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Synthesis and Liquid Crystal Properties of Compounds Incorporating Cyclobutane, Spiro[3.3]Heptane and Dispiro[3.1.3.1]Decane Rings

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A number of esters of structure (I) incorporating the cyclobutane, spiro[3.3]heptane, or dispiro[3.1.3.1]decane rings has been prepared using a diethyl malonate synthesis. Strict comparison of the liquid crystal behaviour amongst the three classes containing a terminal cyano-substituent was not possible because both the cyclobutanes and dispiro[3.1.3.1]decanes are mixtures of *cis*- and *trans*-isomers; the spiro[3.3]heptanes are racemic systems. Using preparative hplc, it was however possible to isolate the pure *cis*- and *trans*-isomers of two of the cyano-substituted cyclobutane esters (I; R = alkyl, — X — = —◇—, Y = CN). From the physical data and the results for the corresponding spiro[3.3]heptane esters, conclusions regarding the effects of these ring systems on liquid crystal behaviour were obtained.

The pure *cis*- and *trans*-isomers of the cyclobutane ester (I, R = C_3H_7, — X — = —◇—, Y = CN) have been assessed for the trends in both order parameter and viscosity with temperature; the results support the idea that the *trans*-cyclobutane ring adopts a more planar conformation at higher temperatures.

Keywords: cyclobutane-and related spiro-systems, cis-/trans-isomerism, order parameter, birefringence, viscosity, structure/property relations

INTRODUCTION

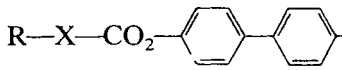
Although there exists a wealth of liquid crystal materials containing many different types of rings, e.g. cyclohexane,[1,2] bicyclo[2.2.2] octane,[3] cubane,[4] pyrimidine,[5,6] pyridine,[7,8] dioxan,[9] naphthalene,[10,11] etc., very few have contained small rings. It was, therefore, considered of interest to prepare some liquid crystal materials incor-

porating the 1,3-disubstituted cyclobutane ring or a combination of such rings.

The combination of more than one adjacent cyclobutane ring linked by a single bond presents many stereochemical problems; even a single 1,3-disubstituted cyclobutane can exist in *cis*- and *trans*-forms. However, an alternative approach is to combine two or more cyclobutane rings in a *spiro*-arrangement, i.e. —◇◇— or —◇◇◇—. This simplifies the stereochemistry considerably. In the case of cyclobutanes (—◇—) and dispiro[3.1.3.1]decanes (—◇◇◇—) the compounds will exhibit *cis*-/*trans*- geometrical isomerism, whereas spiro[3.3]heptanes will exist simply as racemic modifications (optical isomerism).

RESULTS AND DISCUSSION

To investigate the liquid crystal properties of cyclobutanes, spiro[3.3]heptanes, and dispiro[3.1.3.1]decanes, esters of structure (I) were prepared.



(I)

where R = n-alkyl

and when (a) — X — = cyclobutane (—◇—), Y = cyano or n-alkyl;

(b) — X — = spiro[3.3]heptane (—◇◇—), Y = cyano or n-alkyl;

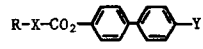
(c) — X — = dispiro[3.1.3.1]decane (—◇◇◇—), Y = cyano

Sixteen esters (I) [nine cyclobutanes, five spiro[3.3]heptanes, and two dispiro[3.1.3.1]decanes] were prepared; their mps and transition temperatures are given in Table I.

These materials clearly give some interesting systems with low mps and broad liquid crystal ranges, but in the case of the cyclobutanes and dispiro[3.1.3.1]decanes, it must be remembered that the compounds are isomeric mixtures containing 55-45/45-55% of the *cis*- and *trans*- isomers. The materials would only be of any commercial interest if a fixed *cis*-/*trans*- ratio could be guaranteed in a given synthesis; in fact variable compositions of isomeric mixture are obtained, and only if the *cis*- and *trans*-isomers had comparable liquid crystal

TABLE I

Transition temperatures (°C) for the esters of structure



(I)

R	Y	-X-	Transition temperatures (°C) C-S_A,S_A,N,I	S_B-I	S_B-N	S_A-N	N-I
CH_3	CN		47.0				78.5
C_2H_5	CN		43.0				86.5
C_3H_7	CN		42.0				101.1
C_4H_9	CN		47.0				103.0
C_5H_{11}	CN		<20			54.0	91.0
C_6H_{13}	CN		35.0			83.2	99.2
C_3H_7	C_5H_{11}		92.5				
C_5H_{11}	C_3H_7		69.5	80.2			
C_6H_{13}	C_3H_7		65.5	80.0			
C_3H_7	CN		82.0				154.7
C_4H_9	CN		78.0				150.1
C_5H_{11}	CN		64.5			129.5	150.0
C_6H_{13}	CN		61.5			138.5	144.5
C_6H_{13}	C_3H_7		67.5		94.0		111.0
C_3H_7	CN		74.0				161.1
C_4H_9	CN		74.5				161.2

behaviour would a comparison of the results in Table I for the cyclobutanes, spiro[3.3]heptanes (racemates), and dispiro[3.1.3.1]decanes be justified.

It is simply noted at this stage that the dialkyl cyclobutane esters gave either no mesophase or ordered smectic B phases, whereas the phases exhibited by the terminally cyano-substituted compounds were S_A/N or N. Only in the case of the dialkyl ester (I) where —X— = — —, R = C_6H_{13}, and Y = C_3H_7, was a nematic phase obtained in addition to the S_B phase.

To make a proper assessment of the relative thermal and physical properties of the esters (I) it was important, at least for one of the series of cyclobutanes or dispiro[3.1.3.1]decanes, to obtain the pure *cis*- and *trans*-isomers. This problem could be approached either by stereospecific synthetic routes[12,13] or by the physical separation of individual isomers, e.g., by preparative glc.[14]

Stereospecific synthetic routes reported in the literature[12,13] were all for the preparation of relatively simple substituted cyclobutanes, and were long and time-consuming. Such methods would severely

curtail the commercial applications of the pure *cis*- and *trans*-isomers even if these should prove to have interesting physical and electro-optical properties.

We therefore elected to approach the synthesis of these materials by simple routes, recognising that in the case of the cyclobutanes and dispiro[3.1.3.1]decanes, mixtures of geometrical isomers would be obtained, and that isomer separation would have to be attempted. By this approach it would also be established whether, for a given material, a more or less constant *cis/trans*-ratio was achieved, so making possible applications involving such constant composition systems. In the event, as noted earlier, significant *cis/trans*-compositional variations did occur using these preparative routes. The routes used to prepare the esters (I) are given in Scheme 1 (see Experimental Section).

