181. The Synthesis and Transition Temperatures of Benzoate Ester Derivatives of 2-Fluoro-4-hydroxy- and 3-Fluoro-4-hydroxybenzonitriles

by **Stephen M. Kelly**

Brown Boveri Research Centre, CH-5405 Baden

(17.VII.84)

Summary

The synthesis and the liquid-crystal temperatures of sixty 4-cyano-2-fluorophenyl and 4-cyano-3-fluorophenyl 4-substituted benzoates are described. The nematic-isotropic liquid transition temperatures of most of these novel esters are only marginally lower than those of the corresponding esters containing an H-atom in place of the F-substituent. In several instances, the clearing points of the F-substituted-phenyl esters are *higher* than those of the non-substituted-phenyl esters. The nematic ranges of several of the new esters are markedly broader than those of the analogous non-F-substituted-phenyl esters.

Introduction. – The effect of lateral substituents on the liquid-crystal transition temperatures of a wide range of compounds has been studied systematically [1–3]. The vast majority of the liquid crystals studied were acids [1] or bore terminal alkyl or alkoxy chains [2] [3].

In contrast, only a small number of compounds bearing a terminal CN-function *and* a lateral substituent have been reported [4] [5]. Therefore, to study the effect of lateral substitution on liquid crystals incorporating a CN-group in a terminal position, we synthesized over one hundred ester derivatives of 2-fluoro- and 3-fluoro-4-hydroxybenzonitrile. The F-atom was chosen as the lateral substituent, because F-substituted liquid crystals generally exhibit nematic-isotropic transition temperatures only a little below those of the corresponding compounds with a H-atom in place of the F-atom. Compounds incorporating larger substituents (*e.g.*, Cl, Br, CN) exhibit *much* lower nematic-isotropic transition temperatures and often do not exhibit observable liquid-crystal phases (see *Table 5*) [1–3]. The acid moiety of the esters contained one or more 1,4-disubstituted rings chosen from benzene, *trans*-cyclohexane and bicyclo[2.2.2]-octane, *i.e.* those rings most commonly found in liquid crystals.

The necessary hydroxy-benzonitriles were produced *via* demethylation [6] of the corresponding anisoles, which were prepared by cyanation of the analogous 4-bromo-2-fluoroanisole and 4-bromo-3-fluoroanisole. The bromides could be synthesized according to [7] from commercially available 2-fluoroanisole and 3-fluoroanisole. The ester derivatives of these nitriles were produced in the usual way *via* interaction with the appropriate acid chloride. The preparation of 3-fluoro-4-hydroxybenzonitrile *via* nitration of 2-fluoroanisole, followed by demethylation to yield phenol, reduction to the amine, and subsequent diazotisation and cyanation with KCN has already been reported [8]. The reaction pathway reported here (see *Exper. Part*) contains one less step and offers a much improved overall yield of nitrile.

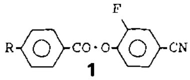
Here, we describe the synthesis and liquid-crystal transition temperatures of those esters only containing substituted benzene rings. The corresponding data for the analogous esters containing *trans*-1,4-disubstituted cyclohexane or 1,4-disubstituted bicyclo-[2.2.2]octane are reported in [9].

The birefringence, the dipole moments, the dielectric, diamagnetic, and elastic constants of several ester derivatives (with equal chain lengths) of 2-fluoro- and 3-fluoro-4-hydroxybenzonitrile containing the above-mentioned ring systems have been measured. These results will be reported in detail elsewhere [10] [11].

Results and Discussion. – The liquid-crystal transition temperatures (C–N/I, N–I) and some enthalpies of fusion (*ΔH*) for the ester derivatives **1** of 4-alkyl (or 4-alkoxy)benzoic acids and 3-fluoro-4-hydroxybenzonitrile are recorded in *Table 1*. In addition the differences between the clearing points (N–I) of the F-substituted esters **1** and those of the corresponding homologues of the analogous non-F-substituted esters (with an H-atom in place of the F-atom) are given in the fourth column. The liquid crystal transition temperatures of the 4-cyano-2-fluorophenyl 4-alkylbenzoates are plotted against the number of C-atoms (n) in the terminal C-chain in *Fig. 1*.

