The 'inverse electron-demand' Diels–Alder reaction in polymer synthesis. Part 4.[1] The preparation and crystal structures of some bis(1,2,4,5-tetrazines)

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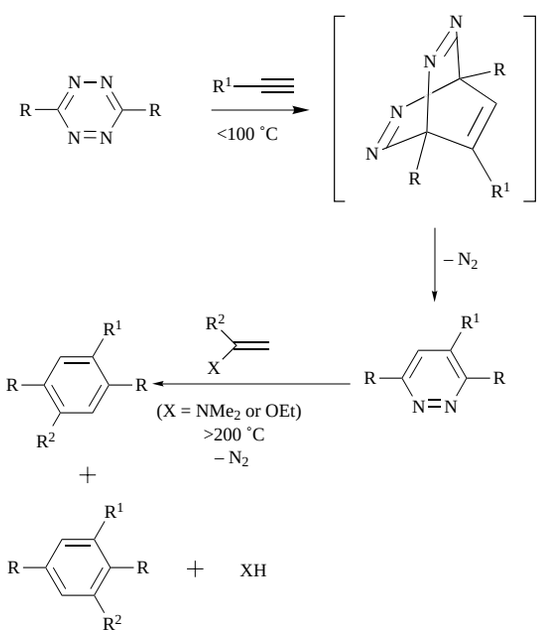
Reaction of 3,6-bis(3,5-dimethylpyrazolyl)-1,2,4,5-tetrazine with mono- and di-amines gives rise to nucleophilic substitution of one or both of the pyrazolyl substituents, and reaction with diamines under appropriate conditions can lead to bis(3-amino-1,2,4,5-tetrazines), *e.g.* **12a, 12b and 13. The crystal structures of two of these (12a and 13) show electronic interaction between the tetrazine rings and the amino groups, but none between the tetrazine and pyrazole rings. In 12a there is an extensive network of N–H · · · N hydrogen bonds.**

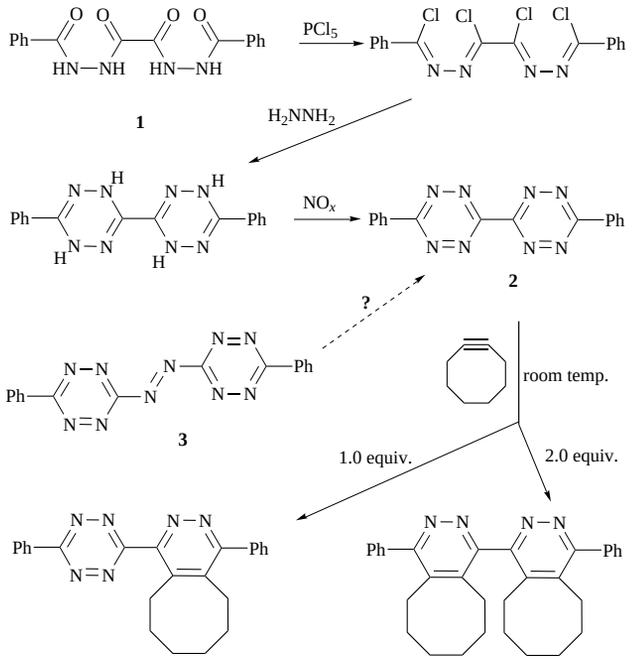
As part of our ongoing investigation of the applicability of the 'inverse electron-demand' Diels–Alder reactions to polymer synthesis, we have previously described methods for the synthesis of novel series of bis(1,2,4-triazines)[2] and bisalkynes[3] which may serve as potential monomers. The use of the 'normal' Diels–Alder reaction as a polymerisation process has been well described for both aliphatic and aromatic systems, the reaction between bisalkynes and bis-maleimides, bis(tetracyclones) or bis-α-pyrones yielding high molecular mass poly(aromatics).[4] On the other hand, although 'inverse electron-demand' Diels–Alder reactions of simple azaheterocycles (*e.g.* pyridazines, 1,2,4-triazines and 1,2,4,5-tetrazines) are well known,[5] the use of this type of cycloaddition in polymerisation has not been recorded. Our previous work has shown[1] that bis-dienophiles as reaction partners for bis(1,2,4-triazines) may not be easily accessible.

Of the above ring systems which undergo 'inverse electron-demand' Diels–Alder reactions, the 1,2,4,5-tetrazines (being the most electron-deficient) are the most reactive. Tetrazines will typically undergo [4 + 2] cycloaddition below 100 °C to give the corresponding pyridazines in high yield, with concomitant elimination of molecular nitrogen. [These pyridazines in turn are capable of a further Diels–Alder reaction to afford benzenoid rings, although high reaction temperatures and/or very reactive dienophiles are required, especially in intermolecular processes (Scheme 1).] We have already shown[1] that some simple 1,2,4,5-tetrazines undergo Diels–Alder reactions at both reactive sites in diethynyl-aromatic compounds and bis(enol trimethylsilyl ethers): bis(1,2,4,5-tetrazines) are thus attractive synthetic targets, since they offer the prospect of irreversible Diels–Alder polymerisation reactions occurring rapidly under mild conditions and in high yield.