SEPARATION OF ISOMERS

This was achieved for the *cis*- and *trans*-isomers of the esters (I), where R = C_3H_7 and C_5H_{11}, —X— = —◇— and Y = CN, by reverse phase preparative hplc (see Experimental Section for details). Approximately 1.0 g quantities of each of the *cis*- and *trans*-isomers were obtained and analytical hplc was used to check the quality of separation and the purities of the isomers. The mps and transition temperatures for the pure *cis*- and *trans*-isomers are given in Table II.

The structural assignment for the *cis*- and *trans*-isomers was achieved by using ^{1}Hnmr (400.13 MHz). The most indicative signal was associated with the ring proton (H_a) adjacent to the ester function (see Figure 1). For the *cis*-isomer, δ (H_a) = 3.23 and for the *trans*-isomer, δ (H_a) = 3.35. A coupling constant of 1.1Hz between the H_a and H_d protons is apparent for the *trans*-isomer, confirming an axial-equatorial arrangement, whereas for the *cis*-isomer, J = 0.0 Hz, indicative of an axial-axial arrangement of protons.

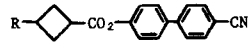
From the above data for the propyl and pentyl homologues (Table II), the following conclusions can be drawn.

1. Both pairs of *cis*- and *trans*-esters have rather similar mps, with the *cis*-isomers having the higher values.

2. The *trans*-esters have much higher T_{N-I} values than the *cis*-isomers. In the case of the propyl homologue, the difference in T_{N-I} between the *cis*- and *trans*-isomer is 78.5°C; for the pentyl homologue, the difference is 76.0°C. For both homologues a strictly linear plot

TABLE II

Transition temperatures (°C) and isomer ratios for *cis*- and *trans*-4'-cyanobiphenyl-4-yl 3-n-propyl- and 3-n-pentyl-cyclobutane-1-carboxylates



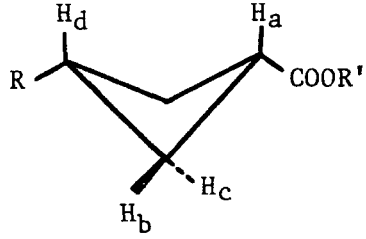
(II)

R	Component	*cis*/*trans* ratio	Transition temperatures (°C) C-S_A,N	S_A-N	N-I
	Original sample	51/49	42.0		101.1
C_3H_7	*cis*-isomer	>99.9/<0.1	55.5		63.0
	trans-isomer	<0.1/>99.9	47.5		141.5
	Original sample	63/37	<20	54.0	91.0
C_5H_{11}	*cis*-isomer	>99.9/<0.1	40.0	47.5	63.5
	trans-isomer	<0.1/>99.9	35.5		139.5

of $T_{N\text{-}I}$ against percentage composition was obtained from the data for the pure isomers, and 5 to 7 binary mixtures prepared from the isomers and containing between 10 and 90% of the *trans*-isomer (II)—see Figure 2.

3. For the pentyl homologue, the *cis*-isomer exhibits an S_A phase whereas the *trans*-isomer is a simple nematogen. This is shown in Figure 2 which illustrates the linear $T_{N\text{-}I}$ curve and the distribution of $T_{S_A\text{-}N}$ values for the various mixtures.

4. When the *trans*-esters are compared with the corresponding racemic spiro[3.3]heptane esters (Table I), the *trans*-isomers have slightly lower $T_{N\text{-}I}$ values (average ca. 12°C; for the propyl homo-



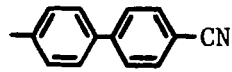
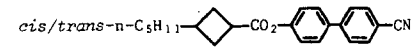
R = n-alkyl; R' = 

FIGURE 1 Stereochemistry of a *cis*-1,3-disubstituted cyclobutane.



(II)

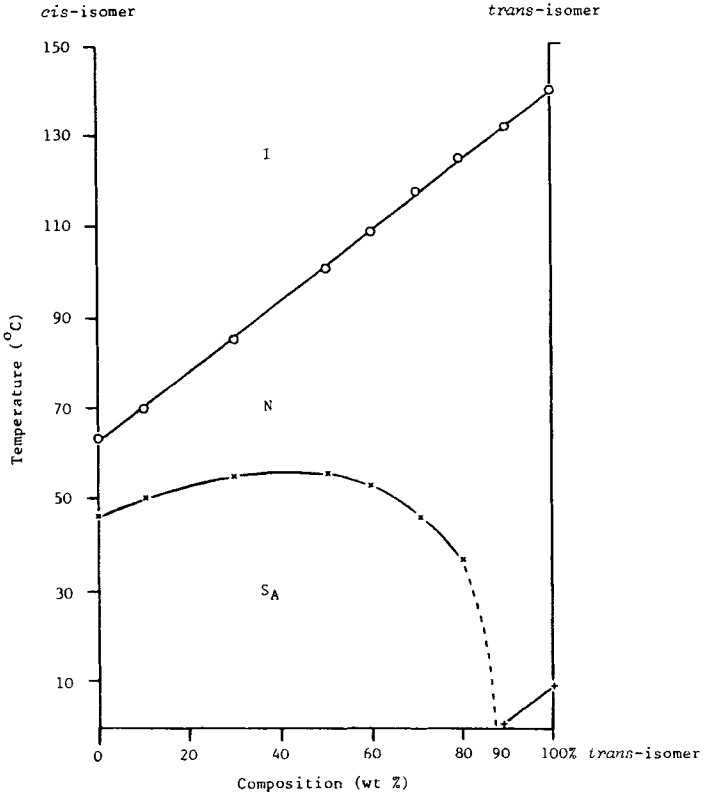


FIGURE 2 Plot of transition temperatures against composition for mixtures of isomeric *cis*- and *trans*-4'-cyanobiphenyl-4-yl 3-n-pentylcyclobutane-1-carboxylates. Key: o,N-I; x, S_A-N; +, recrystallisation.

logue, 13.2°C and for the pentyl homologue, 10.5°C), and mps (average ca. 32°C; for the propyl homologue, 34.5°C and for the pentyl homologue, 29.0°C). However, neither *trans*-ester exhibits a smectic phase, whereas the spiro[3.3]heptane with R = C_5H_{11} has a relatively high $T_{S_A\text{-}N}$ = 129.5°C.

The most surprising result is the very large difference in $T_{N\text{-}I}$ between each of the *cis*- and *trans*-isomers. From the electron diffraction work of Almenningen, Bastiansen, and Walle,[15] a *cis*-1,3- disubstituted cyclobutane is 100% di-equatorial with a calculated dihedral

angle of ring puckering of 33°, whereas a *trans*-isomer is axial-equatorial. For an unsymmetrically 1,3-disubstituted *trans*-isomer there will obviously be an equilibrium, since either group can be axial or equatorial. However, from the nuclear magnetic resonance work of Lillien and Doughty[16] on *cis*- and *trans*-3-isopropylcyclobutanols and -3-isopropylcyclobutylamines, there is good evidence that the *larger* of two substituents occupies the equatorial position. Therefore for the esters (I), the position will be as shown in Figure 3 with the equilibrium possibly lying to the left for the *trans*-isomer.