As can be seen from *Table 1* and *Fig. 1*, the nematic-isotropic liquid transition temperatures of these alkyl-substituted esters exhibit the normal pattern of alternation. Apart from the first member of the series which possesses the highest clearing point (N–I), the clearing point generally increases with increasing chain length. The first four homologues of the esters exhibit monotropic nematic phases while the higher homologues possess enantiotropic nematic phases of a narrow range. The plot of the melting points against the number of CH_2-units in the C-chain is irregular. The melting points

Table 1. *Transition Temperatures* (°C) *and Enthalpies of Fusion* (kcal mol^{-1}) *for Compounds* **1**



1

R	C–N/I	N–I[a])	ΔT_{N-I}(H→F)	ΔH
CH_3	97	(65.5)	−11.5	–
C_2H_5	65	(37)	−23	–
C_3H_7	55.5	(51)	− 0.5	4.3
C_4H_9	46.5	(42)	− 0.5	7.05
C_5H_{11}	53.5	55	− 3	7.65
C_6H_{13}	46	46.5	+ 0.5	8.0
C_7H_{15}	47	54	− 3	7.55
C_8H_{17}	49	50.5	–	7.4
CH_3O	119.5	(93)	–	–
C_2H_5O	112	129	+24	5.75
C_3H_7O	71.5	79.5	–	5.7
C_4H_9O	84.5	(84)	−20	5.85
$C_5H_{11}O$	86.5	(74.5)	− 2.5	8.65
$C_6H_{13}O$	78.5	79.5	− 1.5	9.6
$C_7H_{15}O$	79.5	(76)	− 6	10.5

[a]) () Represents a monotropic transition temperature.

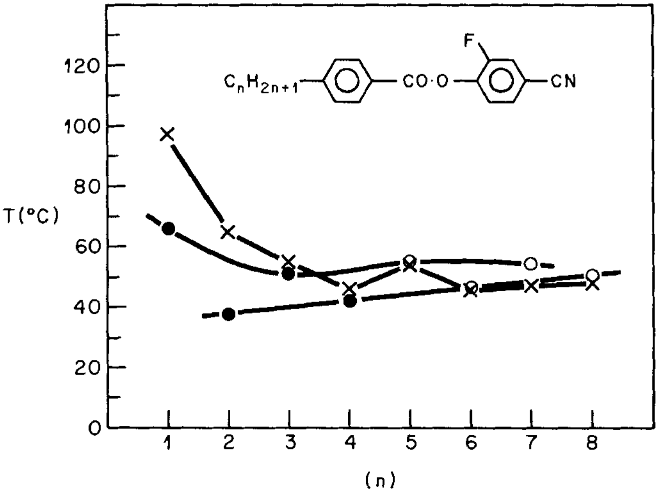


Fig. 1. *Plot of the transition temperatures* vs. *the number of CH_2-groups* (n) *in the C-chain* (C_nH_{2n+1}) *of the esters formulated* (X, crystal-nematic/isotropic liquid transition; O, enantiotropic nematic-isotropic liquid transition; ●, monotropic nematic-isotropic liquid transition)

(C—I, C—N) of the early members of the series are generally higher than those of the later members of the series.

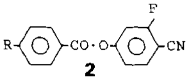
Since the completion of this work, a number of the 4-cyano-3-fluorophenyl 4-alkylbenzoates have been reported [12]. The liquid-crystal transition temperatures reported by the other authors for these esters are in each instance lower (sometimes significantly) than those reported in *Table 1*.

The melting points and clearing points of the corresponding alkoxy-substituted esters **1** are higher than those of the alkyl-substituted esters **1**. The liquid-crystal transition temperatures against the number of C-atoms in the alkoxy chain decrease gradually from high values for short chain lengths to lower values as the chain becomes longer. In this case the second member of the series possesses the highest clearing point.

A striking feature of these results is that the nematic-isotropic transition temperatures of the 2-fluoro-phenyl alkyl(alkoxy)-substituted esters **1** are only marginally lower (*ca.* 4°, on average comparing only C-chains of equal length) than those of the corresponding unsubstituted esters with a H-atom in place of the F-atom [13] [14], see the fourth column of *Table 1*. One homologue ($R = C_6H_{13}$) of the alkyl-substituted esters and one homologue ($R = C_2H_5$) of the alkoxy-substituted esters actually exhibit *higher* clearing points than their non-F-substituted analogues (+0.5° and +24°, respectively). This is in contrast to the large decreases (−28°, on average) in clearing point observed upon introducing a F-substituent into the same position in the corresponding dialkyl benzoates with a terminal alkyl group in place of the CN-function [15]. A discussion of these effects is given in [9] [11].