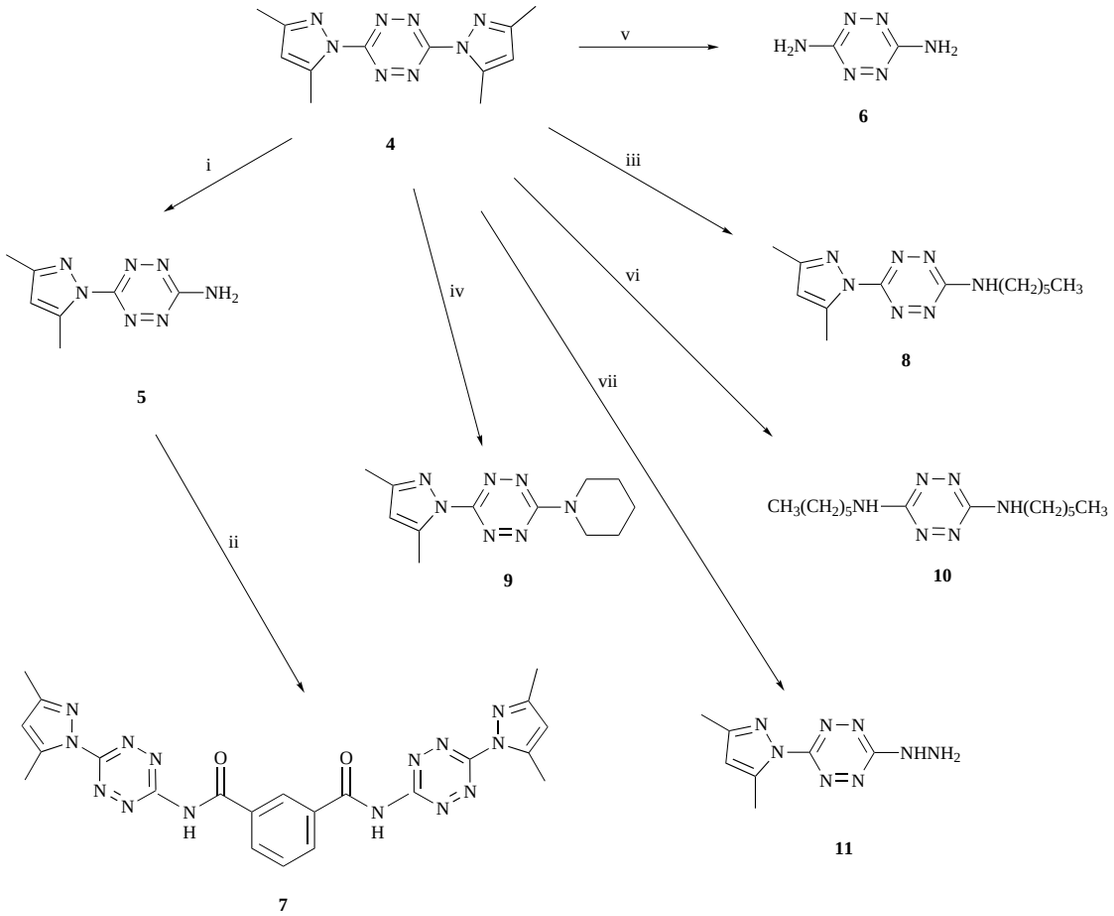
Bis(1,2,4,5-tetrazines) are virtually unknown: indeed, the only well-authenticated example reported in the literature[6] is 6,6′-diphenyl-3,3′-bi-1,2,4,5-tetrazinyl **2**. The structure of this compound, prepared (albeit in low yield) in a linear sequence (Scheme 2) from oxalyl dibenzoylhydrazide **1**, has been con-



Scheme 1



Scheme 2



Scheme 3 *Reagents and conditions:* i, NH_3 (g), PhMe, 20 °C; ii, isophthaloyl dichloride, DMAP, PhCl, 130 °C; iii, hexylamine, PhMe, 20 °C; iv, piperidine, PhMe, 80 °C; v, NH_3 (l), sealed tube, 20 °C; vi, hexylamine (excess), 20 °C; vii, hydrazine hydrate, PhMe, 20 °C

firmed† by X-ray crystallography.[8] Compound **2** exhibits typical [4 + 2] cycloaddition reactions at one or both of the tetrazine rings, according to the proportions of reagents employed.

A synthetic route of this type, involving construction of both heterocyclic moieties in a single step, is unlikely to give bis-tetrazines in good yield, and we have envisaged the coupling of (suitably functionalised) mono-tetrazines to be a more expedient route to such molecules. However, whilst a variety of methods for the preparation of mono-tetrazines exists, there is no general procedure which allows a broad range of substituents to be incorporated. Furthermore, the majority of these procedures rely on a dimerisation step to form the six-membered ring-skeleton and therefore give rise to symmetrically substituted tetrazines;[9] whereas bis-tetrazines, by their very nature, are unsymmetrically substituted. The synthesis of 1,2,4,5-tetrazines where only one of the substituents is capable of reaction (*i.e.* those required for efficient coupling) is generally a more difficult challenge.[10] We now report the results of our initial investigations in this area.

Results and discussion

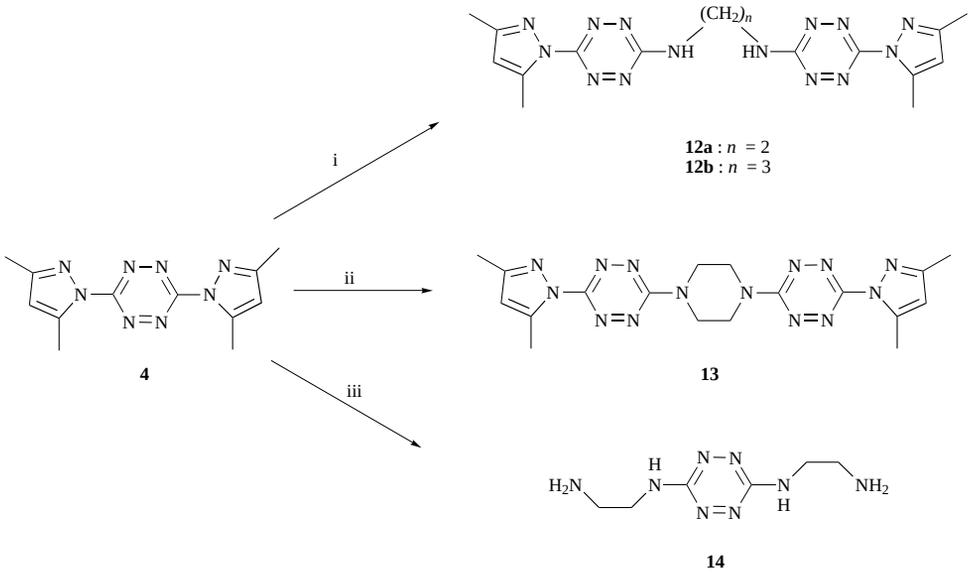
3,6-Bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine **4**, which is simply prepared from triaminoguanidine and acetylacetone with subsequent oxidation of the resulting dihydrotetrazine intermediate,[11] was the starting compound for these studies. The observation[11] that 3-amino-6-(dimethylpyrazol-1-yl)-tetrazine **5** is obtained exclusively and in excellent yield when gaseous ammonia is bubbled through a suspension of compound **4** in toluene at room temperature was very interesting from our perspective, since this unsymmetrically substituted tetrazine **5** bears functionality suitable for further elaboration (Scheme 3).

