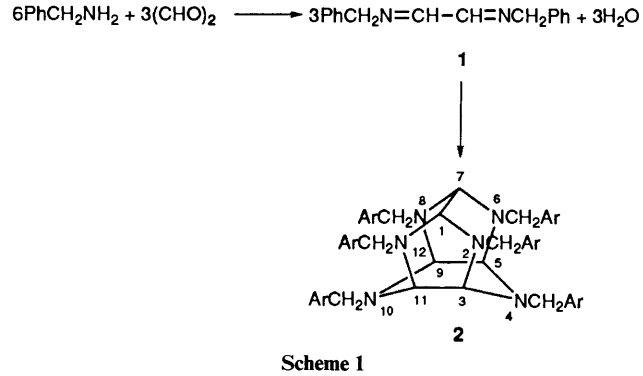
Condensation Products from the Reactions of Glyoxal with 2-Substituted Benzylamines. The Formation and Crystal Structures of 2,2'-Bi(1,2,3,4-tetrahydroquinazoline), and 2,4,6,8,10,12-hexakis(2-methylbenzyl)-2,4,6,8,10,12-hexaazaisowurtzitane

Andrei Batsanov,[a] Jason C. Cole,[a] Michael R. Crampton,*[a] Javid Hamid,[a] Judith A. K. Howard[a] and Ross Millar[b]
[a] *Chemistry Department, Durham University, Durham, UK DH1 3LE*
[b] *DRA, Fort Halstead, Sevenoaks, Kent, UK TN14 7BP*

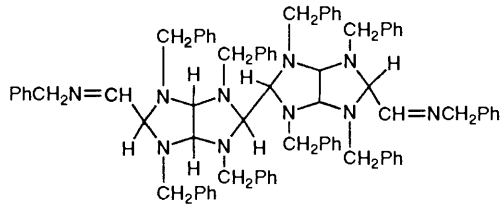
Condensation of glyoxal with 2-aminobenzylamine produces the novel compound 2,2'-bi(1,2,3,4-tetrahydroquinazoline), **6**, the structure of which has been confirmed by X-ray crystallography. However, reaction of glyoxal with other 2-substituted benzylamines yields hexabenzylhexaazaisowurtzitanes. The crystal structure of the derivative prepared from 2-methylbenzylamine has been determined and is compared with that of the derivative from 4-chlorobenzylamine.

It has recently been shown[1,2] that the reaction of glyoxal with benzylamine may produce the interesting cage compound **2** in high yield. There is evidence that **2**, which may be described as a hexabenzylhexaazaisowurtzitane (HBIW), is formed by trimerisation of a diimine intermediate, **1**, as shown in Scheme 1. Small



Scheme 1

quantities, *ca.* 5%, of a bi(2,4,6,8-tetraazabicyclo[3.3.0]octane), **3**, have also been isolated from this reaction.[3] If the reaction between glyoxal and primary amines is carried out in the presence of formaldehyde the major products[4] are 2,4,6,8-tetrasubstituted 2,4,6,8-tetraazabicyclo[3.3.0]octanes, **4**. We now report that reaction of 2-aminobenzylamine with glyoxal produces 2,2'-bi(1,2,3,4-tetrahydroquinazoline), **6**, in high yield.



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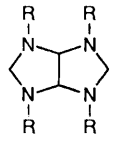

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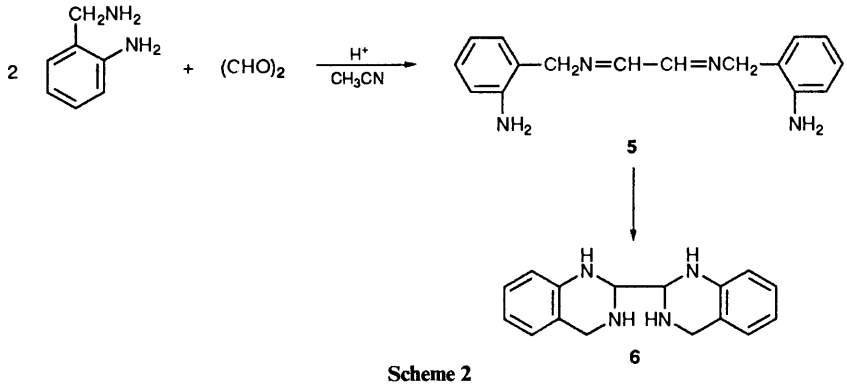
This is presumably formed by intramolecular cyclisation of **5**, the initially formed diimine, as shown in Scheme 2. Evidence for this comes from the observation that dissolution in acetonitrile of the product of the attempted preparation of **5** yielded the cyclised product **6**.