The liquid-crystal transition temperatures and some enthalpies of fusion of the 4-cyano-3-fluorophenyl 4-alkyl-(or 4-alkoxy-)benzoates **2** are recorded in *Table 2*. The trends in the liquid-crystal transition temperatures of the 3-fluorophenyl esters **2** are

Table 2. *Transition Temperatures* (°C) *and Enthalpies of Fusion* (kcal mol^{-1}) *for Compounds* **2**



2

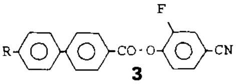
R	C–N/I	N–I[a])	ΔT_{N-I}(H→F)	ΔH
CH_3	129	(36)	–41	–
C_2H_5	78	(8)	–52	–
C_3H_7	70	(20.5)	–31	–
C_4H_9	16	(9)	–33.5	–
C_5H_{11}	30.5	(24.5)	–36	–
C_6H_{13}	35.5	(10)	–36	–
C_7H_{15}	28	28.5	–28.5	4.5
C_8H_{17}	< 21	26.5	–	–
CH_3O	132	(64)	–	–
C_2H_5O	97.5	(65.5)	–39.5	–
C_3H_7O	78	(42)	–	7.9
C_4H_9O	72	(48.5)	–55.5	8.2
$C_5H_{11}O$	68	(42)	–54	9.0
$C_6H_{13}O$	59.5	(50.5)	–30.5	8.5
$C_7H_{15}O$	70.5	(51)	–31	9.7

[a]) ( ) Represents a monotropic transition temperature.

similar to those of the analogous 2-fluorophenyl esters **1** except that the clearing points are still rising for the longest chain lengths studied. The clearing points of all of the 3-fluorophenyl esters **2** are considerably lower (–33° and –39°, on average) than those of the corresponding 2-fluorophenyl esters **1** and the non-F-substituted-phenyl esters [13] [14]. Only two homologues ($R = C_7H_{15}$, C_8H_{17}) of the alkyl-substituted esters exhibit enantiotropic nematic phases (at or just above room temperature). All of the nematic phases of the alkoxy-substituted esters are monotropic. As usual, their transitions to the isotropic liquid occur at higher temperatures than those of the analogous alkyl-substituted esters. The melting points of the homologues of the esters **2** with short C-chains are much higher than those with longer C-chains.

The liquid-crystal transition temperatures of the three-ring esters **3** of 4'-alkyl(or 4'-alkoxy)-4-phenylbenzoic acid and 3-fluoro-4-hydroxybenzonitrile are collated in *Table 3*. The liquid-crystal transition temperatures of the alkyl-substituted esters **3** are plotted against the number of C-atoms (n) in the C-chain in *Fig. 2*.

Table 3. *Transition Temperatures* (°C) *for Compounds* **3**



3

R	C–N	N–I	R	C–N	N–I
CH_3	163	252.5	CH_3O	169.5	282
C_2H_5	132	232	C_2H_5O	170	296
C_3H_7	126	231	C_3H_7O	164	269
C_4H_9	116.5	216	C_4H_9O	149	255
C_5H_{11}	125	211.5	$C_5H_{11}O$	154	233
C_6H_{13}	125	198.5	$C_6H_{13}O$	150.5	223.5
C_7H_{15}	124	195	$C_7H_{15}O$	149.5	216
C_8H_{17}	119	185.5			

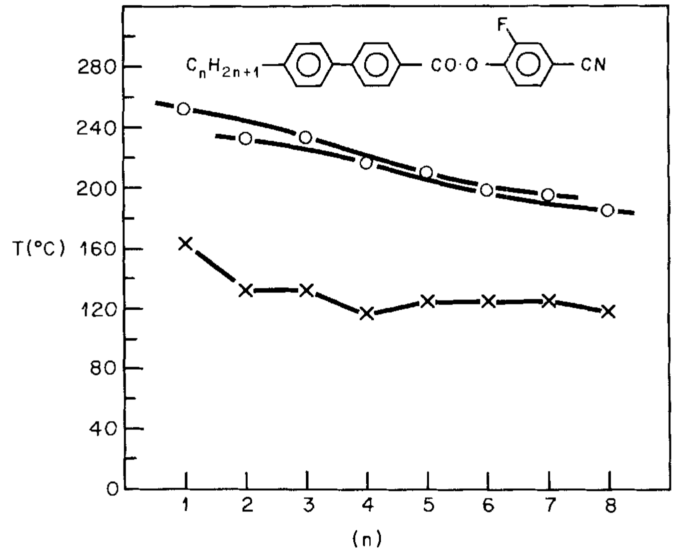


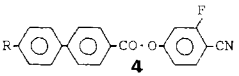
Fig. 2. *Plot of the transition temperatures* vs. *the number of CH_2-groups* (n) *in the C-chain* (C_nH_{2n+1}) *of the esters formulated* (X, crystal-nematic transition; O, enantiotropic nematic-isotropic liquid transition)

As is often the case [16], the introduction of an additional 1,4-disubstituted phenyl ring into the two-ring esters **1** to form **3** results in a much greater increase in the clearing point (+165°, on average) than in the melting point (+62°, on average). As a consequence of this, each homologue of the phenyl-benzoates **3** exhibits a strongly enantiotropic nematic phase.