Preliminary acylation studies, using *N*-benzoylation of **5** as a model, showed that the amino group of **5** was similar in reactivity to that of a 2-aminopyrimidine,[12] and a reaction temperature of 130 °C in the presence of 4-(*N*,*N*-dimethylamino)-pyridine (DMAP: 1.0 equiv.) was necessary for benzoylation to occur. Acylation of **5** with isophthaloyl dichloride (0.5 equiv.) under such conditions led to formation of the corresponding bis-tetrazine **7**, although the purification of this compound proved difficult (it appears as a single streak on TLC and its purity is not improved by reprecipitation from a variety of solvents or by chromatography), and a sample of analytical purity was not obtained. Accordingly, this line of investigation was not pursued further.

Initial experiments revealed that addition of 1 equiv. of amines such as hexylamine (at 20 °C) and piperidine (at 80 °C) to a suspension of compound **4** in toluene also brings about the displacement of one of the dimethylpyrazolyl units. Furthermore, if the amine is used both as solvent and reagent, then both of the dimethylpyrazolyl units may be replaced: elevated temperatures are not essential for the double displacement to occur, as had been implied by previous workers.[11] Indeed, displacement of both groups is also found when **4** is dissolved in liquid ammonia and the mixture allowed to stand at room temperature (in a sealed tube). This affords 1,2,4,5-tetrazine-3,6-diamine **6** in excellent yield, and represents a much more straightforward procedure than any reported to date for the preparation of **6** (Scheme 3).[11,13]

All attempted reactions of **4** with sulfur nucleophiles (thiophenol, thiophenoxide and benzenesulfinate ion) resulted

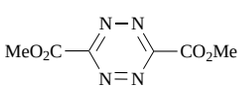
† An earlier report,[7] claiming the synthesis of this compound *via* the thermolysis of the azo(phenyltetrazine) **3**, is open to question. The product is clearly different from **2**, both in physical characteristics and chemical reactivity, and no evidence is presented in the paper even to support the structure **3** for the precursor.



Scheme 4 *Reagents and conditions:* i, $H_2N(CH_2)_nNH_2$ (0.5 equiv.), PhMe, 20 °C; ii, piperazine (0.5 equiv.), PhMe, 80 °C; iii, ethylenediamine, 20 °C

either in decomposition or in no reaction taking place. This was somewhat disappointing, as oxidation of the sulfur atom would have permitted the incorporation of electron-withdrawing substituents, and these might in turn have facilitated 'inverse electron-demand' Diels–Alder reactions.

Extension of the above reactions with amines, involving treatment of a suspension of compound **4** in toluene with the appropriate primary diamine (0.5 equiv.) at room temperature, produces the expected bis(tetrazines) **12a** and **12b** in good yield. When piperazine is used it is necessary to increase the temperature to 80 °C before the bis(tetrazine) **13** can be isolated. Reaction of compound **4** with ethylenediamine (neat) at room temperature, however, leads to the formation almost exclusively of the mono-tetrazine **14**.



15

An alternative strategy which we have also investigated is centred on the coupling of two units of the tetrazinedicarboxylic ester **15**[14] either *via* amide linkages or by transesterification. Reaction of compound **15** with primary amines at room temperature leads to the rapid and vigorous decomposition of the tetrazine ring system (disappearance of the red colour!) with loss of molecular nitrogen. This is presumably the result of nucleophilic attack by the amino group at one of the ring carbons in a similar way to that observed during alkaline or acidic hydrolysis.[15,16] The products of this decomposition process are numerous and complex, and are as yet unidentified. GC–MS analysis of the product mixture from the reaction with hexylamine, however, suggests that one product may be hexyl isocyanate, thus suggesting that the desired nucleophilic attack at the ester carbonyl may at least be one of the primary processes involved. Efforts to achieve the transesterification of **15** using ethylene glycol (0.5 equiv.) have been similarly unsuccessful under all conditions tried, and have resulted only in recovery of starting materials.

X-Ray crystallography

The structures of the bis-tetrazines **12a** and **13**, as well as that of the mono-tetrazine **15** have been determined by single crystal X-ray diffraction: in addition, the structure of 1,2,4,5-tetrazine-3,6-diamine **6** has been redetermined, and this analysis has confirmed in all respects the structure previously reported.[17] Given that there are so few properly authenticated examples of bis(1,2,4,5-tetrazines), an important result of the structure analyses for compounds **12a** and **13** has been the definitive proof of their constitutions.

Only a modest number of structure determinations have been reported for symmetrically disubstituted 1,2,4,5-tetrazines, and it is striking that, with only one exception containing chiral substituents,[18] the molecules all lie across centres of inversion.[17,19–24] Similarly, in compound **15**, the molecules lie across centres of inversion at the centres of the tetrazine rings,

Table 1 Selected molecular dimensions (d/Å, angle/°)[a]

Compound **12a**			
Bond length			
C1–N1	1.363(4)	N1–N2	1.312(3)
C2–N2	1.337(4)	N3–N4	1.326(3)
C2–N3	1.322(4)	C1–N7	1.333(4)
C1–N4	1.351(4)	C2–N5	1.414(4)
N7–C8	1.454(4)	C8–C8^{i}	1.527(6)
Angle			
C8–N7–C1–N1	−178.1(3)	N2–C2–N5–C5	−130.4(4)
Compound **13**			
Bond length			
C1–N1	1.359(4)	N1–N2	1.316(3)
C2–N2	1.337(4)	N3–N4	1.336(3)
C2–N3	1.324(4)	C1–N7	1.335(4)
C1–N4	1.360(4)	C2–N5	1.409(4)
N7–C8	1.456(4)	C8–C9	1.507(6)
N7–C9^{i}	1.460(4)		
Angle			
C8–N7–C1–N1	−178.1(3)	N2–C2–N5–C5	−121.4(4)
C8–N7–C1–N4	4.8(5)	N2–C2–N5–N6	48.8(4)
C9^{i}–N7–C1–N1	9.7(4)	C9^{i}–N7–C1–N4	−167.5(3)
Compound **15**			
Bond length			
C1–N1	1.343(5)	N1–N2^{ii}	1.327(5)
C1–N2	1.328(5)	C1–C2	1.513(6)
Angle			
O2–C2–C1–N1	13.5(7)	O1–C2–C1–N1	−165.2(4)
O2–C2–C1–N2	−164.7(5)	O1–C2–C1–N2	16.5(6)
C3–O1–C2–C1	175.9(4)		

[a] Symmetry codes: (i) $1 - x, -y, 1 - z$; (ii) $1 - x, -y, -z$.