The bond connectivities in **6** are confirmed by our crystal-structure analysis as shown in Fig. 1. The molecule is not quite symmetrical in that there is very nearly, but not quite, a centre of inversion between C(2) and C(21) of the two tetrahydroquinazoline moieties. The nitrogen-containing rings adopt a twist–chair conformation, almost certainly resultant upon the rigidity of the adjacent fused aromatic rings. The C–N and C–C bond lengths are calculated to fall within the normal literature ranges. As indicated in Fig. 2 the molecules stack parallel to the *c*-axis in imine hydrogen-bonded dimers. Hydrogen bonding is indicated by the N–N separations, although the hydrogen atoms were not located in the density maps. Fig. 2 also indicates channel cavities lying parallel to the *c*-axis which are occupied by disordered solvent molecules.

The ^{1}H NMR spectrum of **6**, Fig. 3, shows that in solution in dimethyl sulfoxide (DMSO) the two halves of the molecule become equivalent. An AB system, J = 17 Hz, due to geminal coupling of the methylene hydrogens is observed at δ 3.81 and 3.91. The methine hydrogens give a single band at δ 4.00, and the aromatic hydrogens a multiplet at δ 6.49–6.91. The amino protons on the nitrogen atoms adjacent to the aromatic rings absorb at δ 5.58, this band collapsing on the addition of deuterium oxide. The singlet at δ 3.31 is attributed to the two aliphatic-type amino protons, possibly exchanging rapidly with traces of water in the solvent. The ^{13}C proton-decoupled NMR spectrum of **6** in [$^2H_6$]DMSO showed bands at δ 47.23 (methylene), δ 70.01 (methine) and δ 116–146 (aromatic carbons).

Acetylation, which was achieved by heating **6** with acetic anhydride, produced the tetraacetyl derivative **7**. The ^{1}H NMR spectrum in [^{2}H]chloroform indicates the presence of more than one isomer due to restricted rotation about *N*-acetyl bonds.[5] In the major isomer, the methylene hydrogens appear as an AB system, J = 18 Hz, at δ 4.46 and 5.40. The signal due to methine hydrogens is shifted downfield relative to **6** due to deshielding by the adjacent *N*-acetyl groups and appears as a singlet at δ 6.80. The aromatic hydrogens give a multiplet between δ 7.15 and 7.38, and the acetyl groups give singlets at δ 2.28 and 1.45. The spectrum of the minor isomer(s) shows two AB systems due to methylene protons at δ 4.75 and 4.94 and δ