Although only two pairs of homologues with identical chain lengths (C_5H_{11} and $C_6H_{13}O$) can be compared, the clearing points of the 4-cyano-2-fluorophenyl esters **3** seem to exhibit clearing points not significantly lower (*ca.* −10°→−20°) than the corresponding non-F-substituted-phenyl esters [16].

The liquid crystal transition temperatures of the three-ring 4-cyano-3-fluorophenyl 4′-alkyl(or 4′-alkoxy)-4-phenylbenzoates **4** are recorded in *Table 4*. The liquid-crystal transition temperatures of the esters **4** show the normal pattern of alternation. The plots for the 3-fluorophenyl esters **4** are very similar to those for the corresponding

Table 4. *Transition Temperatures* (°C) *for Compounds* **4**



4

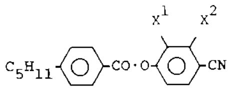
R	C–N	N–I	R	C–N	N–I
CH_3	172.5	227	CH_3O	174	261.5
C_2H_5	130.5	207.5	C_2H_5O	153	260
C_3H_7	98	207	C_3H_7O	141	245.5
C_4H_9	81	192.5	C_4H_9O	94	234
C_5H_{11}	86.5	190	$C_5H_{11}O$	91	216
C_6H_{13}	67.5	179.5	$C_6H_{13}O$	79.5	210
C_7H_{15}	59	176	$C_7H_{15}O$	65	200
C_8H_{17}	56	169.5			

2-fluorophenyl esters **3** except that the melting points decrease more regularly and strongly with increasing chain length.

The three-ring 4-cyano-3-fluorophenyl esters **4** exhibit higher melting points (+37.5°, on average) and much higher clearing points (+177°, on average) than the corresponding homologues of the two-ring esters **2**. In the two cases where comparison is possible (R = C_5H_{11} and $C_6H_{13}O$) the three-ring 3-fluorophenyl esters **4** exhibit lower clearing points (*ca.* $-20° \rightarrow -40°$) than the analogous three-ring, non-F-substituted-phenyl esters [16], which is consistent with the results observed for the analogous two-ring esters.

The effect of replacing one of the H-atoms (X^1 or X^2) of 4-cyanophenyl 4-pentylbenzoate with another element (F or Cl) or functional group (CN) is shown in *Table 5*. Whereas the F-substituted-phenyl esters exihibit observable nematic phases, none could be observed for the compounds containing larger substituents (Cl or CN). This is consistent with the observation [1–3] that a linear relationship with negative slope generally exists between the size of the lateral substituents and the nematic-isotropic transition temperatures of the compounds containing them.

Table 5. *Transition Temperatures* (°C) *for Compounds of Structure:*



X^1	X^2	C–N/I	N–I[a])	Ref.
H	H	64.5	(58)	[16]
F	H	53.5	55	–
CN	H	91	–	[4]
H	F	30.5	(24.5)	–
H	Cl	35	–	[18]
H	CN	36	–	[4]

[a]) ( ) Represents a monotropic transition temperature.

The author thanks Prof. *R. Tabacchi* and Dr. *S. Claude* of the Institut de Chimie, Neuchâtel, for the ^{1}H-NMR and mass spectral data, Dr. *Eder* of the Institut of Microchimie, Geneva, for the combustion analyses, and Miss *H. Field* of the University of Cambridge for the enthalpy data.

Experimental Part

(Mr. *F. Rime* is thanked for exceptionally competent technical assistance)

General. The liquid-crystal transition temperatures of the compounds **1–4** were determined by optical microscopy using a *Leitz Orthoplan* microscope, in conjunction with a *Mettler FP52* heating stage and *FP5* control unit. All of the liquid-crystal phases could be directly observed and no virtual values (extrapolated) had to be determined. When necessary, the *Mettler* stage could be cooled ($< -20°$) by allowing N_2 gas, cooled by liquid N_2, to pass through the stage at a controlled rate. The enthalpies of fusion of the highest melting forms of the esters **1–4** were determined using a *Perkin Elmer DSC-2* differential scanning calorimeter equipped with a *Hewlett Packard 3380A* integrator. Indium was used as a standard for calibration.