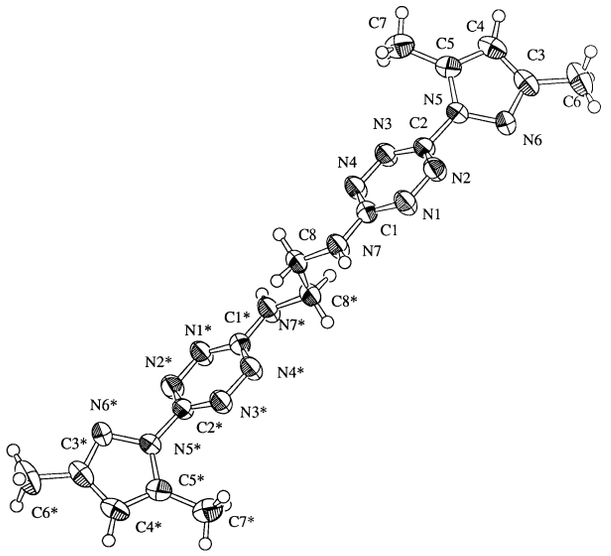


Fig. 1 Perspective view of a molecule of compound **12a**, showing the atom-numbering scheme; atoms labelled with an asterisk occupy the symmetry positions ($1 - x$, $-y$, $1 - z$)

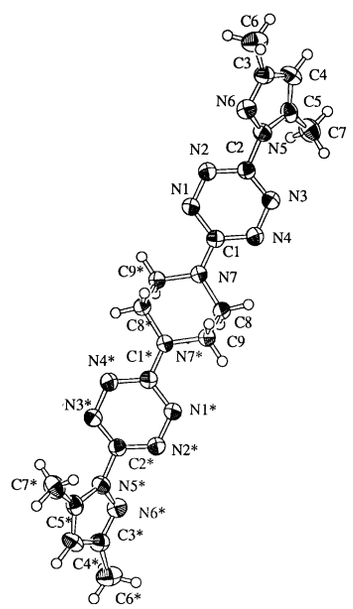


Fig. 2 Perspective view of a molecule of compound **13**, showing the atom-numbering scheme; atoms labelled with an asterisk occupy the symmetry positions ($1 - x$, $-y$, $1 - z$)

and in the bis(tetrazines) **12a** and **13** the molecules again lie across centres of inversion, in these examples at the centres on the diamino spacer units.

Molecular dimensions and conformations‡

In each of **12a, 13** and **15** (Figs. 1–3), the C–N and N–N bond lengths (Table 1) are consistent with extensive electronic delocalisation: in **15** and in other symmetrically disubstituted tetrazines,[17,19–24] this delocalisation is a necessary inference from the centrosymmetry of the tetrazine ring. Similarly, the lengths of the exocyclic bonds C1–N7 in both **12a** and **13** are significantly less than the lower quartile value, 1.363 Å, determined for C(aryl)–NR_2 bonds involving planar nitrogen atoms, using crystallographic data available in 1987;[25] and in compound **13** it is noteworthy that the piperazine nitrogen atoms are essentially planar [sum of bond angles, 359.6(4)°]. These observations are wholly consistent with the view[17] that the 1,2,4,5-tetrazine unit

‡ In this and the following section, the atom numbering is non-systematic, and is as shown in Figs. 1–3.

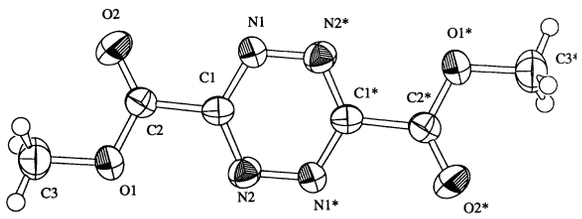


Fig. 3 Perspective view of a molecule of compound **15**, showing the atom-numbering scheme; atoms labelled with an asterisk occupy the symmetry positions ($1 - x$, $-y$, $-z$)

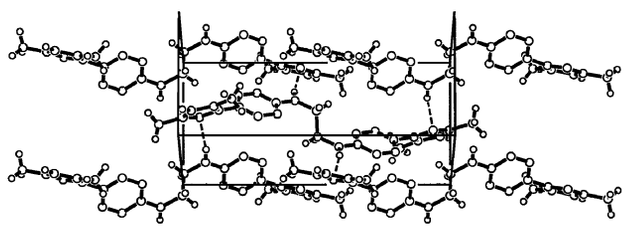


Fig. 4 Perspective view of part of the crystal structure of **12a**, showing the N–H···N hydrogen bonds: the origin is at the top left, with the [100] and [001] directions horizontal and vertical, respectively

behaves as a strong π-acceptor, and that substituents of types OR and NR_2 act as strong π-electron donors towards this ring.

In both **12a** and **13** it is noteworthy that the tetrazine ring is essentially coplanar with the CNRR′ fragment of the central spacer unit, as judged by the C–N–C–N torsional angles about the C1–N7 bond (Table 1). In contrast, the 3,5-dimethylpyrazolyl rings are twisted away from the tetrazine plane by some 50°: at the same time, the bonds C2–N5 in both **12a** and **13** are long, much longer in fact than the upper quartile value, 1.382 Å, for C(aryl)–NR_2 bonds.[25] Thus there is no evidence for any conjugation between the 6π tetrazine ring and the 6π pyrazolyl units, in contrast to the strong interactions involving the aliphatic amino substituents.

In the mono-tetrazine compound **15**, the molecules are almost planar. The exocyclic C–C bond length is well above the upper quartile value,[25] 1.494 Å, for such bonds in esters of aryl carboxylic acids, presumably reflecting the proximity of two electron-acceptor fragments, although the C–O bond lengths are all typical of those found in esters.

Stacking modes and hydrogen-bonding motifs

In each of **12a**, **13** and **15**, the molecular axes are aligned roughly parallel, along a single direction: this phenomenon has also been observed in 6,6′-diphenyl-3,3′-bi(1,2,4,5-tetrazinyl),[8] where the intermolecular interactions include both π-facial stacking and edge-to-face packing of the phenyl rings as well as C–H···N hydrogen bonding. In 6-phenyl-1,2,4,5-tetrazine-3-carbaldehyde benzoylhydrazone, which contains similarly elongated molecules, a herringbone type of stacking is found.[8] The molecular conformations of **12a** and **13** are too remote from coplanarity for any significant π-stacking or edge-to-face stacking to be feasible, and in compound **13** there are no intermolecular distances significantly shorter than the sum of the van der Waals' radii. Although the molecules of **13** contain a large number of potential hydrogen-bond acceptors, evidently none of the C–H bonds is a sufficiently good donor to generate any C–H···N hydrogen bonds. In compound **12a**, however, there is an extensive hydrogen-bonded network, generated by the action of the symmetry elements in propagating a single type of hydrogen bond throughout the structure.