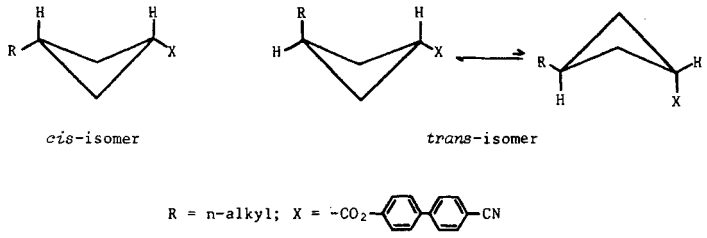
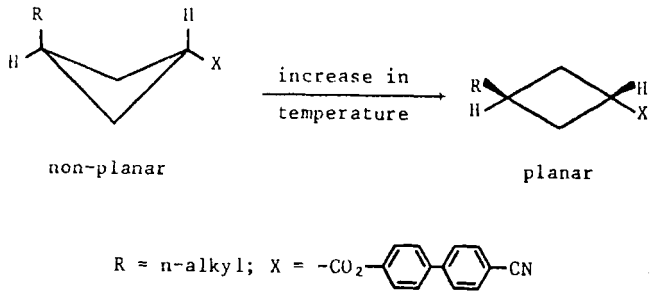


FIGURE 3 Stereochemical models for *cis*- and *trans*-1,3-disubstituted cyclobutanes.

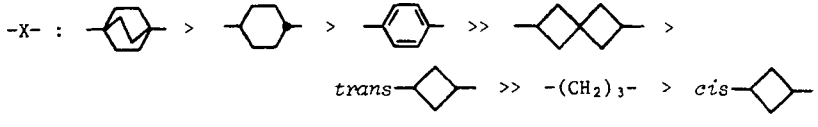
The axial-equatorial arrangement in the *trans*-isomer must give a more linear molecule than the di-equatorial arrangement in the *cis*-isomer, to account for the higher T_{N-I} for the *trans*-isomer. However, a reason for the magnitude of the difference in the T_{N-I} values between the isomers may be provided by the results of infrared and Raman spectroscopic studies by Aleksanyou *et al.*[17]; they found that the spectra were temperature dependent only for the *trans*-isomer of a 1,3-substituted cyclobutane; there was no change in the spectrum for the *cis*-isomer over a wide temperature range. They concluded that the *trans*-isomer should be represented, as shown below, by an equilibrium between a non-planar and a planar form of which the latter may be considered to be a rotationally excited form existing at higher temperatures.



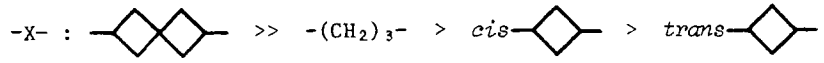
This idea of a relatively rigid, puckered *cis*-isomer and a somewhat more flexible *trans*-isomer was later supported by the work of Lampman *et al.*[18] who concluded that the *cis*-isomers were enthalpically favoured, whereas the *trans*-isomers were entropically favoured. Thus, for the *trans*-isomer, as the temperature is increased, the puckered non-planar conformation changes to a planar form which is certainly structurally more conducive to ordering in a liquid crystal system. If the cyclobutane ring in the esters can be considered as part of the molecular core, this conformational change to a more planar ring could have a significant enhancing effect upon thermal persistence of the nematic phase. Examples where small changes in the geometry of the molecule have a marked effect on liquid crystal behaviour are not uncommon in low molar mass liquid crystal materials. A classic example of this can be found[19] for the ω-phenylalkyl 4-(*p*-cyanobenzylideneamino)cinnamates.

Remembering that the spiro[3.3]heptanes do not involve *cis*-/*trans*-isomerism, we are now in a position to compare the transition temperatures for the esters (I), where R = C_5H_{11}, and — X — represents —$(CH_2)_3$— and the various ring systems indicated in Table III. The trimethylene unit is considered as the open chain equivalent of a cyclobutane ring.

From the data in Table III, the order of decreasing nematic thermal stability of the esters is



Considering only the last four members in the above order of nematic thermal stability, the order for the S_A thermal stability of the esters is

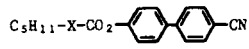


Therefore, although the more flexible *trans*-cyclobutane ring strongly favours nematic order (compared with the *cis*-cyclobutane ring), the effect of the configuration of the ring upon smectic A thermal stability is reversed.

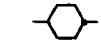
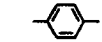
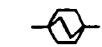
It is clear from these comparisons that if the *trans*-cyclobutane and spiro[3.3]heptane rings are regarded, like the other ring systems given in Table III, as components of the molecular core of a mesogen, they are relatively poor at promoting smectic or nematic liquid crystal properties. However, in relation to a (CH_2)n chain of equivalent

TABLE III

Transition temperatures (°C) for the esters of structure



(III)

-X-	C-S_A,N	S_A-N	N-I	Ref
	85.0		240.8	21
	109.0		237.5	22
	143.0		282.5	23
$-(CH_2)_3-$	42.5	63.0	76.0	20
	64.0	129.5	150.0	Table I
trans- 	35.0		139.5	Table II
cis- 	40.0	47.5	63.5	Table II

length, the *trans*-cyclobutane and the spiro[3.3]heptane rings are more efficient in promoting nematic properties; in this context it is better to regard these rings as effective chain "stiffeners" rather than useful components of the molecular core.

PHYSICAL MEASUREMENTS

Some results of measurements of the birefringence, order parameters, and viscosities for the pure *cis*-isomer, the pure *trans*-isomer and a *cis*/*trans*-isomeric mixture of ester (I), where R = C_3H_7, Y = CN and — X — = — —, are expressed graphically in Figures 4, 5 and 6. The extrapolated viscosities for a selected number of esters (V) are given in Table IV.

