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Synthesis and mesomorphic properties of some disubstituted unsymmetrical phenyl-1,2,4,5-tetrazines

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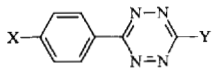
The synthesis of unsymmetrical phenyl-1,2,4,5-tetrazines containing a cyano group either on the phenyl ring (**1a**) or the tetrazine ring (**11a, 11b**) has been accomplished by the introduction of the cyano group after formation of the tetrazine ring. The mesomorphic, solubility and absorption properties of these tetrazines and a series of alkoxy tetrazines (**12a–d**) has been studied. The compounds containing the cyano group on the tetrazine ring showed smectic A phases while nematic phases were observed in some of the alkoxy tetrazines.

1. Introduction

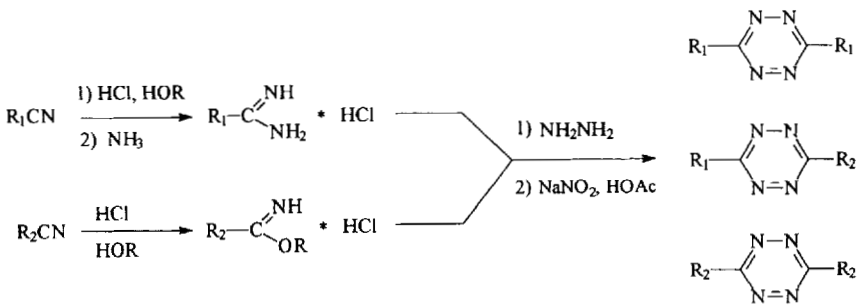
The development and wide use of pleochroic dyes for guest–host liquid crystal displays are primarily dependent on the dye's stability, solubility and degree of order in the host liquid crystal mixture [1, 2]. While much is known about the azo and anthraquinone dyes and their use for display applications in the visible range, significantly less is known about the properties and applications of tetrazine dyes [3–5]. Some tetrazine dyes are known to be photostable, possess liquid crystalline properties and have good solubility in liquid crystalline hosts [6]. We were interested in the synthesis of dyes of type **1** as potential high birefringence liquid crystal dye components to include in the formulation of wide temperature range liquid crystal mixtures for low voltage infrared or millimeter wave applications. The structural similarity of **1** to that of the commonly used 4-alkyl/alkoxy-cyanobiphenyls led us to believe they would have a high solubility in these liquid crystalline hosts.



1

1a $X = CN$ $Y = R$
1b $X = R$ $Y = CN$
1c $X = R$ $Y = OR$
1d $X = OR$ $Y = CN$

The primary problem associated with the synthesis of tetrazines of this type lies in the formation of the tetrazine ring. Typical conditions for the formation of tetrazines are shown in scheme 1 [6–8]. Treatment of a mixture of an imino ester hydrochloride and an amidine hydrochloride with hydrazine followed by oxidation with nitrous acid usually gives a mixture of one unsymmetrical and two



Scheme 1.

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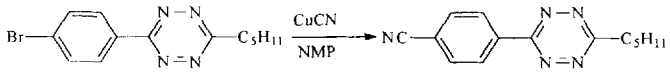
symmetrical tetrazines which can be readily separated by silica gel chromatography. The required imino ester and amidine hydrochloride are formed by treatment of the nitrile precursors with HCl or HCl followed by NH_3 [9]. Synthesis of the desired cyano substituted tetrazines, **1a**, **1b** and **1d** would therefore require introduction of the cyano group after formation of the tetrazine ring had been completed.

2. Synthesis

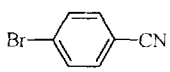
The initial route by which we attempted to synthesize the tetrazine **1a** relied on cyanide displacement of the bromine in tetrazine **2**, shown in scheme 2.



2 1 a ($R = C_5H_{11}$) 10–20 per cent

Scheme 2.

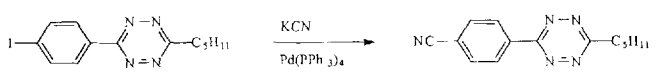
The bromotetrazine **2** was easily synthesized according to scheme 1. Attempts to displace the bromine in tetrazine **2** by a cyano group using CuCN in refluxing 1-methyl-2-pyrrolidinone [10] led to poor and inconsistent yields of the pentyl homologue of nitrile **1a** (10–20 per cent) along with a significant amount of black tar. No organic soluble material could be isolated by extraction of this black tar with dichloromethane. In one reaction the tetrazine **1a**, with $R = C_5H_{11}$, isolated after silica gel chromatography, was contaminated with material tentatively assigned as the nitrile **3** based on ^{1}H NMR and IR spectra. Clearly a new means of introducing the cyano group was required.



3

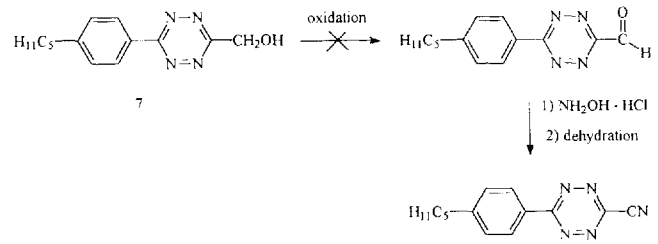
Treatment of aryl bromides with NaCN, $Pd(PPh_3)_4$ and alumina in toluene has also been reported to yield aryl cyanides [11]. Treatment of the bromotetrazine, **2**, under these conditions led to a 90 per cent yield of recovered starting material. Nucleophilic displacement of an iodide by a cyanide is known to proceed under mild conditions in the presence of $Pd(PPh_3)_4$ [12]. To test this milder approach as a means of introducing the cyano group the iodotetrazine, **5**, was synthesized from 4-iodobenzonitrile, as shown in scheme 3.

While no symmetrical aromatic tetrazine was isolated from this reaction a 7:1:1 ratio of **4**:**5**:**6** was obtained. The undesired tetrazole, **4** [8*c*], could be separated from the crude reaction mixture by filtration and the desired iodotetrazine **5** separated from the dialkyltetrazine **6** by silica gel chromatography. Treatment of the iodide **5** with KCN in the presence of a catalytic amount of $Pd(PPh_3)_4$ led cleanly to the nitrile **1a** in a 70 per cent isolated yield.