Nitrogen atom N7 (Fig. 1) in the asymmetric unit of **12a** at (x, y, z) acts as hydrogen-bond donor to the pyrazolyl nitrogen atom N6 in the unit at ($1.5 - x$, $-y$, $0.5 + z$), in a molecule related to the first by the action of the 2_1 screw axis at (0.75, 0, z): the N7 atom in this second molecule in turn acts as

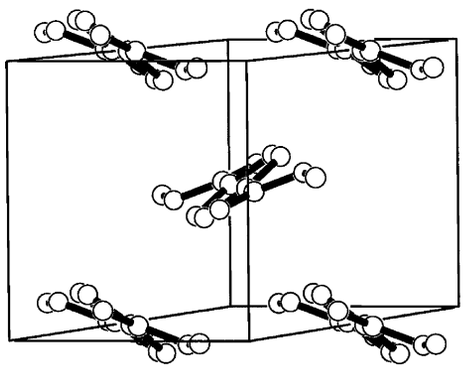


Fig. 5 Section of the crystal structure of **15**, showing molecules centred at $z = 0.5$: hydrogen atoms are omitted for the sake of clarity. The origin is at the top left, with the [001] direction vertical; the direction of view is approximately along [1 − 10].

hydrogen-bond donor to the N6 atom in the unit at (x, y, 1 + z) (Fig. 4). The N · · · N distance is 3.025(4) Å. Repetition of this C(8) motif[26,27] generates a spiral of hydrogen-bonded molecules parallel to the [001] direction. At the same time, the symmetry-related atom N7* of the initial molecule centred at (0.5, 0, 0.5) similarly acts as hydrogen-bond donor to the atom N6 in a unit at (−0.5 + x, y, 0.5 − z), and repetition of this interaction generates a second spiral of hydrogen-bonded molecules around the 2_1 screw axis at (0.25, 0, z), of opposite hand to the first. Units in these two spirals are, of course, connected by the central N7–C8–C8*–N7* fragments of the molecules and the overall result is the generation of a continuous two-dimensional network of molecules, with the individual nets lying parallel to (010) and built up from a series of $R_4^4(38)$ rings.[26,27]

The molecules of compound **15** are all aligned along the long axis of the unit cell, and their centres occupy the Wyckoff *b* sites; thus there are almost square arrays of molecules centred at $z = 0$, 0.5, 1.0 and so on. Each of these arrays exhibits a herringbone type of stacking (Fig. 5), but with no significant intermolecular contacts closer than the sum of van der Waals' radii.

Experimental

Melting points were determined on an Electrothermal 9100 apparatus and are uncorrected; IR spectra, recorded on a Perkin-Elmer 1710 FT spectrophotometer, are those of Nujol mulls; UV–VIS spectra, recorded on a Philips PU-8730 spectrophotometer, are those of solutions in acetonitrile. ^{1}H and ^{13}C NMR spectra are those obtained at either 300 or 200 MHz and 75.1 or 50.3 MHz, respectively, for solutions in $CDCl_3$ unless indicated otherwise; chemical shifts are expressed relative to $SiMe_4$ ($\delta_H = \delta_C = 0$) and coupling constants (J) in Hz. Mass spectra were obtained using a VG Autospec HR instrument, under electron impact unless indicated otherwise. Dichloromethane was dried by distillation from calcium hydride, and toluene was dried by storage over sodium wire; other commercially available starting materials were used as received. Light petroleum refers to the fraction of bp 40–60 °C unless indicated otherwise.

3,6-Bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine, 4

Dihydro-3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine was prepared from triaminoguanidine (35.15 g, 0.25 mol) and acetylacetone (50.06 g, 0.5 mol) according to the method of Coburn *et al.*[11] Yield 29.38 g (86%), mp 150.5–152 °C (lit.,[11] 150 °C). The crude material was used directly in the next stage.

A stock solution of nitrogen dioxide (from a lecture bottle) in dichloromethane was prepared with a concentration of *ca.* 10 mmol cm^{-3}. This solution (32.5 cm^3, 325 mmol) was added dropwise, over 5 min, to a rapidly stirred solution of the dihydrotetrazine (29.30 g, 108 mmol) in dichloromethane (500 cm^3). Stirring was continued for 3 h at room temp., then the solvent and excess nitrogen dioxide were removed by evaporation at reduced pressure. The red solid residue was re-dissolved in dichloromethane (400 cm^3) and this solution was washed with saturated aqueous sodium hydrogen carbonate (200 cm^3) then water (200 cm^3) before being dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave a bright-red solid which was recrystallised from ethyl acetate to afford pure **4** (22.10 g, 82 mmol, 76%), mp 225–226 °C (lit.,[11] 226 °C).

3-Amino-6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine, 5

This was prepared from the tetrazine **4** (10.00 g, 37 mmmol) according to the method of Coburn *et al.*[11] Yield 6.79 g (96%); mp 217–219 °C (lit.,[11] 218 °C). δ_H[300 MHz, $(CD_3)_2SO$ at 30 °C] 2.23 and 2.40 (each 3H, s, 2 × Me), 6.18 (1H, s, 4′-H), 8.19–8.28 (2H, br s, NH_2); δ_C[75.4 MHz, $(CD_3)_2SO$] 12.3 and 13.5 (2 × Me), 108.5 (C-4′), 141.5 (C-5′), 150.1 (C-3′), 157.2 (C-6), 163.2 (C-3); *m/z* 191 ($M^{+\bullet}$, 80%), 121 (100), 106 (24) and 80 (17); λ_{max}/nm 264 (ε 26 700), 386 (1900), 520 (640).