Scheme 2

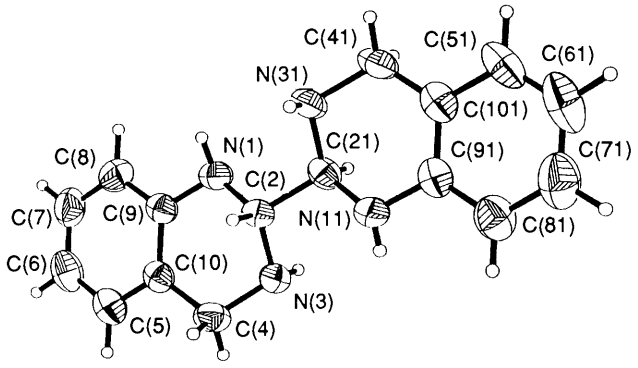


Fig. 1 X-ray crystal structure of 2,2′-bi(1,2,3,4-tetrahydroquinazoline) **6**

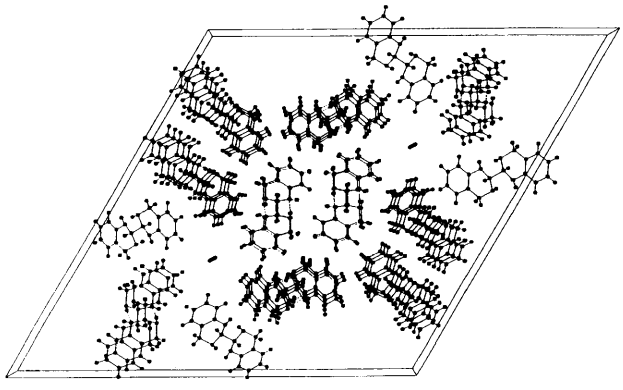


Fig. 2 View parallel to the *c*-axis showing the molecular packing of **6**

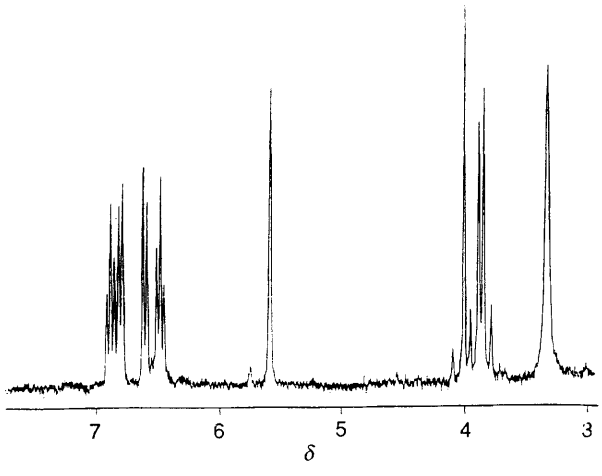
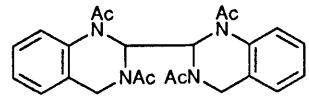


Fig. 3 ^{1}H NMR spectrum of **6** in [$^2H_6$]dimethyl sulfoxide

4.42 and 5.34, together with acetyl signals at δ 2.12 and 1.28. The ^{13}C proton-decoupled spectrum of **7** shows bands at δ 61.64 and 41.71 attributed to the methine and benzyl carbon atoms,



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respectively. The acetyl groups give bands at δ 19.94 and 23.91 (methyl) and δ 170.18 and 170.97 (carbonyl), and the aromatic carbons are found in the range δ 124.98–134.66.

Although tetrahydroquinazoline is known, **6** has not been previously reported. Its formation indicates that for the diimine **5**, the preferred pathway is intramolecular cyclisation rather than intermolecular addition which would lead to a derivative of **2**. A related intramolecular cyclisation is observed in the reaction of glyoxal with 2-aminobenzoic acid.[6]

It should be noted that there is no intrinsic steric problem associated with the intermolecular addition of diimines formed from 2-substituted benzylamines. Thus derivatives of **2** have been prepared from benzylamines substituted at the *ortho*-position with chloro-, methyl-, bromo-, fluoro- and methoxy-groups.[2] The X-ray molecular structure of the 2-methyl derivative **8**, is shown in Fig. 4. Comparison with the structure of the 4-chloro-derivative,[2] **9** indicates (Table 1) that bond lengths and bond angles in the central cages of both molecules are almost identical. Thus there is no evidence for particularly unfavourable steric effects engendered by the 2-substituent. An interesting feature of both structures is the strongly non-equivalent geometry of the chemically equivalent atoms N(1) and N(2). The former has a pyramidal bond geometry (the sums of bond angles being 324.4° in the 2-methyl and 326.6° in the 4-chloro derivatives) while the latter is significantly flattened (the corresponding sums being 347.2 and 347.9°). As shown in Fig. 5, the lone electron pair of N(1) is directed over the seven-membered ring while that of N(2) is over the five-membered ring. The orientations of the benzyl groups at N(1) differ in the two structures and the preferred orientations are presumably those which minimise intermolecular interactions in the solid state.

Experimental

^{1}H and ^{13}C NMR spectra were recorded using Bruker AC 250 or AMX 500 instruments with 0.01 mol dm^{-3} concentrations of substrates in deuteriated solvents.

Preparation of **6**.—2-Aminobenzylamine (10 g, 0.082 mol) was dissolved in acetonitrile (200 cm^3) containing 70% aqueous nitric acid (0.30 cm^3). 40% Aqueous glyoxal (5.95 g, 0.041 mol) was added dropwise over 45 min at room temperature (25 °C). Precipitation of **6** occurred during the addition of the glyoxal. After addition of the glyoxal the mixture was stirred for 24 h. The crude product was filtered and washed with acetonitrile (50 cm^3) before being dried under vacuum to give a fine white

Table 1 Comparison of bond distances/Å and angles/° in **8** and **9**, the 2-methyl- and 4-chloro-benzylhexaazaisowurtzitanes