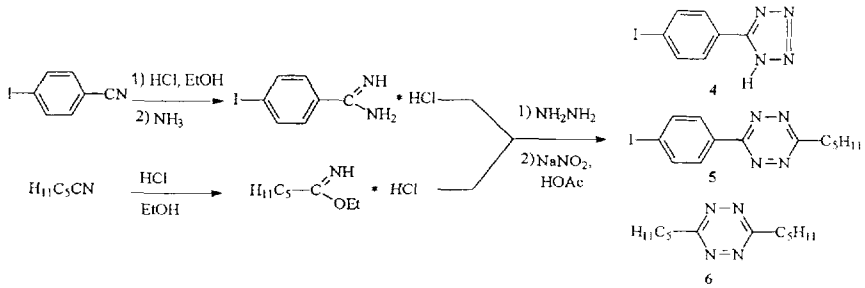
5 **1a** ($R = C_5H_{11}$) 70 per cent

Our initial approach to the synthesis of the isomeric cyanotetrazine **1b** is outlined in scheme 4 [13].



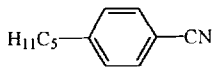
Scheme 4.

While the desired alcohol **7** was easily prepared from hydroxyacetronitrile and 4-pentylbenzonitrile, all attempts to oxidize it to the aldehyde (Swern, PCC or oxoammonium salt oxidation [14]) failed to show an aldehyde peak in the crude ^{1}H NMR spectrum and led to the formation of brown solids that stayed at the origin during silica gel chromatography. Only once on a small scale did an MnO_2 oxidation show some aldehyde in the crude ^{1}H NMR spectrum (in addition to a significant increase in the complexity of the aromatic region). However, when the reaction was repeated and the crude



Scheme 3.

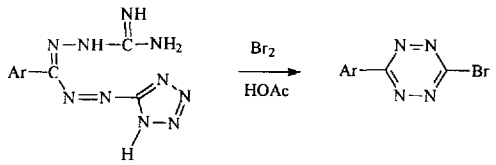
material treated with $NH_2OH \cdot HCl$ followed by dehydration using a Dean–Stark trap only the alkylbenzonitrile **8** was obtained in a 21 per cent yield.



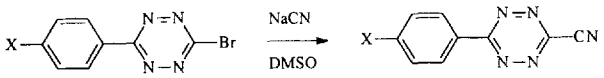
8

Isolation of the nitrile **8** suggested that the tetrazine ring was decomposing either during the oxidation or upon workup.

In 1958, Horwitz and co-workers, reported a novel synthesis of unsymmetrical bromotetrazines [8 *a*]. They found that compounds such as **9** when treated with bromine in acetic acid led to the formation of unsymmetrical bromotetrazines (**10**) [15]. The bromine in the tetrazine **10** could successfully be displaced by nucleophiles such as hydroxy, alkoxy, ammonia, disubstituted amines and the sodium salt of diethyl malonate [8 *a*, *c*]. We found that treatment of these unsymmetrical bromotetrazines with NaCN in DMSO led to rapid displacement of the bromine by cyanide to give the nitrile **11**.



9 **10**



10 a $X = C_7H_{15}$ **11 a** 54 per cent
10 b $X = C_4H_9O$ **11 b** 67 per cent

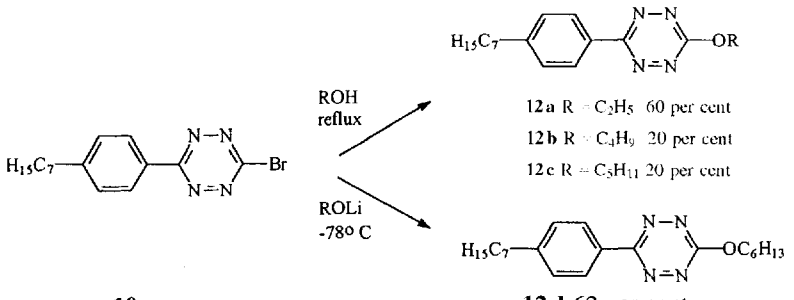
Quite often the reaction was complete within 5 min. While the IR spectrum of **11 a** and **11 b** failed to show a 2200 cm^{-1} peak, this behaviour is not unprecedented for nitriles [16]. The ^{13}C NMR spectrum clearly showed the introduction of a new carbon at 113 ppm and the elemental analysis was consistent with the formation of the nitriles **11 a** and **11 b**. *To our knowledge, these represent the first published syntheses of unsymmetrical phenyl-1,2,4,5-tetrazines containing a cyano group on the tetrazine ring* [17].

The original authors reported that they were unable to displace the bromine in **10** with alkoxides. Instead they obtained the hydroxy derivatives [8 *a*]. Subsequently, it was reported that treatment of unsymmetrical bromotetrazines with sodium methoxide or sodium ethoxide led clearly to the formation of unsymmetrical alkoxy tetrazines [8 *c*, 18]. We were interested in the liquid crystalline properties of these unsymmetrical alkoxy tetrazines and synthesized a series as shown in scheme 5. The shorter chain alcohols successfully displaced the bromine by simply refluxing the bromotetrazine in the desired alcohol. The longer chain alcohols led to poor yields under these conditions. However, we found that use of a lithium alkoxide in these cases led to clean displacement of the bromine in higher yields.

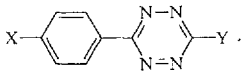
3. Mesomorphic properties

Mesomorphic properties for all of the unsymmetrical tetrazines are given in table 1. Mesophases were observed in both compounds in which the cyano group was on the tetrazine ring but not in the compound with the cyano group on the benzene ring. Both the alkyl and alkoxy series showed smectic A (S_A) phases when the tetrazine ring contained a cyano or bromo substituent. The compounds bearing an alkoxy group on the tetrazine ring with 4, 5 or 6 carbons showed low temperature nematic mesophases with the 5 and 6 carbon alkoxy compounds also displaying a monotropic smectic C (S_C) phase. All of the phase transitions for the compounds in which X = alkyl, Y = cyano, bromo or alkoxy occurred at temperatures less than 100°C. When X = alkoxy, the transitions occurred at significantly higher temperatures.

Mesomorphic properties for some of the cyanotetrazines and for the analogous known biphenyl and nitrogen containing heterocyclic compounds are given in table 2. A comparison of these properties indicates that the addition of nitrogen atoms to a ring favours the formation of S_A phases. With an increasing number of nitrogen atoms



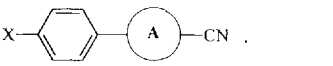
10 a **12 d** 62 per cent

Table 1. Transition temperatures (°C) for  .