Aroylation of compound 5

With benzoyl chloride. A mixture of the aminotetrazine **5** (0.764 g, 4 mmol), benzoyl chloride (0.562 g, 4 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP; 0.480 g, 4 mmol) in chlorobenzene (10 cm^3) was heated under reflux for 5 h, then cooled; the solvent was evaporated under reduced pressure and the red solid residue dissolved in dichloromethane (30 cm^3). This solution was washed with dilute brine§ (2 × 30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to leave a red solid foam (0.86 g), the spectral data of which were consistent with 3-benzamido-6-(3,5-dimethylpyrazol-1yl)-1,2,4,5-tetrazine (yield, 73%). ν_{max}/cm^{-1} 3380 (N–H str.), 1700 (C=O), 1645 (N–H bend) and 1599; δ_H 2.30 and 2.66 (each, 3H, s, 2 × Me), 6.15 (1H, s, 4′-H), 7.40–7.62 (3H, m, Ar-H) and 8.01–8.12 (2H, m, Ar-H), 9.86–9.98 (1H, br s, NH); *m/z* 295 ($M^{+\bullet}$, 18%), 121 (77), 105 (100), 95 (12).

With isophthaloyl dichloride. A procedure similar to the above was followed, using the tetrazine **5** (1.91 g, 10 mmol), isophthaloyl dichloride (1.02 g, 5 mmol) and DMAP (1.22 g, 10 mmol) in chlorobenzene (25 cm^3). Double volumes of dichloromethane and dilute brine were used during the work-up, and the crude product was purified by dissolution in the minimum volume of dichloromethane and reprecipitation by dropwise addition to diethyl ether. This gave a pink powder which according to the spectral data was predominantly 3,3′-(isophthaldiamido)bis[6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine] **7**; however all attempts at recrystallisation or chromatography failed to effect purification of this material. ν_{max}/cm^{-1} 3385 (N–H str.), 1702 (C=O), 1648 (N–H bend) and 1601; δ_H 2.11 and 2.48 (each 6H, s, 4 × Me), 5.98 (2H, s, 2 × 4′-H), 7.45–7.56 (1H, t, *J* 9, 5-H), 8.14–8.28 (4H, d, *J* 9, 4,6-H; also br s, 2 × NH), 9.02–9.10 (1H, br t, 2-H); δ_C 13.5 and 14.4 (4 × Me), 111.4 (pyrazole C-4), 127.9 (Ar CH), 129.4 (Ar CH), 133.0 (2 × Ar CH), 133.2 (2 × Ar quat.), 143.7 (2 × pyrazole C-5), 153.9 (2 × pyrazole C-3), 158.4 (tetrazine C-6), 159.9 (tetrazine C-3) and 164.6 (C=O); *m/z* (FAB) 513 (MH^+, 100%) (Found: *m/z* 513.1961. $C_{22}H_{21}N_{14}O_2$ requires *m/z* 513.1972).

3-(3,5-Dimethylpyrazol-1-yl)-6-(hexylamino)-1,2,4,5-tetrazine, 8

Hexylamine (0.202 g, 2 mmol) was added to a vigorously stirred slurry of the tetrazine **4** (0.54 g, 2 mmol) in dry toluene (10 cm^3). The resulting suspension was stirred at room temp. for 4 h and the solvent then removed under reduced pressure to leave a thick, red syrup. This was dissolved in dichloromethane (30 cm^3) and the solution washed with water (2 × 20 cm^3), dried ($MgSO_4$) and concentrated (reduced pressure). The remaining

§ A saturated solution diluted with an equal volume of water.

3,5-dimethylpyrazole was separated by Kugelrohr distillation (bp 110 °C at 15 mmHg) to leave a red tar, the NMR and mass spectra of which are consistent with its formulation as **8**. δ_H 0.86 (3H, t, *J* 7, Me of C_6H_{13}), 1.29–1.43 (6H, m, 3 × CH_2), 1.62–1.72 (2H, m, CH_2), 2.32 and 2.52 (each 3H, s, 2 × Me), 3.54–3.63 (2H, m, C*H*$_2$NH), 6.07 (1H, s, 4′-H), 6.16 (1H, bs, NH); δ_C 13.2, 13.5 and 13.8 (3 × Me), 22.3, 26.3, 28.8 and 31.2 (4 × CH_2), 41.5 ($NHCH_2$), 109.4 (C-4′), 141.7 (C-5′), 151.8 (C-3′), 157.4 (C-3), 161.2 (C-6); *m/z* 275 ($M^{+\bullet}$, 14%), 121 (15), 95 (100), *etc*.

3-(3,5-Dimethylpyrazol-1-yl)-6-piperidino-1,2,4,5-tetrazine, 9

Piperidine (0.16 g, 1.8 mmol) was added to a stirred slurry of the tetrazine **4** (0.50 g, 1.8 mmol) in dry toluene (15 cm^3) and the mixture was heated under reflux for 1 h then allowed to cool. The solvent was evaporated under reduced pressure to leave a thick red syrup which was dissolved in diethyl ether (40 cm^3). The solution was washed with water (4 × 25 cm^3), dried ($MgSO_4$) and concentrated (reduced pressure) to give compound **9** as a crimson red solid (0.36 g, 76%), mp 108–111 °C (Found: C, 55.5; H, 6.6; N, 37.6. $C_{12}H_{17}N_7$ requires C, 55.6; H, 6.6; N, 37.8%). δ_H 1.62–1.80 (6H, m, 2 × β- and γ-CH_2 of piperidine), 2.33 and 2.52 (each 3H, s, 2 × Me), 3.94–4.02 (4H, m, 2 × α-CH_2 of piperidine), 6.09 (1H, s, 4′-H); δ_C 13.8 and 14.2 (2 × Me), 24.9 (2 × γ-CH_2), 25.9 (2 × β-CH_2), 45.2 (2 × α-CH_2), 109.8 (C-4′), 142.2 (C-5′), 152.3 (C-3′), 158.0 (C-3), 161.6 (C-6); *m/z* 259 ($M^{+\bullet}$, 22%), 244 (3), 121 (7), 110 (43), 96 (100), 95 (87) and 84 (24).