The purity of the compounds was determined by TLC and GLC. A *Perkin Elmer Sigma 1* gas-chromatographic system and also a *Perkin Elmer 3920B* gas chromatograph with a *Hewlett Packard 3380A* integrator were used.

The structures of the compounds were checked by analysis of their IR, ^{1}H-NMR, and mass spectra; the instruments used were a *Perkin Elmer PE683* IR spectrometer with model *3600* data station, a *Brucker WP 200 NMR* spectrometer, and a *Hitachi RMU 6L* mass spectrometer, respectively.

4-Bromo-2-fluoroanisole. Br_2 (40 g, 0.22 mol) was added dropwise over *ca.* 3 h to a solution of 2-fluoroanisole (28 g, 0.22 mol) and $CHCl_3$ (50 ml) under anh. conditions at r.t. The red colour disappeared immediately on addition and a steady flow of HBr was observed. After the addition was complete the resultant solution was heated under gentle reflux for *ca.* 1 h. The cooled solution was then washed with brine (2 × 200 ml), with 10% NaOH (2 × 200 ml), and finally with brine (2 × 500 ml) and then dried ($MgSO_4$). The solvent was removed from the filtered solution under slightly reduced pressure to give crude product which was distilled under reduced pressure to yield pure *4-bromo-2-fluoroanisole* (42 g, 92%), b.p. 98°/20 Torr ([7]: 148–150°/14 Torr). MS: 204, 206 (M^+).

4-Bromo-3-fluoroanisole was prepared similarly (77%); b.p. 214–216° at atm. pressure. MS: 204, 206 (M^+).

4-Methoxy-3-fluorobenzonitrile. A solution of 4-bromo-2-fluoroanisole (31.5 g, 0.15 mol), anh. CuCN (16.5 g, 0.18 mol) and dry DMF (30 ml) was heated at 185° for 3 h under anh. conditions. The cooled mixture was added to a solution of anh. $FeCl_3$ (30 g) and conc. HCl (2 ml) in H_2O (300 ml) and stirred for 30 min at 50–60°. The resultant mixture was shaken with Et_2O (4 × 250 ml) and the combined org. layers were washed with brine (2 × 1,000 ml) and dried ($MgSO_4$). The filtered solution was evaporated under slightly reduced pressure to yield a residue, which was taken up in a minimum amount of solvent and eluted from a silica-gel column with toluene. The crude product was crystallized from MeOH to yield pure *4-methoxy-3-fluorobenzonitrile* (13.6 g, 58%), m.p. 98–99° ([17]: 96.5°). IR (KBr): 1285, 2845 ($ArOCH_3$), 2215 (CN). MS: 151 (M^+). Anal. calc. for C_9H_6FNO (151.14): C 63.57, H 4.01, F 12.57, N 9.26; found: C 63.54, H 4.06, F 12.64, N 9.17.

4-Methoxy-2-fluorobenzonitrile was prepared similarly (60%), m.p. 59–60°. IR (KBr): 2215 (CN). MS: 151 (M^+). Anal. calc. for C_9H_6FNO (151.14): C 63.57, H 4.01, F 12.57, N 9.26; found: C 63.75, H 4.26, F 12.62, N 9.20.

4-Hydroxy-3-fluorobenzonitrile. A homogeneous mixture of finely powdered 4-methoxy-3-fluorobenzonitrile (25 g, 0.17 mol), crushed, anh. $AlCl_3$ (44 g, 0.33 mol), and analar NaCl (9.7 g, 0.17 mol) was heated at an oilbath temperature of 190° for 45 min. Analysis by TLC indicated complete absence of starting material. The molten raw product was added carefully to H_2O (100 ml) and the resultant mixture shaken with $CHCl_3$ (3 × 100 ml). The combined org. extracts were washed with 10% Na_2CO_3 solution (2 × 200 ml) and H_2O (2 × 500 ml) and then dried ($MgSO_4$). The filtered solution was evaporated under reduced pressure. The residue was taken up in a minimum volume of solvent and eluted from a silica-gel column with toluene/AcOEt 4:1. Single-spot fractions were collected and evaporated together. The raw product thus produced was crystallized from toluene/hexane 9:1 to yield *4-hydroxy-3-fluorobenzonitrile* (15 g, 66%), m.p. 134–135° ([8]: 134°). IR (KBr): 3220 (OH), 2220 (CN). MS: 137 (M^+). Anal. calc. for C_7H_4FNO (137.11): C 61.31, H 2.94, F 13.86, N 10.22; found: C 61.55, H 3.20, F 13.68, N 10.33.