X	Y	Cr†	S_C	S_A	N	I
CN	C_5	71·8				77·2–78·0
C_7	Br	37·0		49·5–50·2		76·4–76·8
	CN	30·5		55·1–55·6		101·1–102·3
	NHC_4H_9	137·5–136·1				138·8–140·5
	OC_2	39·9–37·2				42·8–45·2
	OC_4	29·2–28·8			39·4–41·0	44·0–44·3
	OC_5	25·9–23·9	(29·8–31·3)‡		37·6–41·0	42·9–43·8
	OC_6	30·4–27·5	(42·3–43·5)		45·1–46·4	52·4–53·1
OC_4	Br	97·9		107·8–108·9		136·1–137·8
	CN	103·9		107·2–107·7		150·1–150·6
	OC_6	51·9–51·2	(65·4–67·4)		69·8–70·8	76·8–77·2

† Cr = crystallization temperature obtained on cooling the melt 2°C min^{-1}, S_C = smectic, C, S_A = smectic A, N = nematic and I = isotropic.

‡ Numbers in parentheses denote monotropic phases.

Table 2. A comparison of mesomorphic properties for  .

X	A	S_A†	N	I	S_A phase range °C	N phase range ° C
C_5	 ‡		22·5	35	0	12·5
C_7			28·5	42	0	13·5
C_5O			53	67·5	0	14·5
C_7O			53·3	75	0	21·5
C_5	 §		47·4	68·0	0	20·6
C_7		(47·2)††	66·8	70·3	m	3·5
C_5O			59·3	96·4	0	35·3
C_7O		(60·2)	89·2	99·0	m	9·8
C_5	 ‡			73	0	0
C_7			(56)	66	0	m††
C_5O			69	82	0	13
C_7O		62	86	91	24	5
C_5	 ‡	(93·5)	96	109	m	13·0
C_7		96·5		109	12·5	0
C_5O		98	102·5	133	4·5	30·5
C_7O		102·5	127	129·5	24·5	2·5
C_5	 ‡¶			108·5	0	0
C_7				107	0	0
C_5O				100	0	0
C_7O		93		94	1	0
C_5O	 ‖		72	90	0	18
C_7O		65	95	100	30	5
C_7		55·6		102·3	46·7	0
C_4O		107·7		150·6	42·9	0

† S_A = smectic A phase, N = nematic phase and I = isotropic liquid.

‡ Reference [19].

§ Reference [20].

¶ Reference [21].

‖ Reference [22].

†† ( ) indicates a monotropic phase which occurs below the melting temperature.

An m indicates this in the N phase range column since no enantiotropic range is available for comparison.

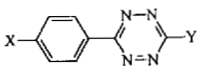
in the ring, formation of the S_A phase becomes so favoured that in the tetrazines no nematic phases occur. Transition temperatures are higher for the pyridine containing heterocycles than for the analogous biphenyl compounds and a further increase occurs with two nitrogen atoms in the ring. However, the addition of four nitrogen atoms to the ring does not always give higher temperatures than those with two since the temperatures for the nitrogen ring systems vary with the location of these atoms.

4. Dye properties

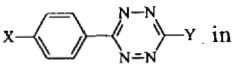
Absorption maxima (λ_{max}) and extinction coefficients (ε) for several of the phenyltetrazine dyes are summarized in table 3. The UV absorption wavelength appeared to be dominated by the conjugated core, but showed some effect due to the terminal groups. A comparison of the data for the alkyl substituted dye **11 a** with that for the alkoxy terminated dye **11 b** showed a 30 nm red shift. The position of the cyano group also affected the UV and visible absorption wavelengths as can be seen by comparing tetrazine **11 a** containing the cyano group on the tetrazine ring with tetrazine **13** in which the cyano group is on the phenyl ring. A comparison of the UV spectra for the three heptylphenyl tetrazine dyes showed an increase in wavelength from the hexyloxy, **12 d**, to the *N*-butylamino, **14**, to the cyano, **11 a**, substituted tetrazines. Additional peaks were exhibited in the 350–400 nm region by dyes **12 d** and **14**.

It has been reported that the HOMO of symmetrical dialkylamino tetrazines is not a linear combination of the four lone pairs of electrons on the nitrogen atoms but is instead a π-MO [23]. In the case of the dye **14**, an unsymmetrical monoalkylamino tetrazine, it would appear that the transition responsible for the absorption at 555 nm continues to be an $n-\pi^*$ as indicated by the relatively small extinction coefficient.

In the design of high birefringence materials, a linearly conjugated system with a long wavelength absorption band and a large extinction coefficient when the light is polarized along a direction parallel to the long axis of the molecule is desired [24]. The dichroic ratios, $D = (A_\perp/A_\parallel)$, and order parameters, $S = (A_\parallel - A_\perp/A_\parallel + 2A_\perp)$ [where $A_\parallel$ is the absorbance of light polarized parallel to the liquid crystal director and $A_\perp$ is the absorbance of light polarized perpendicular to the liquid crystal director] of several of the dyes were determined in the visible region as 1 per cent mixtures in host liquid crystal mixture Merck ZLI-2359 [25] and are given in table 4. All dyes tested exhibited negative dichroism ($S < 0$) in the visible region, as had been previously reported for several other tetrazines [3, 5, 6 *b*]. This property was unaffected by the presence of a cyano group on the tetrazine ring. The dichroic ratios of the dyes **11 a**, **11 b** and **12 d** are comparable to those reported for known two ring tetrazine dyes while the dichroic ratio of **14** is comparable to those reported for three ring tetrazine dyes [6 a].

Table 3. Absorption properties in acetonitrile for  .

Dye	*X*	*Y*	λ_{max} UV/nm	ε(UV)	λ_{max} Vis/nm	ε(Vis)
11 a	C_7	CN	310	$2{\cdot}55 \times 10^4$	521	$5{\cdot}13 \times 10^2$
11 b	OC_4	CN	340	$2{\cdot}36 \times 10^4$	521	$4{\cdot}56 \times 10^2$
12 d	C_7	OC_6	268	$2{\cdot}90 \times 10^4$	533	$4{\cdot}92 \times 10^2$
			355	$1{\cdot}34 \times 10^3$		
13	CN	C_5	263	$2{\cdot}78 \times 10^4$	540	$4{\cdot}52 \times 10^2$
14	C_7	NHC_4H_9	287	$3{\cdot}54 \times 10^4$	555	$5{\cdot}7 \times 10^2$
			404	$1{\cdot}51 \times 10^3$		

Table 4. Dichroic properties of  in ZLI-2359.