3,6-Bis(hexylamino)-1,2,4,5-tetrazine 10

The tetrazine **4** (0.300 g, 1.1 mmol) was added, in a single portion, to hexylamine (3 cm^3) (slight exotherm!) and stirring was continued at room temp. for 3 h, during which time a red solid crystallised. The slurry was diluted with toluene (10 cm^3) and the red crystals filtered off, then washed sequentially with toluene (3 cm^3) and light petroleum (10 cm^3) to leave pure **10** (0.27 g, 87%), mp 138 °C (Found: C, 60.0; H, 10.0; N, 29.6. $C_{14}H_{24}N_8$ requires C, 60.0; H, 10.1; N, 29.95%). δ_H 0.90 (6H, t, *J* 8.1, 2 × Me), 1.26–1.45 (12H, m, 6 × CH_2), 1.60–1.72 (4H, m, 2 × CH_2), 3.46 (4H, m, 2 × NHC*H*$_2$), 5.06–5.15 (2H, br t, 2 × NH); δ_C 13.9 (Me), 22.5, 26.3, 29.3 and 31.4 (8 × CH_2), 41.7 ($NHCH_2$), 160.5 (C-3 and 6); *m/z* 280 ($M^{+\bullet}$, 100%), 127 (88), 85 (29), *etc.*

3-Hydrazino-6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine 11

Hydrazine monohydrate (98%; 0.19 g, 3.7 mmol) was added to a rapidly stirred slurry of the tetrazine **4** (1.00 g, 3.7 mmol) in toluene (30 cm^3). The red suspension was stirred at room temp. for 3 h (during which time it became orange–red), then filtered off, washed sequentially with toluene (2 × 10 cm^3) and diethyl ether (2 × 15 cm^3) prior to being dried *in vacuo*. This gave **11** as an orange–red solid (0.66 g, 86%), mp 146–147 °C (from ethyl acetate) (Found: C, 40.95; H, 4.7; N, 54.3. $C_7H_{10}N_8$ requires C, 40.8; H, 4.9; N, 54.3%). δ_H 2.37 and 2.58 (each 3H, s, 2 × Me), 3.60–4.60 (3H, br s, $NHNH_2$), 6.13 (1H, s, 4′-H); δ_C 13.5 and 13.6 (2 × Me), 110.0 (C-4′), 142.2 (C-5′), 152.5 (C-3′), 158.3 (C-6), 163.0 (C-3); *m/z* (ESI)¶ 229 (M + Na^+, 31%), 207 (MH^+, 100).

3,6-Bis-(2-aminoethylamino)-1,2,4,5-tetrazine 14

The tetrazine **4** (0.300 g, 1.1 mmol) was added, as a single portion, to ethylenediamine (3.5 cm^3) (slight exotherm!) and the resulting solution stirred at room temp. for 4 h. The excess of diamine was evaporated under reduced pressure until a solid was seen to precipitate out. Toluene (5 cm^3) was added and the precipitate collected by filtration, washed with light petroleum (bp 60–80 °C; 10 cm^3) and dried at 40 °C *in vacuo* to give **13** as a red powder (0.201 g, 92%), mp 133–135 °C. The compound could not be obtained in analytical purity, even after repeated recrystallisation from ethyl acetate, possibly because of contamination by small amounts of polymeric material; however, the spectroscopic properties are in accord with the proposed structure. $\delta_H(CD_3OD)$ 2.91 and 3.53 (each 4H, t, *J* 6, 4 × CH_2); $\delta_C[(CD_3)_2SO]$ 41.1 and 44.7 (4 × CH_2), 160.8 (C-3 and 6); *m/z* 198 ($M^{+\bullet}$, 100%), 169 (96), 111 (12), 85 (16).

1,2,4,5-Tetrazine-3,6-diamine, 6

The tetrazine **4** (4.00 g, 14.8 mmol) was placed inside a glass pressure vessel with a tap closure and the system cooled to −20 °C. Liquid ammonia (30 cm^3) was introduced, the tap closed, and the mixture swirled to effect complete dissolution. The solution was left to stand at room temp. for 18 h, then cooled once again to −20 °C before the tap was opened (care!). The excess of ammonia was allowed to evaporate and the residual crimson–red solid triturated with diethyl ether (30 cm^3), filtered off, washed with diethyl ether (2 × 30 cm^3) and sucked dry. Sublimation (190 °C at 0.4 mmHg) gave pure **6** as a bright-red powder (1.98 g, 97%) which decomposes above 350 °C but does not melt below 400 °C (lit.,[15] subl. 200–240 °C; mp >300 °C). $\delta_H[(CD_3)_2SO]$ 6.76 (4H, br s, 2 × NH_2); $\delta_C[(CD_3)_2SO]$ 162.0; *m/z* 112 ($M^{+\bullet}$, 72%), 43 (100) and 42 (78). For confirmation of structure, see the X-ray crystallography section above.

***N*,*N*′-Bis[6-(3,5-Dimethylpyrazol-1-yl)-1,2,4,5-tetrazin-3-yl]-ethane-1,2-diamine, 12a**

The tetrazine **4** (2.70 g, 10 mmol) was added in a single portion (slight exotherm observed) to a stirred solution of ethylenediamine (0.30 g, 5 mmol) in dry toluene (50 cm^3). The slurry was stirred for 18 h at room temp., and the orange–red solid was filtered off, washed sequentially with dry toluene (30 cm^3) and diethyl ether (2 × 30 cm^3), sucked dry, and recrystallised from acetic acid–propan-2-ol (1:1) to give pure **12a** (1.98 g, 97%) as bright-red blocks, mp 222–224 °C (decomp.) (Found: C, 47.35; H, 5.0; N, 47.9. $C_{16}H_{20}N_{14}$ requires C, 47.1; H, 4.9; N, 48.0%). λ_{max}/nm 273 (ε 48 300), 404 (2800), 519 (1100); $\delta_H[(CD_3)_2SO]$ 2.25 and 2.41 (each 6H, s, 4 × Me), 3.80 (4H, s, 2 × CH_2), 6.21 (2H, s, 2 × H-4′), 8.80–9.10 (2H, br s, 2 × NH); δ_C 12.5 and 13.5 (4 × Me), 39.4 (2 × CH_2), 109.8 (2 × C-4′), 141.6 (2 × C-5′), 150.3 (2 × C-3′), 157.1 (2 × C-6), 161.7 (2 × C-3); *m/z* (CI) 409 (MH^+, 100%), 408 (10).

***N*,*N*′-Bis[6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazin-3-yl]-propane-1,3-diamine, 12b**

This compound was prepared from the tetrazine **4** (2.47 g, 9.1 mmol) and 1,3-diaminopropane (0.34 g, 4.55 mmol) using the above method. Recrystallisation from acetic acid–propan-2-ol (1:1) gave pure **12b** (1.18 g, 61%) as fine, red needles, mp 203–205 °C (decomp.) (Found: C, 48.4; H, 5.3; N, 46.3. $C_{17}H_{22}N_{14}$ requires C, 48.3; H, 5.25; N, 46.4%). λ_{max}/nm 272 (ε 48 600), 403 (2400), 520 (1100); δ_H 2.11–2.28 (2H, m, central CH_2), 2.31 and 2.52 (each 6H, s, 4 × Me), 3.73–3.87 (4H, m, 2 × NHC*H*$_2$), 6.08 (2H, s, 2 × H-4′), 7.29–7.40 (2H, br t, 2 × NH); δ_C 13.4 and 13.6 (4 × Me), 28.2 (central CH_2), 38.8 (2 × $NHCH_2$), 109.7 (2 × C-4′), 141.9 (C-5′), 152.2 (C-3′), 157.5 (2 × C-6), 161.4 (2 × C-3); *m/z* 422 ($M^{+\bullet}$, 44%), 232 (19), 121 (100), 106 (29), 95 (30), *etc*.