4-Hydroxy-2-fluorobenzonitrile was prepared using the same method (61%), m.p. 117–118°. IR (KBr): 3220 (OH), 2220 (CN). MS: 137 (M^+). Anal. calc. for C_7H_4FNO (137.11): C 61.31, H 2.94, F 13.86, N 10.22; found: C 67.49, H 2.98, F 13.61, N 10.26.

4-Cyano-2-fluorophenyl 4-Pentylbenzoate. A solution of 4-pentylbenzoyl chloride (1.1 g, 0.005 mol; prepared from the corresponding acid using $SOCl_2$), 4-hydroxy-3-fluorobenzonitrile (0.7 g, 0.005 mol), sieve-dried pyridine (2 ml), and Na-dried toluene (20 ml) was heated at 80° for 2 h under anh. conditions. The cooled mixture was then added to cold, dil. HCl and shaken with $CHCl_3$ (3 × 50 ml). The combined org. layers were washed with H_2O and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was taken up in a small amount of solvent and eluted from a silica-gel column with toluene. Single-spot fractions were collected and evaporated together and the residue was crystallized from MeOH until constant transition temperatures were obtained for the *4-cyano-2-fluorophenyl 4-pentylbenzoate* (see *Table 1–5* for the liquid crystal transition temperatures of this ester and the other esters prepared by this procedure). The yield of the pure ester was 1.0 g, 62%). IR (KBr): 2215 (CN), 1750 (C=0). MS: 311 (M^+). Anal. calc. for $C_{19}H_{18}FNO$ (311.36): C 80.14, H 6.94, N 6.03; found: C 80.05, H 6.80, N 6.07.

REFERENCES

[1] *G. W. Gray*, 'Advances in Liquid Crystals', Vol. 2, Academic Press, London, 1976 and references contained therein.

[2] *G. W. Gray & S. M. Kelly*, Mol. Cryst. Liq. Cryst. *75*, 109 (1981); *S. M. Kelly & Hp. Schad*, Mol. Cryst. Liq. Cryst. *110*, 239 (1984).

[3] *M. A. Osman & T. Huynh-Ba*, Z. Naturforsch., B *38*, 1221 (1983).

[4] *M. A. Osman*, Helv. Chim. Acta *65*, 2450 (1982); *M. A. Osman & T. Huynh-Ba*, Mol. Cryst. Liq. Cryst. Lett. *82*, 331 (1983).

[5] *S. M. Kelly*, J. Chem. Soc., Chem. Commun. *1983*, 366.

[6] *G. Adamska, R. Dobrowski & J. Dziabuszek*, Mol. Cryst. Liq. Cryst. *76*, 93 (1981).

[7] *G. W. Gray & B. Jones*, J. Chem. Soc. *1954*, 1467.

[8] *S. S. Berg & Newberry*, J. Chem. Soc. *1949*, 647.

[9] *S. M. Kelly & Hp. Schad*, Helv. Chim. Acta *67*, 1580 (1984).

[10] *Hp. Schad & S. M. Kelly*, J. Chem. Phys. *81*, 1514 (1984).

[11] *Hp. Schad & S. M. Kelly*, to be published.

[12] *M. Sasaki, H. Tokatsu, H. Sato, T. Shimamura, K. Toriyama & T. Nokagomi*, German Patent Application DE 3 241 822 A1 (1982).

[13] *R. T. Klingbiel, D. J. Genova, T. R. Criswell & J. P. van Meter*, J. Am. Chem. Soc. *96*, 7651 (1974).

[14] *A. V. Ivaschenko, V. V. Titov & E. I. Kovshev*, Mol. Cryst. Liq. Cryst. *33*, 195 (1976).

[15] *C. Hogg, G. W. Gray & D. Lacey*, Mol. Cryst. Liq. Cryst. *67*, 1 (1981).

[16] *D. Coates & G. W. Gray*, Mol. Cryst. Liq. Cryst. *37*, 249 (1976).

[17] *J. English, J. F. Mead & C. Nieman*, J. Am. Chem. Soc. *62*, 350 (1940).

[18] *H. Sato, H. Kozu & Y. Fujita*, Japanese Patent 7940, 144 (1979).