Dye	*X*	*Y*	λ/nm	$A_\parallel$†	$A_\perp$‡	*D*§	*S*¶
11 a	C_7	CN	531	0·005	0·014	2·8	−0·27
11 b	OC_4	CN	524	0·004	0·019	4·8	−0·36
12 d	C_7	OC_6	543	0·005	0·020	4·0	−0·33
14	C_7	NHC_4H_9	541	0·0016	0·013	8·1	−0·41

† $A_\parallel$ is the absorbance of light polarized parallel to the liquid crystal director.
‡ $A_\perp$ is the absorbance of light polarized perpendicular to the liquid crystal director.
§ $D = A_\perp/A_\parallel$.
¶ $S = A_\parallel - A_\perp/A_\parallel + 2\,A_\perp$.

The solubilities of some of the tetrazine dyes were tested by dissolving each candidate at an elevated temperature in the liquid crystal mixture BDH-E7 [26]. These dye–liquid crystal mixtures were cooled to room temperature and checked for dye precipitation. Since the solubility characteristics of liquid crystal dyes and eutectic mixture formation are governed by their melting temperature and heat of fusion enthalpy, these properties were determined by DSC for the phase transitions of several of the tetrazine dyes and given in table 5 along with their solubilities. Several of the dyes showed high solubility (two >20 per cent) in the liquid crystalline mixture.

5. Conclusions

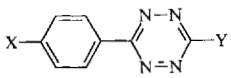
We have successfully synthesized unsymmetrical phenyl-1,2,4,5-tetrazines containing a cyano group either on the phenyl ring or on the tetrazine ring by introduction of the cyano group after formation of the tetrazine ring. Tetrazines containing a cyano group showed S_A mesophases only when the cyano group was on the tetrazine ring. Nematic phases were observed in some of the tetrazines bearing alkoxy groups on the tetrazine ring. All dyes tested exhibited negative dichroism in the visible region and thus would not be of interest for infrared or millimetre wave applications.

6. Experimental

6.1. *Analysis*

A Nicolet Magna FT-IR 550 spectrophotometer was used to record IR spectra. ^1H and ^{13}C NMR spectra were run with TMS as the internal standard using a Varian Gemini-200 spectrometer equipped with a VXR-400 data station at 200 and 50 MHz, respectively. Absorption properties were measured with a Perkin–Elmer Lambda 9 spectrophotometer using spectral grade acetonitrile as a reference and as a solvent for the dye solution in 1 cm path length cells. DSC measurements were run on a Perkin–Elmer DSC 7 equipped with a TAC7/PC instrument controller at a range of 5°C min^{-1}. Capillary G.C. analysis was obtained using a Hewlett–Packard model 5890 instrument equipped with an HP 3395 integrator, an FID detector and a Hewlett-Packard 5 m methyl silicone gum column. Elemental analyses and mass spectra were obtained from Oneida Research Services, Inc., Whitesboro, NY.

Flash column chromatography was done using Mallinckrodt silica gel (230–400 mesh) unless otherwise stated. TLC data were obtained using Anal-Tech silica gel GHLF Uniplates with UV light as the detector. Anhydrous THF was purchased from Aldrich and used without further drying. DMSO was dried for 24 h over 4 Å molecular sieves before use.

Table 5. Enthalpy values (ΔH) for transitions in  .

X	*Y*	Phase transition†	Temperature/°C	ΔH (kJ mole)	Solubility (BDH-E7)/per cent
CN	C_5	Cr_1–I	77·6	26·64	>20
		I–Cr_1	68·3	19·51	
		Cr_1–Cr_2	58·0	7·97	
C_7	OC_6	Cr–N	47·9	30·12	$>7<14$
		N–I	52·6	1·85	
		I–N	50·1	2·51	
		N–S_C	40·9	1·24	
		S_C–Cr	29·0	17·44	
C_7	NHC_4H_9	Cr–I	138·8	38·48	6
		I–Cr	132·9	38·03	
C_7	CN	Cr–S_A	54·5	20·04	>20
		S_A–I	99·2	5·42	
		I–S_A	97·9	5·44	
		S_A–Cr	31·1	19·50	
OC_4	CN	Cr–S_A	106·3	14·99	>7
		S_A–I	147·4	6·61	
		I–S_A	144·3	6·52	
		S_A–Cr	96·6	15·17	

† Cr = crystallization temperature, S_C = smectic C phase, S_A = smectic A phase, N = nematic phase and I = isotropic liquid.

Melting points were determined using a Thomas–Hoover Uni-melt apparatus and corrected. Melting points were not obtained when transition temperatures were determined by microscopy. Transition temperatures (°C) were determined using a Leitz Laborlux 12 POL polarizing microscope fitted with a modified and calibrated Mettler FP-2 heating stage at a heating rate of 2° min^{-1}. Crystallization temperatures were obtained by cooling the melt at 2°C min^{-1} until crystals were formed to ensure that all mesophases had been observed before this temperature. These crystals were reheated to obtain the melting temperatures and to confirm that these were not mesophases.

6.2. *3-(4-bromophenyl)-6-pentyl-1,2,4,5-tetrazine* (**2**)

HCl gas was bubbled through a stirred solution of hexanenitrile (1·0 g, 22 mmol) at 0°C for 12 min. The reaction mixture was placed under N_2, allowed to warm to room temperature and after 64 h diluted with abs EtOH (50 ml). This solution and a solution of 4-bromobenzamidine hydrochloride [27] (3·3 g, 14 mmol) were added dropwise and simultaneously within 15 min to a stirred solution of hydrazine hydrate (9·9 g, 309 mmol) in abs EtOH (30 ml) at 0°C. The ice bath was removed and the reaction mixture stirred 3 h at room temperature. The EtOH was taken off *in vacuo*, the reaction diluted with water and the solids collected by suction filtration. The filtrate was extracted with CH_2Cl_2, the organic layer added to the water insoluble solids and the solvent removed *in vacuo* to give the crude dihydrotetrazine. Acetic acid (23 ml) was added dropwise to a stirred solution of this material in 3 M $NaNO_2$ (15 ml) at 0°C. Stirring was continued for 2 h at room temperature and then the resulting purple precipitate collected by suction filtration. These solids were dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. This material was chromatographed through 75 g silica gel using 50 per cent ether/hexane followed by recrystallization from hexane to afford 0·54 g (13 per cent) of the desired tetrazine as a purple solid: TLC (100 per cent CH_2Cl_2) $R_f = 0·73$; m.p. 107·4–109·4°C; ^1H NMR ($CDCl_3$) δ 8·48 (d, 2 H, $J = 8·7$ Hz), 7·74 (d, 2 H, $J = 8·7$ Hz), 3·36 (t, 2 H, $J = 7·7$ Hz), 1·99 (quint, 2 H, $J = 7·6$ Hz), 1·46–1·40 (m, 4 H), 0·96–0·92 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 170·4, 163·5, 132·5, 130·7, 129·2, 127·6, 34·8, 31·3, 28·0, 22·3, 13·9; IR (Nujol/NaCl) 3094, 1595, 1372 cm^{-1}.

