.[2,14] Additional research is required to ascertain the relative merits of the various classes of liquid crystals in the multitude of electrooptical applications that are now known.

In earlier work in this laboratory,[14] it was demonstrated that liquid crystals derived from phenyl 4-benzoyloxybenzoate melt at a significantly lower temperature than the corresponding isomeric liquid crystals derived from hydroquinone or terephthalic acid. It was also shown that the combination of terminal dialkyl substituents along with a chlorine atom ortho to the carbonyl of the ester linkage resulted in very low-melting compounds in the phenyl 4-benzoyloxybenzoate series. This paper describes the preparation of several homologous series of low-melting phenyl 4-benzoyloxybenzoate liquid crystals. Some of these compounds afforded room temperature compositions upon mixing.

Results and Discussion

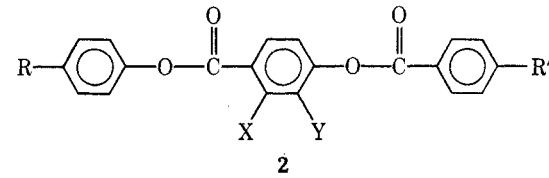
The phenyl 4-benzoyloxybenzoates were conveniently prepared in two steps. The first involved an acid-catalyzed esterification of a 4-alkylphenol with 4-hydroxybenzoic acid or one of its chlorinated derivatives to give a substituted phenyl 4-hydroxybenzoate (eq 1). The catalyst used in



(1)

1

this reaction was a combination of sulfuric acid and boric acid as described by Lowrance.[15] This catalyst was found to be remarkably specific in that only the hydroxyl group of the 4-alkylphenol was involved in ester formation. No esters or polymers resulting from the participation of the hydroxyl group of the 4-hydroxybenzoic acid were formed in the reaction. The reaction of 1 with a 4-alkylbenzoyl chloride gave the desired liquid crystal (2). In contrast to this



2

procedure, Young and Green[16] have prepared some low-melting nematic derivatives of phenyl 3-methyl-4-benzoyloxybenzoate by a six-step method.

The compounds prepared in this study along with their mesomorphic transition temperatures are recorded in Table I. The effect of changing molecular structure on the transition temperatures for these compounds is consistent with well-known observations and can be briefly summarized as follows. A small, laterally placed substituent can be very effective in reducing the crystal-to-mesophase transition temperature.[17] The chlorine substituent reduced the nematic-to-isotropic transition temperature approximately 50–60° as a result of the increase in the width of the molecule. The even–odd effect in the nematic-to-isotropic transition temperatures was observed. The nematic-to-isotropic transition temperatures for these homologous series decrease with increasing carbon chain length, which is in

agreement with de Jeu,[18] who has shown that this trend is usually observed for series with relatively high transition temperatures.

The transition temperatures for the phenyl 3-methyl-4-benzoyloxybenzoates prepared by Young[16] and the 3-chloro derivatives in Table I are very similar, with most of the nematic-to-isotropic transitions as close as 1–2° for a chloro vs. methyl comparison. This again demonstrates the lack of influence permanent dipole moments have on the nematic-to-isotropic transition temperature.[19]

The optimum location for the chlorine substituent in obtaining low-melting phenyl 4-benzoyloxybenzoates is in a position ortho to the carbonyl of the ester linkage. In the comparisons in this study, the 2-chloro derivatives provided the lowest melting compounds compared to the 3-chloro and nonchlorinated analogs. The laterally placed chlorine atom coupled with terminal dialkyl substitution has resulted in some phenyl 4-benzoyloxybenzoates with nematic ranges extending from below 40° to above 100°. Room temperature compositions can be obtained easily by mixing two or more of these materials; for example, a 1:1 by weight mixture of 4-pentylphenyl 2-chloro-4-(4-pentylbenzoyloxy)-benzoate and 4-octylphenyl 2-chloro-4-(4-heptylbenzoyloxy)benzoate is nematic from 5° to 111°.

The effect of structural changes on the dielectric anisotropy of liquid crystals derived from phenyl 4-benzoyloxybenzoate has been discussed in a separate paper.[12] These compounds are also of special interest in that the dielectric anisotropy changes sign at relatively low frequencies,[13,20,21] which offers an additional means of modifying the operational characteristics of liquid crystal devices.[22]

Experimental Section

The 4-alkylphenols,[23] 4-alkylbenzoic acids,[24] and 2-chloro-4-hydroxybenzoic acid were prepared by known methods or were obtained from Eastman Organic Chemicals. 3-Chloro-4-hydroxybenzoic acid was obtained from Aldrich Chemical Co. The transition temperatures were determined in an open capillary tube and are uncorrected. Satisfactory elemental analyses were obtained for all new compounds. A representative procedure for the preparation of these liquid crystals is given below.

4-*n*-Hexylphenyl 2-Chloro-4-hydroxybenzoate. A mixture of 4-*n*-hexylphenol (40.0 g, 0.22 mol) and 2-chloro-4-hydroxybenzoic acid (34.5 g, 0.20 mol) in toluene (1 l.) containing concentrated sulfuric acid (1.0 g, 10 mmol) and boric acid (0.6 g, 10 mmol) was refluxed for 65 hr, a Dean-Stark trap being used to remove the water formed in the reaction. The solution was cooled and the solvent was removed under reduced pressure. The resulting solid was recrystallized twice from ethanol–water to give 53.9 g (81%) of 4-*n*-hexylphenyl 2-chloro-4-hydroxybenzoate: mp 141–143°; ir (KBr) 3320, 2900, 1700, 1590, 1560 cm^{-1}. The analytical sample melted at the same temperature.

4-*n*-Hexylphenyl 2-Chloro-4-(4-*n*-hexylbenzoyloxy)benzoate. To a solution of 4-*n*-hexylphenyl 2-chloro-4-hydroxybenzoate (1.15 g, 4.7 mmol) in dry pyridine (25 ml) was added 4-*n*-hexylbenzoyl chloride (1.13 g, 5.0 mmol). After standing at room temperature for 18 hr, the reaction mixture was poured into an ice–water mixture and the product was isolated by filtration. Recrystallization from ethanol gave 1.9 g (77%) of 4-*n*-hexylphenyl 2-chloro-4-(4-*n*-hexylbenzoyloxy) benzoate: K39N105I;[25] ir (KBr) 2900, 1740, 1600 cm^{-1}. The analytical sample was obtained from ethanol: K40N106I.

Registry No.—4-*n*-Hexylphenyl 2-chloro-4-hydroxybenzoate, 56363-83-8; 4-hexylphenol, 2446-69-7; 2-chloro-4-hydroxybenzoic acid, 56363-84-9; 4-*n*-hexylphenyl 2-chloro-4-(4-*n*-hexylbenzoyloxy)benzoate, 56363-85-0; 4-hexylbenzoyl chloride, 50606-95-6.

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