The plots of birefringence (Δn) and order parameter (S) (Figures 4 and 5 respectively) as a function of reduced temperature are typical of other mesogens. It is interesting to note, however, in the plot of S against reduced temperature (Figure 5) that for any given reduced temperature the slope of the curve is *less* for the *trans*-isomer (which also has the higher order parameter) than for the *cis*-isomer, e.g., at $T/T_c = 0.9$:

	slope
trans-isomer	−1.00
cis/*trans*-mixture	−1.06
cis-isomer	−1.24

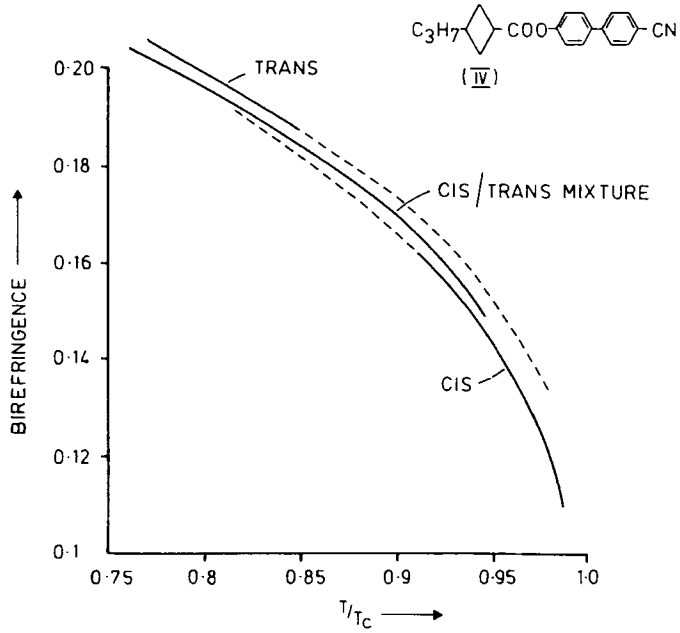


FIGURE 4 Plot of birefringence against reduced temperature (T/Tc) for *cis*-(IV), *trans*-(IV), and a mixture of these isomers.

This means that the *trans*-isomer has a lower temperature dependence of S than the *cis*-isomer. This could again be due to the fact that, as the temperature is increased, the *trans*-isomer changes from the butterfly conformation to one that is more planar, so giving a more linear molecule and a nematic phase that more effectively resists the disordering process.

The viscosity of a 10 wt% solution of each of the *cis*- and *trans*-esters in ZLI 1132† was measured over a wide temperature range and the results are shown in Figure 6. There is a small but measurable difference in viscosity for the two mixtures at high temperature, the mixture containing the *trans*-isomer having the lower value. Normally, one would expect this difference in viscosity to become greater at lower temperatures, but, as can be seen from Figure 6, the curve for the mixture containing the *trans*-isomer rises more rapidly than that for the *cis*-isomer as the temperature falls. The presence of an underlying smectic phase for the *trans*-mixture could produce this effect, but no smectic phases were detected in these mixtures. An

†This is a commercially available liquid crystal mixture from E. Merck, Darmstadt, FRG.

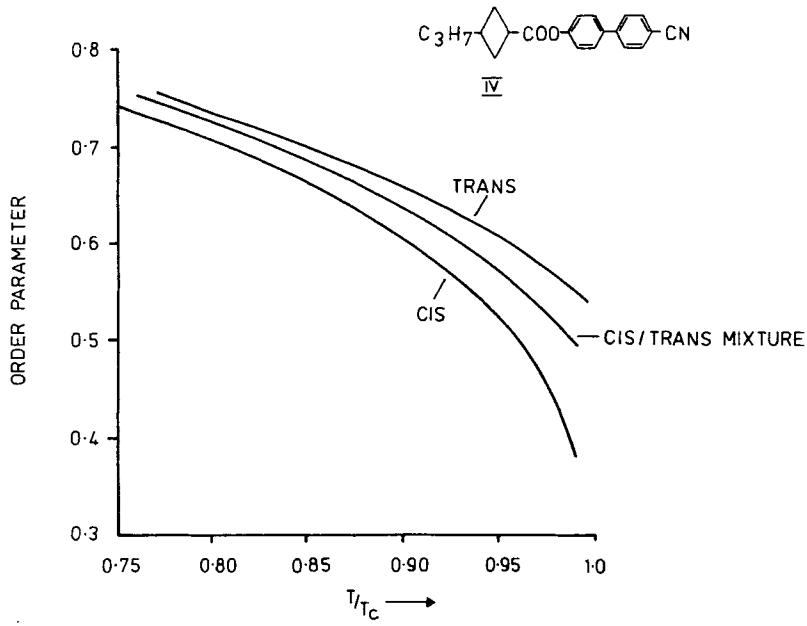


FIGURE 5 Plot of order parameter against reduced temperature (T/Tc) for *cis*-(IV), *trans*-(IV), and a mixture of these isomers.

alternative explanation for this unusual behaviour could be that, on increasing the temperature, the molecules of the *trans*-isomer adopt a more linear arrangement, with a more planar cyclobutane ring.

The extrapolated viscosities (20 wt% in ZLI 1132† at 20°C) for a selected number of esters are given in Table IV. The large difference between the viscosities of the *cis*- and *trans*-isomers shows that the *cis*-isomer, containing the rigid puckered structure of the 1,3-disubstituted cyclobutane ring, has a less linear molecular structure than the *trans*-isomer with its more flexible cyclobutane ring and a more linear arrangement of the 1,3-substituents. Changing the ring X in the esters (V) from cyclobutane to spiro[3.3]heptane substantially increases the viscosity to 170cP.

CONCLUSIONS

From these investigations of the properties of a number of cyclobutane, spiro[3.3]heptane, and dispiro[3.1.3.1]decane esters (I), we can reach the following conclusions.

1. From the thermal data for the cyclobutane systems and some related materials containing other rings or alkyl chains, it is best to

†This is a commercially available liquid crystal mixture from E. Merck, Darmstadt, FRG.