6.3. *4-Iodobenzamidine hydrochloride*

HCl gas was bubbled through a solution of 4-iodobenzonitrile (6·0 g, 26 mmol) and abs EtOH (3·0 g, 65·2 mmol) in ether (40 ml) at 0°C for 20 min. The reaction mixture was placed under N_2, allowed to warm to room temperature and stirred for 64 h. In a separate flask, NH_3 was bubbled into abs EtOH (150 ml) for 20 min at room temperature. This solution was added dropwise to the crude imino ester formed above and the reaction stirred under N_2 for 24 h. The crude product was collected by suction filtration, dissolved in a minimum amount of hot water, acidified with HCl and the product allowed to slowly crystallize while cooling to room temperature to yield 5·5 g (74 per cent) of the desired product as tan needles. An analytically pure sample was obtained by recrystallization from abs EtOH: m.p. 287·5–289·0°C; ^1H NMR (DMSO) δ 9·51 (br, s, 2 H), 9·31 (br, s, 2 H), 8·02 (δ, 2 H, $J = 8·5$ Hz), 7·62 (d, 2 H, $J = 8·7$ Hz); ^{13}C NMR (DMSO) δ 165·2, 137·8, 129·8, 127·4, 102·3; IR (Nujol/NaCl) 3500, 3427, 3151 (br), 1677 cm^{-1}; Anal. Calcd for $C_7H_8ClIN_2$; C, 29·74; H, 2·85; N, 9·92. Found C, 29·58; H, 2·87; N, 9·90 per cent.

6.4. *3-(4-Iodophenyl)-6-pentyl-1,2,4,5-tetrazine* (**5**)

HCl gas was bubbled through a stirred solution of 1-hexanenitrile (1·0 g, 10 mmol) and 1-propanol (0·70 g, 12 mmol) at 0°C for 40 min. The reaction was placed under N_2 and allowed to warm to room temperature. After 1 h the reaction mixture was diluted with MeOH (10 ml). In a separate flask, NH_3 gas was bubbled through MeOH (7·0 ml) for 10 min at room temperature. This MeOH/NH_3 solution was added dropwise to the imino ester formed above and the reaction mixture stirred 30 min at room temperature. The reaction mixture was diluted with Et_2O (10 ml), filtered and the solids washed with Et_2O. A solution of this hexanimidamide monohydrochloride in EtOH (25 ml) and a slurry of 4-iodobenzamidine hydrochloride in EtOH (35 ml) were added dropwise and simultaneously within 10 min to a stirred solution of hydrazine hydrate (5·0 g, 156 mmol) in EtOH (30 ml) at 0°C. After the addition was complete, the reaction mixture was stirred for 2·5 h at room temperature, diluted with water and the EtOH taken off *in vacuo*. The insoluble material was collected by suction filtration and washed with H_2O. The filtrate was extracted with CH_2Cl_2 and the organic layer added to the water insoluble solid and the solvent removed *in vacuo* to give the crude dihydrotetrazine. Acetic acid (13 ml) was added dropwise to a stirred solution of this material in 2·5 M $NaNO_2$ (10 ml) at 0°C. Stirring was continued at room temperature for 2 h and then the resulting purple precipitate collected by suction filtration. These solids were triturated with CH_2Cl_2 to separate the CH_2Cl_2 soluble tetrazines from 1·3 g of the CH_2Cl_2 insoluble white solid tetrazole (**4**). The CH_2Cl_2 was removed *in vacuo* and the purple material chromatographed through 30 g silica, 10 per cent CH_2Cl_2/hexane to afford 0·18 g, (6 per cent) of the desired unsymmetrical tetrazine **5** as a purple solid and 0·18 g of the symmetrical tetrazine **6** as a red liquid. For **4**, recrystallized from abs EtOH: m.p. 274·5–276·5°C; ^1H

NMR (DMSO) δ 7·99 (d, 2 H, J = 8·3 Hz), 7·67 (d, 2 H, J = 8·5 Hz); ^{13}C NMR (DMSO) δ 155·3, 138·2, 128·0, 123·1, 98·3; IR (Nujol/NaCl) 2361 (br), 1914, 1604, 1550 cm^{-1}; Anal. Calcd for $C_7H_5IN_4$: C, 30·88; H, 1·84; N, 20·59. Found C, 31·47; H, 1·95; N, 20·20 per cent. For **5**: TLC (50 per cent CH_2Cl_2/hexanes) R_f = 0·50; m.p. 108·4–110·4°C; ^{1}H NMR ($CDCl_3$) δ 8·33 (dt, 2 H, J_d = 8·7 Hz, J_t = 2·0 Hz), 7·95 (dt, 2 H, J_d = 8·7 Hz, J_t = 2·0 Hz), 3·35 (t, 2 H, J = 7·7 Hz), 1·99 (p, 2 H, J = 7·5 Hz), 1·49–1·25 (m, 4 H), 0·96–0·89 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 170·4, 163·8, 139·5, 131·3, 129·2, 100·1, 34·8, 31·3, 28·0, 22·3, 13·9; IR (CCl_4 solution/NaCl) 2966, 2953, 2861, 1593, 1404 cm^{-1}. For **6**: TLC (50 per cent CH_2Cl_2/hexanes) R_f = 0·40; ^{1}H NMR ($CDCl_3$) δ 3·21 (t, 4 H, J = 7·7 Hz), 1·87 (quint, 4 H, J = 7·7 Hz), 1·38–1·27 (m, 8 H), 0·87–0·80 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 170·2, 35·3, 31·4, 28·0, 22·5, 14·0; IR (Neat/NaCl) 2956, 2858, 1463, 1398 cm^{-1}.