***N*,*N*′-Bis[6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazin-3-yl]-piperazine, 13**

A suspension of the tetrazine **4** (2.70 g, 10 mmol) and piperazine (0.41 g, 5 mmol) in dry toluene (50 cm^3) was heated to 80 °C for 3 h, then allowed to cool. The orange–red product was collected by filtration, then washed sequentially with dry toluene (20 cm^3) and diethyl ether (2 × 20 cm^3), sucked dry, and recrystallised from ethanol–acetic acid (2:1) giving pure **13** (1.78 g, 82%) as fine, red needles, mp 271–273 °C (decomp.) (Found: C, 49.8; H, 5.1; N, 45.2. $C_{18}H_{22}N_{14}$ requires C, 49.8; H,

¶ This was obtained on a VG Platform using a methanol–water (9:1) solvent system and a cone voltage of 3.85 kV.

Table 2 Summary of crystal data, data collection and refinement details

	12a	**13**	**15**
(*a*) Crystal data			
Empirical formula	$C_{16}H_{20}N_{14}$	$C_{18}H_{22}N_{14}$	$C_6H_6N_4O_4$
Molar mass	408.43	434.47	198.14
Colour, habit	Red, plate	Red, needle	Red, plate
Crystal size, mm	0.40 × 0.30 × 0.05	0.50 × 0.20 × 0.15	0.40 × 0.35 × 0.05
Crystal system	Orthorhombic	Monoclinic	Orthorhombic
a/Å	15.747(5)	7.273(3)	21.233(6)
b/Å	16.912(3)	13.218(5)	6.602(7)
c/Å	7.218(4)	10.793(4)	5.837(4)
α(°)	90	90	90
β(°)	90	100.62(4)	90
γ(°)	90	90	90
V/Å^3	1922(1)	1019.8(7)	818(1)
Space group	*Pbca*	$P2_1/a$	*Pbca*
Z	4	2	4
F(000)	856	456	408
D_{calc}/g cm^{-3}	1.411	1.415	1.608
μ/mm^{-1}	0.092	0.091	0.137
(*b*) Data acquisition			
Unit-cell reflcns (2θ-range°)	20 (7.1–12.0)	25 (23.4–24.7)	25 (23.3–24.9)
Max. 2θ (°) for reflcns	50.0	50.0	50.0
hkl range of reflcns	0,18; 0,20; 0,8	0,8; 0,15; −12,12	0,25; 0,7; −6,4
Variation in 3 standard reflcns	<0.2%	<0.2%	<1.0%
Reflcns measured	1984	2029	1037
Unique reflcns	1984	1878	889
R_{int}	—	0.031	0.095
Reflcns with $I > 3\sigma(I)$	900	1245	506
(*c*) Structure solution and refinement			
Solution method	Direct	Direct	Direct
No. of variables in LS	137	146	65
Abs. corr. transmission Factors: max., min.	—	1.000, 0.765	—
Sec. extinction. coeff (×10^6)	0.659	1.479	1.823
R, R_w	0.041, 0.030	0.047, 0.042	0.061, 0.050
Density range in final Δ-map/e Å^{-3}	−0.14, 0.17	−0.28, 0.24	−0.27, 0.22
Final shift/error ratio	0.000	0.000	0.005

5.1; N,45.1%). λ_{max}/nm 285 (ε 56 500), 418 (2200), 524 (1000); δ_H 2.37 and 2.60 (each 6H, s, 4 × Me), 4.26 (8H, s, 4 × CH_2), 6.13 (2H, s, 2 × H-4′); δ_C 13.7 and 13.8 (4 × Me), 43.2 (4 × CH_2), 110.0 (2 × C-4′), 142.1 (2 × C-5′), 152.4 (2 × C-3′), 157.2 (2 × C-6), 160.6 (2 × C-3); *m/z* (CI) 435 (MH^+, 100%), 434 (22).

Reactions of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate 15

The diester **15** was obtained, essentially by the published procedure,[14] as described in Part 3.[1]

Attempted amide formation. Treatment of the diester **15** with 1 or 2 equiv. of hexylamine or 1 equiv. of ethylenediamine led to rapid decomposition of the tetrazine ring, as evidenced by vigorous evolution of gas and disappearance of the red colour. GC–MS showed a complex product mixture (at least nine compounds), one of which corresponded to hexyl isocyanate [*m/z* 127 ($M^{+\bullet}$, 3%), 112 (18), 99 (100), 84 (27), 56 (58), *etc*.].

Attempted transesterification. Attempted reaction of the diester **15** with ethylene glycol under a variety of reaction conditions gave only unchanged starting materials.

X-Ray structure determination

Crystals of compounds **12a**, **13** and **15** suitable for single-crystal X-ray diffraction were grown from solutions in acetic acid–propan-2-ol (1:1), ethanol–acetic acid (2:1), and ethyl acetate, respectively. Table 2 summarises the details of the crystal data, the data collection, and the refinements. The systematic absences allowed unique assignment of all the space groups: $P2_1/a$ for compound **13**, and *Pbca* for compounds **12a** and **15**. All intensity data were recorded at 293(1) K with a Rigaku AFC7S diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.7107 Å). The structures were solved by direct methods using SIR92[28] and refined by full-matrix least-squares on *F*, using the TEXSAN system.[29] An absorption correction was applied for compound **13** using the Ψ-scan method; no correction was necessary for either **12a** or **15**. All hydrogen atoms were located from difference maps, and were included in the refinements as riding atoms in idealised positions with isotropic displacement parameters; all non-hydrogen atoms were refined anisotropically. The figures were prepared using ORTEPII;[30] selected geometric parameters are given in Table 1.

Refined atomic coordinates, displacement parameters and full lists of bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre.‖

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‖ For details of the CCDC deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 188/67.

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