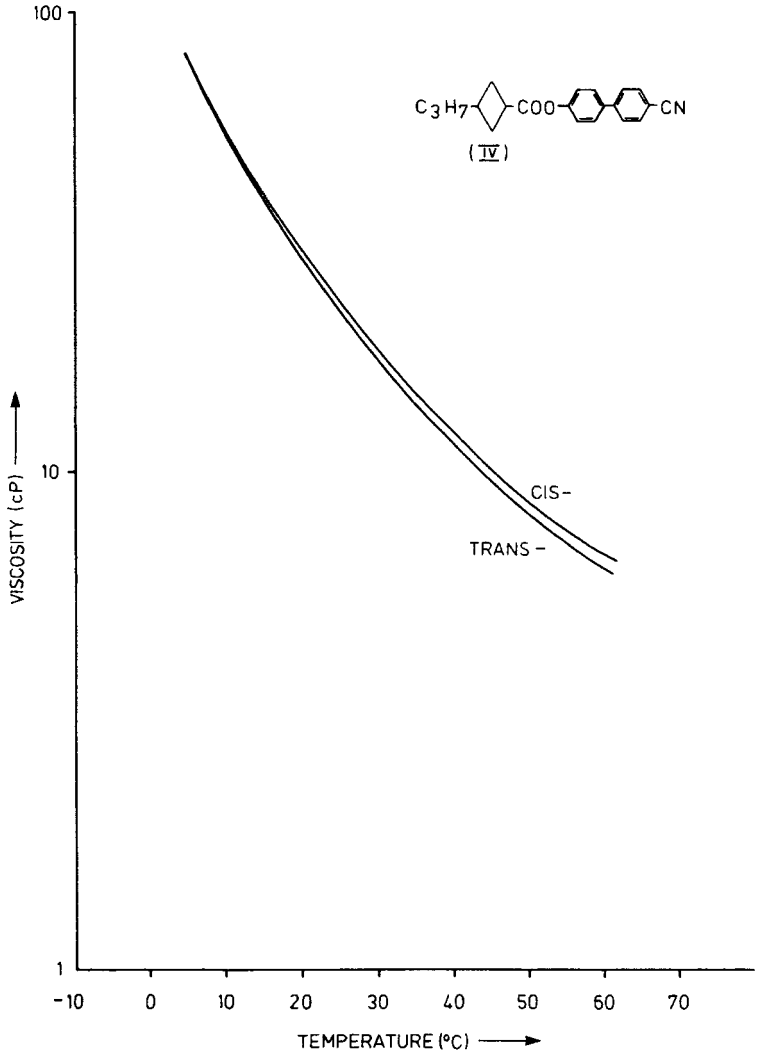


FIGURE 6 Plot of viscosity (cP) against temperature (°C) for *cis*-(IV) and *trans*-(IV).

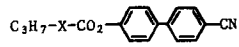
view the cyclobutane and spiro[3.3]heptane rings as "chain stiffeners," rather than as small ring core components.

2. In the cyclobutane esters (I), the *trans*-isomer has a substantially higher $T_{N\text{-}I}$ value than the *cis*-isomer, consistent with the more linear structure.

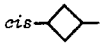
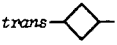
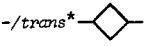
3. Evidence to support the idea that the *trans*-isomer adopts a more linear, planar conformation at higher temperatures was obtained from trends in order parameter and in viscosity with temperature.

TABLE IV

Extrapolated viscosities (20°C) for materials of structure (V)



(V)

-X-	Extrapolated viscosity at 20°C (cP)
cis- 	133
trans- 	74
cis-/*trans**- 	100
	170

* 45% *cis*/55% *trans*

EXPERIMENTAL

Materials

The reaction pathway used in the preparation of the cyclobutane esters of structure (I) is given in Scheme 1. Small-scale distillations were accomplished by using a modified sublimation apparatus in which a cup has been fitted to the lower end of the "cold-finger." This so-called "short-path" (SP) distillation apparatus is especially suitable for handling small amounts of suitably volatile materials, ranging from 0.1 g to 5 g. When this technique has been used to purify a compound, the symbol (SP) is inserted after the temperature and pressure, e.g. 60°C/0.5mmHg (SP). The temperature here does not refer to the boiling point of the liquid, but to the temperature of the surrounding oil bath.

In the following text, whenever hplc is used in checking the purity of a sample, the mobile phase employed is signified by the following notation.

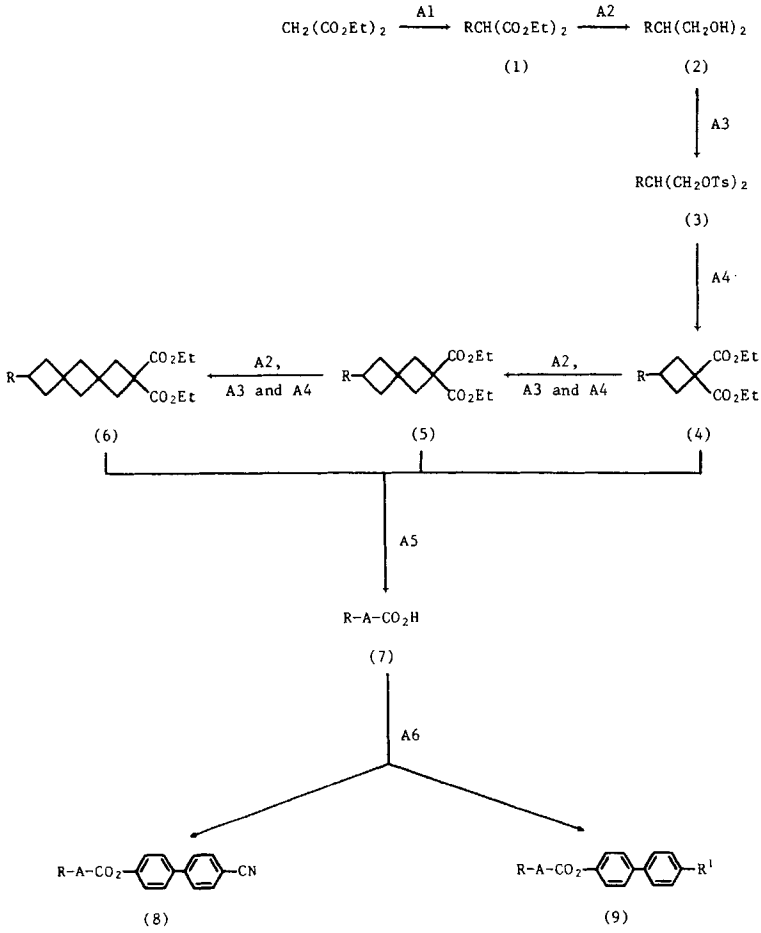
Code	Mobile Phase
A	Methanol
B	Methanol : water (90 : 10)
C	Methanol : water (80 : 20)

The analytical hplc was carried out on a Whatman Partisil ODS II column.

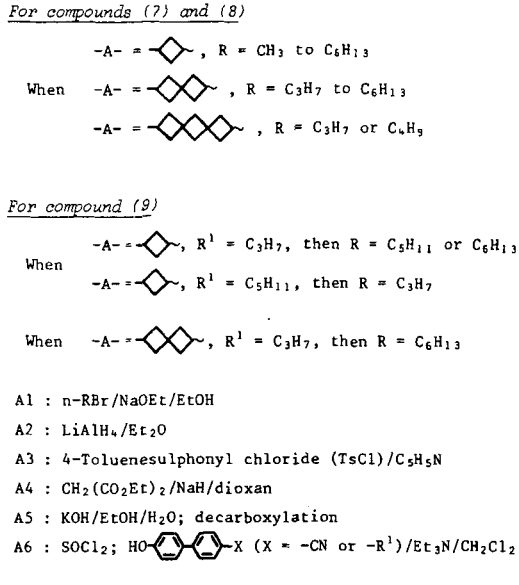
Physical Measurements

All final products were shown to be pure by various standard techniques (tlc,glc,hplc). Structural confirmation for these products (and, where necessary, for any of the intermediates) was obtained by ^{1}Hnmr spectroscopy (Jeol JNMPM $\times 60$ spectrometer), infrared spectroscopy (Perkin-Elmer 457 grating spectrometer), and mass spectrometry (AEI MS902 mass spectrometer). Each of the final products (the esters) gave satisfactory elemental analysis data.

Transition temperatures were measured using a Mettler FP5 hot stage and control unit, in conjunction with a Vickers M72C polarising microscope.