6.5. *3-(4-Cyanophenyl)-6-pentyl-1,2,4,5-tetrazine* (**1 a**) $R = C_5H_{11}$

A stirred solution of powdered KCN (0·09 g, 1·4 mmol), **5** (0·29 g, 0·82 mmol) and $Pd(PPh_3)_4$ (0·11 g, 0·09 mmol) was refluxed under N_2 for 4 h. Additional $Pd(PPh_3)_4$ (0·05 g, 0·04 mmol) was added and heating continued for 2 h. The reaction mixture was cooled, filtered, concentrated *in vacuo* and the crude material diluted with H_2O (20 ml). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 ml), the organic fractions combined, dried over $MgSO_4$, concentrated *in vacuo* and chromatographed through 25 g silica gel with a gradient elution from 40 per cent CH_2Cl_2/hexane to 100 per cent CH_2Cl_2 to afford 0·14 g (70 per cent) of the desired nitrile as a purple solid: TLC R_f = 0·35 (100 per cent CH_2Cl_2); m.p. 77·2–78·0°C; ^{1}H NMR ($CDCl_3$) δ 8·73 (d, 2 H, J = 8·7 Hz), 7·84 (d, 2 H, J = 8·6 Hz), 3·34 (t, 2 H, J = 7·6 Hz), 2·00 (quint, 2 H, J = 7·4 Hz) 1·47–1·38 (m, 4 H), 0·95–0·88 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 170·9, 162·9, 135·9, 132·9, 128·2, 118·0, 115·9, 34·8, 31·2, 27·9, 22·3, 13·8; IR (CCl_4/NaCl) 2959, 2933, 2855, 2244, 1399 cm^{-1}; Anal. Calcd for $C_{14}H_{15}N_5$: C, 66·40; H, 5·93; N, 27·67. Found: C, 66·06; H, 6·05; N, 27·15 per cent.

6.6. *3-Hydroxymethyl-6-(4-pentylphenyl)-1,2,4,5-tetrazine* (**7**)

HCl gas was bubbled through a stirred solution of 4-pentylbenzonitrile (15·0 g, 86·7 mmol) and abs EtOH (4·0 g, 87·0 mmol) at 0°C for 20 min. The reaction mixture was placed under N_2, the ice bath removed and the reaction mixture stirred for 16 h at room temperature. A solution of this imino ester in abs EtOH (100 ml) and a slurry of 2-hydroxyacetamidine hydrochloride [25] (9·6 g, 87 mmol) in 200 ml abs EtOH were added dropwise and simultaneously within 20 min to a stirred solution of hydrazine hydrate (56 g, 1·8 mol) in EtOH (100 ml) at 0°C. After the addition was complete, the reaction mixture was stirred for 3 h at room temperature, then diluted with H_2O (250 ml), the solvent removed *in vacuo* and the aqueous fraction extracted with CH_2Cl_2 (2 × 150 ml). All organic fractions were combined, concentrated *in vacuo*, the crude dihydrotetrazine dissolved in aq. 3 M $NaNO_2$ (90 ml) and the reaction mixture cooled to 0°C. HOAc (13 ml) was added dropwise, the reaction mixture was stirred 2 h at room temperature, and then extracted with CH_2Cl_2 (3 × 200 ml). All organic fractions were combined, washed with saturated $NaHCO_3$ (2 × 250 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was chromatographed through 500 g neutral alumina using a gradient elution from 100 per cent CH_2Cl_2 to 100 per cent ethyl acetate to afford 3·0 g (13 per cent) of the desired tetrazine **7** as red plates, 2·9 g of the symmetrical tetrazine 3,6-bis(4-pentylphenyl)-1,2,4,5-tetrazine as purple plates and 3·3 g (22 per cent) recovered 4-pentylbenzonitrile. For **7**: TLC (100 per cent EtOAc) R_f = 0·72; m.p. 74·1–76·6°C; ^{1}H NMR ($CDCl_3$) δ 8·55 (d, 2 H, J = 8·4 Hz), 7·42 (d, 2 H, J = 8·5 Hz), 5·32 (d, 2 H, J = 6·1 Hz), 3·08 (t, 1 H, J = 6·2 Hz), 2·73 (t, 2 H, J = 7·6 Hz), 1·77–1·61 (m, 2 H), 1·4–1·32 (m, 4 H), 0·91 (t, 3 H, J = 6·6 Hz); ^{13}C NMR ($CDCl_3$) δ 167·1, 165·3, 148·7, 129·4, 128·7, 128·1, 62·7, 36·0, 31·4, 30·7, 22·4, 14·0; IR (CCL_4 solution/NaCl) 3567, 2929, 1742, 1619, 1379 cm^{-1}; Anal. Calcd for $C_{14}H_{18}N_4O$: C, 65·08; H, 7·04; N, 21·69. Found: C, 64·96; H, 6·99; N, 22·04 per cent. For the symmetrical aromatic tetrazine 3,6-bis(4-pentylphenyl)-1,2,4,5-tetrazine: R_f = 0·57 (50 per cent CH_2Cl_2/hexanes); transitions (°C) Cr_1 155·2 Cr_2 161·1 N 169·6 I (lit [28] Cr 163 N 172·5 I); ^{1}H NMR ($CDCl_3$) δ 8·55 (d, 4 H, J = 8·5 Hz), 7·42 (d, 4 H, J = 8·7 Hz), 1·73–1·60 (m, 4 H), 1·39–1·31 (m, 8 H), 0·91 (t, 6 H, J = 2·2 Hz); ^{13}C NMR ($CDCl_3$) δ 163·8, 148·2, 129·4, 129·3, 127·8, 36·0, 31·5, 30·8, 22·5, 14·0; IR (CCl_4 solution/NaCl) 2940, 1618, 1460, 1394 cm^{-1}.

6.7. *Synthesis of the unsymmetrical bromotetrazines* (**10**)

These compounds were prepared according to the procedure of Horwitz and co-workers [8 *a*, 15].

6.8. *3-Bromo-6-(4-heptylphenyl)-1,2,4,5-tetrazine* (**10 a**)

TLC (50 per cent CH_2Cl_2/hexanes) R_f = 0·49; ^{1}H NMR ($CDCl_3$) δ 8·45 (d, 2 H, J = 8·4 Hz), 7·39 (d, 2 H, J = 8·3 Hz), 2·72 (t, 2 H, J = 7·6 Hz), 1·72–1·64 (m, 2 H), 1·35–1·20 (m, 8 H), 0·88 (t, 3 H, J = 6·4 Hz); ^{13}C NMR ($CDCl_3$) δ 167·5, 164·4, 149·2, 129·5, 128·3, 127·7, 36·0, 31·7, 31·0, 29·2, 29·1, 22·6, 14·0; IR (CCl_4 solution/NaCl) 2983, 2858, 1608, 1425, 1350 cm^{-1}.