SCHEME 1



SCHEME 1 (*continued*)

The differential scanning calorimetric measurements were carried out using a Perkin-Elmer DSC 2C with data station.

The compounds containing a cyclobutane or dispiro[3.1.3.1]decane ring are mixtures of *cis*- and *trans*-isomers. In these cases, the purities (where given) relate to the isomeric mixtures, and in two cases (see the following text), the *cis*- and *trans*-isomers were successfully separated and isolated.

In the case of the spiro[3.3]heptanes, the purity (where given) relates to the racemic system and no attempt has been made to resolve these into their enantiomeric forms.

Diethyl n-alkylmalonates[24] (1)

Diethyl malonate (140 g, 0.81 mol) was slowly added to a stirred solution of sodium ethoxide, prepared by interaction of sodium (18.4 g, 0.80g atom) and super-dry ethanol (500 cm^3) at about 50°C, under anhydrous conditions. The appropriate *n*-alkyl bromide(0.80 mol) was then added dropwise, over a period of 1 h to the resulting clear solution. The reaction mixture was then heated under reflux until it was neutral to moist litmus (about 2 h). When cooled, the solvent was removed under reduced pressure and water (300 cm^3) was added to the residue with vigorous stirring. The product was extracted into ether (3 × 200 cm^3) and the combined extracts were washed with

water (200 cm^3) and then dried ($MgSO_4$). After removal of the solvent, the crude diester was distilled under reduced pressure to give a colourless liquid. Results for the compounds (1) prepared are as follows (see also footnote to Table V).

1, R = CH_3: yield 129 g (85%); bp 197°C (Lit.[25] bp. 198–199°C).

1, R = C_2H_5: yield 133.5 g (82%); bp 211°C (Lit.[26] bp. 75–77°C/5 mm Hg).

1, R = C_6H_{13}: yield 122 g (62%); bp 170°C/15 mm Hg.

2-n-Alkylpropan-1,3-diols (2a-c)

To a stirred suspension of lithium aluminium hydride (41.8 g, 1.1 mol) in sodium-dried ether (1000 cm^3) was added dropwise, over a period of 45 min, a solution of the appropriate compound (1) (0.50 mol) in sodium-dried ether (200 cm^3). The resultant mixture was heated under reflux for 3 h. When cooled, the unreacted lithium aluminium hydride was destroyed by the careful addition of ethyl ethanoate (100 cm^3), followed by water (200 cm^3) and 20% w/v potassium hydroxide solution (200 cm^3). The product was extracted from the aqueous phase into ether (3 × 300 cm^3) and the combined extracts were washed with water (300 cm^3) and dried ($MgSO_4$). After removal of the solvent, the crude diol was distilled *in vacuo* to give the compound (2a-c) as a colourless liquid.

Results for the compounds (2a-c) prepared are given in Table V, which also includes data for cyclobutanes (2d-g) and spiro[3.3]heptanes (2h-i) prepared using the same procedure. The purities of the compounds (2a-i) were checked (glc) and shown to be >96%. The ir data for these compounds are exemplified by the values given below for compounds (2c), (2g) and (2i).

For compound (2c): ir (neat) 3330 (broad), 2920, 2849, 1452, 1031 cm^{-1}.

For compound (2g): ir (KCl) 3290 (broad), 2918, 2848, 1470, 1019 cm^{-1}.

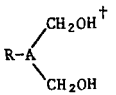
For compound (2i): ir (KCl) 3305 (broad), 2940, 2840, 1425, 1045, 1025 cm^{-1}.

Ditosylates of 2-n-alkylpropan-1,3-diols (3a-f)

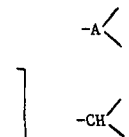
To a cooled, stirred solution of toluene-4-sulphonyl chloride (112.5 g, 0.59 mol) in freshly distilled pyridine (110 cm^3) was added dropwise, over a period of 30 min, a solution of the appropriate diol (2a-

TABLE V

The yields, boiling points, *m/z* values, and solvents used for crystallisation of 2-substituted propan-1,3-diols



(2a–i)

Compound No	R	-A	Yield (%)	bp/mp (°C)	m/z (M^+)	Solvent (crystallisation)
(2a)	CH_3		85	80–82°/0.5 mm Hg	90	-
(2b)	C_2H_5		90	88–92°/0.6 mm Hg	104	-
(2c)	C_6H_{13}		82	110°/0.2 mm Hg	160	-
(2d)	C_3H_7		85	58 (crude)	158	-
(2e)	C_4H_9		80	52 (crude)	172	-
(2f)	C_5H_{11}		91	49 (crude)	186	-
(2g)	C_6H_{13}		82	55	200	hexane
(2h)	C_3H_7		93	70 (crude)	198	-
(2i)	C_4H_9		78	85	212	hexane

† The 2-n-propyl-, -butyl- and -pentyl-propan-1,3-diols (2) were supplied by E Merck, Darmstadt, FRG, under a collaborative research agreement

c) (0.283 mol) in dry pyridine (75 cm^3). The mixture was stirred for 16 h at room temperature. The mixture was then chilled in an ice-bath and acidified with 18 wt% hydrochloric acid solution. The product was extracted into chloroform (3 × 200 cm^3) and the combined extracts were washed with water (200 cm^3) and dried ($MgSO_4$). After removal of the solvent, the crude product was crystallised from a suitable solvent (see Table VI) to give the compound (3a-f) as a colourless crystalline solid.

Results for the compounds (3a-f) prepared are given in the following table (Table VI) which also includes data for the cyclobutane (3g-j) and spiro[3.3]heptanes (3k-l) prepared using the same procedure.

The purities of the compounds (3a-l) were checked [hplc (A)] and shown to be >98%. The ir and ^1H nmr data for these compounds are exemplified by the values given below for compounds (3f), (3i) and (3l).

For compound (3f): ir (KCl), 2958, 2935, 2860, 1600, 1365, 1190, 1175, 832, 818 cm^{-1};
^1H nmr ($CDCl_3$) δ 0.64–1.68 (13H, m), 1.72–2.24 (1H, m), 2.46 (6H, s), 3.82–4.08 (4H, d), 7.18–7.92 (8H, m).

For compound (3i): ir (KCl), 2956, 2930, 2858, 1598, 1365, 1190, 1176, 842, 822 cm^{-1};
^1H nmr ($CDCl_3$) δ 0.88–2.12 (16H, m), 2.48 (6H, s), 3.94–4.08 (4H, d), 7.24–7.92 (8H, m).

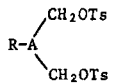
For compound (3l): ir (KCl), 2957, 2920, 2843, 1598, 1365, 1190, 1175, 830, 809 cm^{-1};
^1Hnmr ($CDCl_3$) δ 0.68–2.12 (18H, m), 2.38 (6H, s), 3.74, (4H, s), 6.94–7.60 (8H, m).

Diethyl 3-n-alkylcyclobutane-1,1-dicarboxylates (4a-f) and the diesters (5a-d) and (6a-b)

A vigorously stirred solution of the appropriate compound (3a-l) (0.20 mol) and sieve-dried diethyl malonate (35.1 g, 0.22 mol) in freshly distilled, sieve-dried dioxan (400 cm^3) was warmed until almost boiling under an atmosphere of dry nitrogen. A suspension of sodium hydride (80% in mineral oil, 6.7 g, 0.22 mol) in dry dioxan (100 cm^3) was then cautiously added dropwise, over a period of about 1.5 h. After heating the reaction mixture under reflux for 30 min, a

TABLE VI

The yields, melting points, and solvents used for crystallisation of the ditosylates of 2-substituted propan-1,3-diols



(3a-l)

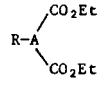
Compound no	R	-A<	Yield (%)	mp (°C)	Solvent (crystallisation)
(3a)	CH_3		74	65	
(3b)	C_2H_5		64	64	
(3c)	C_3H_7	-CH<	71	66	Ethanol
(3d)	C_4H_9		83	61	
(3e)	C_5H_{11}		81	62	
(3f)	C_6H_{13}		65	59	
(3g)	C_3H_7		63	97	
(3h)	C_4H_9		85	92	Ethanol
(3i)	C_5H_{11}		74	71	
(3j)	C_6H_{13}		89	64	
(3k)	C_3H_7		68	90	Pet fraction (bp 40-60°C)
(3l)	C_4H_9		78	74	

further amount of sodium hydride (80%, 6.7 g, 0.22 mol) in dry dioxan (100 cm^3) was added over a period of 1 h. The resultant mixture was then heated under reflux for 4 h. When cooled, the solvent was removed by distillation under reduced pressure. Water (300 cm^3) was then added to the residue and the product was extracted into ether (3 × 200 cm^3). The combined extracts were washed with water (200 cm^3) and dried ($MgSO_4$). After removal of the solvent, the residue was distilled under reduced pressure to give compound (4a-f) as a colourless liquid.

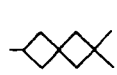
Using Steps A2, A3, and A4, compound (4) was converted into the dispiro-compound (6a-b), *via* the spiro-compound (5a-b). The yields and bps for all the diethyl esters—compounds (4a-f), (5a-d) and (6a-b)—are given in Table VII. The purities of the compounds

TABLE VII

The yields, boiling points, and *m/z* values for diethyl 3-substituted cyclobutane-1,1-dicarboxylates



(4a-f, 5a-d, 6a and 6b)

Compound no	R	-A	Yield (%)	bp (°C/mm Hg)	m/z (M^+)
(4a)	CH_3		55	52/0.2	214
(4b)	C_2H_5		63	127/2.0	228
(4c)	C_3H_7		55	84/0.05††	242
(4d)	C_4H_9		74	92/0.2	256
(4e)	C_5H_{11}		64	100/0.1	270
(4f)	C_6H_{13}		60	115/0.2	284
(5a)	C_3H_7		56	110/0.1	282
(5b)	C_4H_9		58	115/0.1	296
(5c)	C_5H_{11}		40	120/0.1	310
(5d)	C_6H_{13}		63	130/0.1 (SP)	324
(6a)	C_3H_7		≈50†	-	322
(6b)	C_4H_9			-	336

† Decomposition occurred at temperatures exceeding 160°C/0.01 mm Hg during the distillation stage. The yields of these two crude esters (6a and b) were estimated to be about 50%

†† Lit bp 115-130°C/18 mm Hg

(4a-f), (5a-d) and (6a-b) prepared by this method were all >97% (glc). The ir absorptions for these compounds are exemplified by the values given below for compounds (4d), (5b) and (6b).

For compound (4d): ir (neat) 2980, 2932, 2870, 1730, 1262, 1140 cm^{-1}.

For compound (5b): ir (neat) 2960, 2928, 2858, 1732, 1290, 1258, 1138 cm^{-1}.

For compound (6b): ir (neat) 2930, 2850, 1730, 1295, 1258, 1133 cm^{-1}.

3-n-Alkylcyclobutane-1-, 6-n-alkylspiro[3.3]heptane-2- or 8-n-alkyldispiro[3.1.3.1]decane-2-carboxylic acids (7a-l)

The appropriate compound (4, 5 or 6) was added to a solution of potassium hydroxide (28.0 g, 0.50 mol) in water (100 cm^3) and ethanol (200 cm^3) and the reaction mixture was heated under reflux for 4 h. When cooled, the ethanol was removed by distillation under reduced pressure. Water (50 cm^3) was added to the residue and whilst being cooled in an ice bath, the mixture was acidified with 18 wt% hydrochloric acid solution. The free dicarboxylic acid was extracted into ether (3 × 100 cm^3) and the combined ether extracts were washed with water (100 cm^3) and dried ($MgSO_4$). After removal of the solvent, the crude dicarboxylic acid (a colourless solid) was dried in a desiccator *in vacuo*. The dried dicarboxylic acid was decarboxylated by heating at a temperature of 180–200°C for about 30 min; the oily residue was then distilled, under reduced pressure, to give the acid (7a-l) as a colourless liquid. Results for the prepared compounds (7a-l) are given in Table VIII.

The purities of the prepared compounds (7) were all >98% (glc). The ir data for these compounds are exemplified by the values given below for compounds (7c), (7g) and (7k).

For compound (7c): ir (neat) 2960, 2932, 2860 (broad), 2750, 2660, 2550, 1708, 935 cm^{-1}.

For compound (7g): ir (neat) 2960, 2925, 2850 (broad), 2751, 2545, 1705, 940 cm^{-1}.

For compound (7k): ir (neat) 2920, 2842 (broad), 2740, 2655, 2550, 1705, 935 cm^{-1}.