6.9. *3-Bromo-6-(4-butoxyphenyl)-1,2,4,5-tetrazine* (**10 b**)

TLC (100 per cent CH_2Cl_2) R_f = 0·60; ^{1}H NMR ($CDCl_3$) δ 8·45 (d, 2 H, J = 9·0 Hz), 7·03 (d, 2 H, J = 9·0 Hz), 4·06

(t, 2H, $J = 6.5$ Hz), 1.90–1.78 (m, 2H), 1.58–1.47 (m, 2H), 1.00 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$) δ 164.20, 163.64, 159.85, 130.23, 122.36, 115.36, 68.06, 31.10, 19.18, 13.80. IR (CCl_4 solution/NaCl) 2957, 2880, 1610, 1517, 1350 cm^{-1}. A minor amount of material in which the benzene ring appeared, by ^{1}H NMR, to have undergone bromination was always obtained in this reaction. This material could be readily separated by silica gel chromatography using 30 per cent CH_2Cl_2/hexanes.

6.10. *3-Cyano-6-(4-heptylphenyl)-1,2,4,5-tetrazine* (**11 a**)

A solution of the tetrazine **10 a** (0.31 g, 0.92 mmol) in DMSO (6 ml) was treated with NaCN (0.10 g, 2.0 mmol) at room temperature for 15 min. TLC of the reaction mixture showed no remaining starting material. The reaction mixture was poured onto ice, warmed to room temperature and the aqueous layer extracted with ether (3 × 50 ml). All organic fractions were combined, washed with H_2O, dried over $MgSO_4$, concentrated *in vacuo* and chromatographed through 20 g silica gel (60–100 mesh) using 25 per cent CH_2Cl_2/hexane to afford 0.14 g (54 per cent) of the desired product as a red solid that was recrystallized from hexanes: TLC (50 per cent CH_2Cl_2/hexanes) $R_f = 0.46$; ^{1}H NMR ($CDCl_3$) δ 8.58 (d, 2H, $J = 8.5$ Hz), 7.46 (d, 2H, $J = 8.4$ Hz), 2.75 (t, 2H, $J = 7.7$ Hz), 1.69 (quint, 2H, $J = 7.5$ Hz), 1.35–1.28 (m, 8H), 0.89 (t, 3H, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$) δ 163.4, 151.3, 150.7, 130.0, 129.8, 129.6, 127.4, 113.1, 36.2, 31.7, 31.0, 29.2, 29.1, 22.6, 14.0; IR (CCl_4 solution/NaCl) 2931, 2861, 1607, 1434, 1383 cm^{-1}; MS (EI) *m/z* (relative intensity) 281 (M^+, 8.3); Anal. Calcd for $C_{16}H_{19}N_5$: C, 68.28; H, 6.81; N, 24.91. Found: C, 68.29; H, 6.48; N, 24.82 per cent.

6.11. *3-(4-Butoxyphenyl)-6-cyano-1,2,4,5-tetrazine* (**11 b**)

This compound was prepared in the same manner as **11 a** but using 13 ml of 3:10 THF:DMSO as the solvent. The crude product was chromatographed through 30 g silica gel (60–100 mesh) using 50 per cent CH_2Cl_2/hexanes followed by recrystallization from hexanes to afford 0.16 g (67 per cent) of the desired product as a red solid: TLC (50 per cent CH_2Cl_2/hexanes) $R_f = 0.24$; ^{1}H NMR ($CDCl_3$) δ 8.60 (d, 2H, $J = 8.4$ Hz), 7.10 (d, 2H, $J = 8.9$ Hz), 4.12 (t, 2H, $J = 6.3$ Hz), 1.88–1.81 (m, 2H), 1.60–1.49 (m, 2H), 1.02 (t, 3H, 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 165.0, 162.9, 150.1, 131.8, 121.9, 115.8, 113.2, 68.3, 31.0, 19.1, 13.8; Anal. Calcd for $C_{13}H_{13}N_5O$: C, 61.13; H, 5.14; N, 27.45. Found: C, 61.19; H, 5.01; N, 27.80 per cent.

6.12. *3-Ethoxy-6-(4-heptylphenyl)-1,2,4,5-tetrazine* (**12 a**)

A solution of the bromotetrazine **10 a** (0.15 g, 0.31 mmol) in 5 ml abs EtOH was refluxed for 1.5 h, cooled to room temperature, concentrated *in vacuo* and the crude material recrystallized from EtOH/water to afford 56 mg (60 per cent) of the desired tetrazine as a red solid. TLC (50 per cent CH_2Cl_2/hexanes) $R_f = 0.28$; ^{1}H NMR ($CDCl_3$) δ 8.40 (d, 2H, $J = 8.5$ Hz), 7.38 (d, 2H, $J = 8.3$ Hz) 4.77 (q, 2H, $J = 7.1$ Hz), 2.71 (t, 2H, $J = 7.7$ Hz), 1.75–1.63 (m, 2H), 1.60 (t, 3H, $J = 7.0$ Hz), 1.40–1.20 (m, 8H), 0.89 (t, 3H, $J = 6.3$ Hz); ^{13}C NMR ($CDCl_3$) δ 166.3, 163.0, 147.2, 129.2, 129.1, 127.2, 65.8, 35.9, 31.7, 31.2, 29.2, 29.1, 22.6, 14.3, 14.0; IR (CCl_4 solution/NaCl) 2927, 2855, 1618, 1479, 1450, 1417, 1384, 1354 cm^{-1}.

6.13. *3-(4-Heptylphenyl)-6-hexyloxy-1,2,4,5-tetrazine* (**12 d**)

A solution of hexan-1-ol (0.24 g, 2.4 mmol) in THF (3 ml) was cooled to −78°C, treated with butyllithium (1.1 ml, 1.6 M in hexanes, 1.8 mmol). The ice bath was removed and the reaction stirred for 25 min at room temperature. The temperature was then decreased to −78°C, a solution of the bromotetrazine **10 a** (0.19 g, 0.57 mmol) in THF (2 ml) added, the ice bath removed and the reaction stirred 30 min at room temperature. The reaction mixture was poured into water, the solvent taken off *in vacuo* and the aqueous layer extracted with hexane (3 × 20 ml). All organic fractions were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was recrystallized from CH_3CN/water to yield 0.12 g (62 per cent) of the desired product as a red solid. TLC (100 per cent CH_2Cl_2) $R_f = 0.76$; ^{1}H NMR ($CDCl_3$) δ 8.40 (d, 2H, $J = 8.3$ Hz), 7.38 (d, 2H, $J = 8.4$ Hz), 4.69 (t, 2H, $J = 6.6$ Hz), 2.71 (t, 2H, $J = 7.6$ Hz), 2.05–1.92 (m, 2H), 1.75–1.64 (m, 2H), 1.42–1.29 (m, 14H), 0.92 (t, 3H, $J = 6.8$ Hz), 0.89 (t, 3H, $J = 6.7$ Hz); ^{13}C NMR ($CDCl_3$) δ 166.5, 163.0, 147.3, 129.3, 129.2, 127.2, 69.9, 35.9, 31.8, 31.4, 31.2, 29.2, 29.1, 28.6, 25.4, 22.6, 22.5, 14.1, 14.0; IR (CCl_4 solution/NaCL) 2940, 1618, 1492, 1450, 1420, 1350 cm^{-1}.

6.14. *3-Butoxy-6-(4-heptylphenyl)-1,2,4,5-tetrazine* (**12 b**)

This material was prepared in the same manner as that described above for the formation of **12 d**. From the bromotetrazine **10 a** (80 mg, 0.26 mmol) was obtained **12 b** (75 mg, 88 per cent) as a red solid. TLC (50 per cent CH_2Cl_2/hexanes) $R_f = 0.28$; ^{1}H NMR ($CDCl_3$) δ 8.40 (d, 2H, $J = 8.3$ Hz), 7.38 (d, 2H, $J = 8.4$ Hz), 4.69 (t, 2H, $J = 6.6$ Hz), 2.70 (t, 2H, $J = 7.8$ Hz), 2.05–1.91 (m, 2H), 1.70–1.50 (m, 4H), 1.40–1.25 (m, 8H), 1.02 (t, 3H, $J = 7.2$ Hz), 0.88 (t, 3H, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$) δ

166·5, 162·9, 147·2, 129·2, 127·2, 69·6, 35·9, 31·8, 31·2, 30·6, 29·2, 29·1, 22·6, 19·0, 14·0, 13·7; IR (CCl_4 solution/NaCl) 2938, 1613, 1485, 1466, 1428, 1377, 1357 cm^{-1}.

6.15. *3-(4-Heptylphenyl)-6-pentyloxy-1,2,4,5-tetrazine* (**12 c**)

This material was prepared in the same manner as that described above for the formation of **12 d**. From the bromotetrazine **10 a** (0·14 g, 0·42 mmol) was obtained **12 c** (0·10 g, 76 per cent) as a red solid. Although TLC showed only one spot, GC analysis of this material revealed the presence of approximately 10 per cent of some impurity. This material was chromatographed through 20 g silica gel, 20 per cent CH_2Cl_2/hexane. The first fraction off the column showed only product by GC. analysis and was used for characterization. TLC (50 per cent CH_2Cl_2/hexanes) $R_f = 0·44$; ^1H NMR ($CDCl_3$) δ 8·40 (d, 2 H, $J = 8·4$ Hz), 7·38 (d, 2 H, $J = 8·6$ Hz), 4·68 (t, 2 H, $J = 6·6$ Hz), 2·70 (t, 2 H, $J = 7·7$ Hz), 1·97 (quint, 2 H, $J = 7·4$ Hz), 1·80–1·24 (m, 14 H), 0·95 (t, 3 H, $J = 7·2$ Hz), 0·90–0·85 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 166·5, 163·0, 147·3, 129·3, 129·2, 127·3, 69·9, 36·0, 31·8, 31·2, 29·2, 29·1, 28·3, 27·9, 22·6, 22·3, 14·1, 14·0; IR (CCl_4 solution/NaCl) 2929, 1613, 1484, 1456, 1427, 1373 cm^{-1}.

6.16. *3-(4-Butoxyphenyl)-6-hexyloxy-1,2,4,5-tetrazine*

This material was prepared in the same manner as that described above for the formation of **12 d**. From the bromotetrazine **10 b** (56 mg, 0·18 mmol) was obtained the desired product (37 mg, 63 per cent) as a red solid. TLC (100 per cent CH_2Cl_2) $R_f = 0·55$; ^1H NMR ($CDCl_3$) δ 8·42 (d, 2 H, $J = 8·7$ Hz), 7·05 (d, 2 H, $J = 8·8$ Hz), 4·66 (t, 2 H, $J = 6·6$ Hz), 4·06 (t, 2 H, $J = 6·4$ Hz), 1·99–1·78 (m, 4 H), 1·58–1·34 (m, 8 H), 1·00 (t, 3 H, $J = 7·4$ Hz), 0·95–0·89 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 166·4, 162·7, 162·2, 128·9, 123·9, 115·0, 69·8, 67·9, 31·4, 31·2, 28·6, 25·4, 22·5, 19·2, 14·0, 13·8; IR (CCl_4 solution/NaCl) 2966, 1611, 1575, 1516, 1475, 1450 cm^{-1}.

6.17. *3-(N-Butylamino)-6-heptylphenyl-1,2,4,5-tetrazine* (**14**)

A solution of the bromotetrazine **10 a** (0·58 g, 1·7 mmol) in 10 ml of benzene was treated with butylamine (0·22 g, 3·0 mmol) for 5 min at room temperature. The solvent was removed *in vacuo*, the crude material poured into water and the resulting precipitate collected by suction filtration. Recrystallization of this material from EtOH/water gave 0·38 g (70 per cent) of the desired product as orange crystals: TLC (100 per cent CH_2Cl_2) $R_f = 0·34$; ^1H NMR ($CDCl_3$) δ 8·30 (d, 2 H, $J = 8·3$ Hz), 7·33 (d, 2 H, $J = 8·1$ Hz), 5·86 (br s, 1 H), 3·66 (q, 2 H, $J = 6·7$ Hz), 2·68 (t, 2 H, 7·6 Hz), 1·81–1·19 (m, 14 H), 0·99 (t, 3 H, $J = 7·1$ Hz), 0·88 (t, 3 H, $J = 6·5$ Hz); ^{13}C NMR ($CDCl_3$) δ 161·3, 160·4, 145·9, 130·2, 129·0, 126·2, 41·2, 35·9, 31·8, 31·3, 29·2, 29·1, 22·6, 20·0, 14·1, 13·7; IR (Nujol/NaCl) 3241, 1610, 1588, 1505, 1475 cm^{-1}; Anal. Calcd for $C_{19}H_{29}N_5$: C, 69·65; H, 8·95; N, 21·40. Found: C, 69·54; H, 8·92; N, 21·31 per cent.

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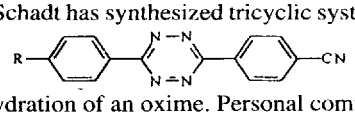

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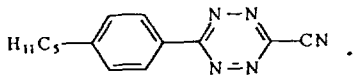

However we, were unable to find any published synthesis of this material.

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