TABLE VIII

The yields and boiling points for 3-n-alkylcyclobutane-1-, 6-n-alkylspiro[3.3]heptane-2- and 8-n-alkyldispiro[3.1.3.1]decane-2-carboxylic acids

$R\text{-}A\text{-}CO_2H$ (7a-l)

Compound no	R	-A-	Yield (%)	bp (°C/mm Hg)	Lit[27] bp (°C/mm Hg)
(7a)	CH_3		84	57/0.2	-
(7b)	C_2H_5		80	125/20	95/0.7
(7c)	C_3H_7		85	135/20	135/20
(7d)	C_4H_9		85	145/20	155/40
(7e)	C_5H_{11}		88	122/0.1	128-131/0.7
(7f)	C_6H_{13}		84	100/0.01	-
(7g)	C_3H_7		88	90/0.1	-
(7h)	C_4H_9		77	125/0.2	-
(7i)	C_5H_{11}		82	120/0.1	-
(7j)	C_6H_{13}		80	125/0.01	-
(7k)	C_3H_7		67	155/0.1 (SP)	-
(7l)	C_4H_9		77	120/0.1 (SP)	-

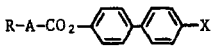
4'-n-Alkyl- or 4'-cyano-biphenyl-4-yl 3-n-alkylcyclobutane-1-, 6-n-alkylspiro[3.3]heptane-2- or 8-n-alkyldispiro[3.1.3.1]decane-2-carboxylates (8a-l and 9a-d)

The preparation of the esters (8 and 9) was achieved using a standard literature method.[28] For the compounds (8), the appropriate carboxylic acid (7a-e) (0.010 mol) was esterified with 4'-cyano-4-hydroxybiphenyl (0.010 mol), and for the compounds (9), the carboxylic acid (7a-i) (0.010 mol) was esterified with the appropriate 4'-n-alkyl-4-hydroxybiphenyl (0.010 mol). The crude products were purified by column chromatography on silica gel, using chloroform:petroleum fraction (bp 60–80°C) (1:1) as eluent. The fractions containing the ester were collected and the product crystallised from a suitable solvent. The results for compounds prepared by the above procedure are given in Table IX.

The purities [hplc B] of the esters prepared above were all shown to be >99.8%. The mps and transition temperatures are given in Table I. The ir and ^1H nmr results for these compounds are exem-

TABLE IX

The yields, *m/z* values, and solvents used for crystallisation of 4′-n-alkyl- or 4′-cyano-biphenyl-4-yl 3-n-alkylcyclobutane-1-, 6-n-alkylspiro[3.3]heptane-2- and 8-n-alkyldispiro[3.1.3.1]decane-2-carboxylates



(8a–l and 9a–d)

Compound no	R	-A-	X	Yield (%)	m/z (M^+)	Solvent (crystallisation)
(8a)	CH_3		CN	63	291	Hexane
(8b)	C_2H_5		CN	59	305	Ethanol
(8c)	C_3H_7		CN	60	319	Ethanol
(8d)	C_4H_9		CN	60	333	Hexane
(8e)	C_5H_{11}		CN	71	347	Ethanol
(8f)	C_6H_{13}		CN	67	361	Hexane
(9a)	C_3H_7		C_5H_{11}	41	364	Ethanol
(9b)	C_5H_{11}		C_3H_7	42	364	Ethanol
(9c)	C_6H_{13}		C_3H_7	52	378	Ethanol
(8g)	C_3H_7		CN	60	359	Ethanol
(8h)	C_4H_9		CN	62	373	Ethanol
(8i)	C_5H_{11}		CN	58	387	Ethanol
(8j)	C_6H_{13}		CN	57	401	Ethanol
(9d)	C_6H_{13}		C_3H_7	54	418	Ethanol
(8k)	C_3H_7		CN	55	399	Ethanol
(8l)	C_4H_9		CN	51	413	Ethanol

plified by the values given below for compounds (8c, 8h, 8l, 9a and 9d).

For compound (8c): ir (KCl) 2960, 2930, 2852, 2224, 1752, 1608, 1495, 845, 815 cm^{-1};
^1H nmr ($CDCl_3$) δ 0.73–1.03 (3H, t), 1.03–1.70 (4H, m), 1.70–2.70 (5H, m), 2.90–3.60 (1H, m), 7.03–7.87 (8H, m).

For compound (8h): ir (KCl) 2958, 2920, 2843, 2223, 1750, 1605, 1495, 840, 828 cm^{-1};
^1H nmr ($CDCl_3$) δ 0.65–1.40 (9H, m), 1.40–2.48 (9H, m), 2.76–3.40 (1H, m), 6.72–7.48 (8H, m).

For compound (8l): ir (KCl) 2950, 2912, 2800, 2222, 1748, 1605, 1492, 840, 828 cm^{-1};
^1H nmr ($CDCl_3$) δ 0.77–1.52 (9H, m), 1.56–2.62 (13H, m), 3.00–3.64 (1H, m), 7.36–8.12 (8H, m).

For compound (9a): ir (KCl) 2960, 2920, 2850, 1700, 1495, 841, 798 cm^{-1};
^1H nmr ($CDCl_3$) δ 0.82–1.12 (6H, m), 1.12–2.80 (17H, m), 2.84–3.50 (1H, m), 6.92–7.60 (8H, m).

For compound (9d): ir (KCl) 2958, 2920, 2850, 1702, 1494, 864, 795 cm^{-1};
^1H nmr ($CDCl_3$) δ 0.67–1.37 (16H, m), 1.37–2.73 (13H, m), 2.80–3.50 (1H, m), 6.88–7.58 (8H, m).

Separation of cis- and trans-4′-cyanobiphenyl-4-yl 3-n-alkylcyclobutane-1-carboxylates (8c and 8e) by preparative HPLC

Procedure

A Gilson Autoprep system was initially programmed so that a 1.0 cm^3 (i.e., approximately 50 mg sample) solution of the appropriate

isomeric mixture of compound (8c or e) in methanol:chloroform (9:1) was automatically injected onto the column (a Whatman Magnum 20 Partisil 10 ODS-2 reverse phase column). The mobile phase (methanol:water; 80:20) was then passed through the column continuously at a constant rate (17 cm^3 min^{-1}). The output from the column was monitored by a uv detector (λ = 254 nm) and the signal generated was registered by a recorder. The appropriate fractions corresponding to the *cis*-and *trans*-isomer were manually collected and then concentrated. A large number of passes were repeated until a required amount of the separated materials had been collected. At this stage, however, a small amount of contaminant (<3%) corresponding to 4'-cyano-4-hydroxybiphenyl was shown to be present (tlc and hplc analysis). This impurity was removed by column chromatography using silica gel, eluting with chloroform:petroleum fraction (bp 60–80°C) (2:1) in the usual manner. The appropriate *cis*-and *trans*-isomers were then crystallised from methanol at −15°C. The transition temperatures for these compounds are given in Table II. The retention times, yields, and hplc results are given in Table X.

TABLE X

The retention times, yields, and isomeric purities for *cis*- and *trans*-4'-cyanobiphenyl-4-yl 3-n-alkylcyclobutane-1-carboxylates

Structure[a]		Retention time[b] (min)	Yield (g)	Isomeric purity (%) [hplc (C)]
(8c)	*cis*-	52	1.12 [c]	>99.9 in all cases
	trans-	60	1.05 [c]	
(8e)	*cis*-	58	0.23 [d]	
	trans-	65	0.20 [d]	

a : confirmation of the stereochemistry of the *cis*- and *trans*-isomers was achieved using high resolution ^1H nmr (400 MHz, University of Sheffield) spectroscopy. The authors are grateful to Dr DF Ewing for his expert interpretation of the spectroscopic data.

b : based on the experimental conditions outlined

c : after 75 passes

d : after 18 passes

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