	8	9		8	9		8	9
C(1)–C(1′)	1.569(6)	1.579(3)	N(1)–C(1)–N(2′)	101.9(3)	102.1(2)	C(1)–N(1)–C(3)	101.9(2)	102.4(2)
C(1)–N(1)	1.468(4)	1.465(3)	N(1)–C(1)–C(1′)	111.3(3)	110.5(2)	C(1)–N(1)–C(10)	110.9(3)	110.8(2)
C(1)–N(2′)	1.460(5)	1.461(3)	N(2′)–C(1)–C(1′)	116.0(3)	115.7(2)	C(3)–N(1)–C(10)	111.6(3)	113.4(2)
N(1)–C(3)	1.496(4)	1.493(3)	N(2)–C(2)–N(3)	119.7(3)	119.1(2)	C(1′)–N(2)–C(2)	105.4(3)	105.6(2)
N(2)–C(2)	1.448(5)	1.460(3)	N(2)–C(2)–C(3′)	101.5(3)	101.1(2)	C(1′)–N(2)–C(20)	121.4(3)	122.4(2)
C(2)–N(3)	1.469(4)	1.455(3)	N(3)–C(2)–C(3′)	108.3(3)	108.8(2)	C(2)–N(2)–C(20)	120.4(3)	119.9(2)
C(3)–N(3)	1.437(5)	1.438(3)	N(1)–C(3)–N(3)	113.2(3)	112.5(2)	C(2)–N(3)–C(3)	112.2(3)	113.1(2)
C(2)–C(3′)	1.572(5)	1.561(3)	N(1)–C(3)–C(2′)	106.0(3)	106.7(2)	C(2)–N(3)–C(30)	115.1(3)	119.5(2)
N(1)–C(10)	1.493(4)	1.475(3)	N(3)–C(3)–C(2′)	110.7(3)	109.8(2)	C(3)–N(3)–C(30)	114.9(2)	115.9(2)
N(2)–C(20)	1.461(4)	1.455(3)						
N(3)–C(30)	1.469(5)	1.453(3)						

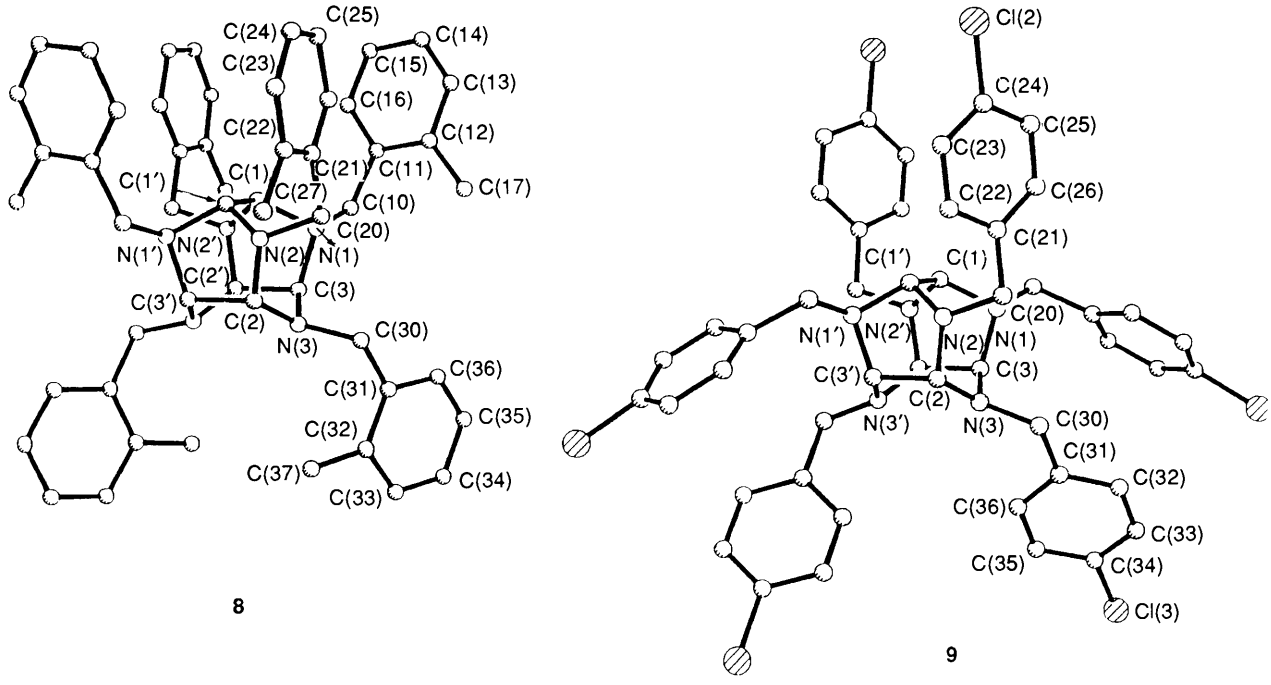

Fig. 4 Comparison of the X-ray crystal structures of **8** and **9**. Primed atoms are symmetrically related *via* twofold axes through the mid points of C(1)–C(1′) bonds.

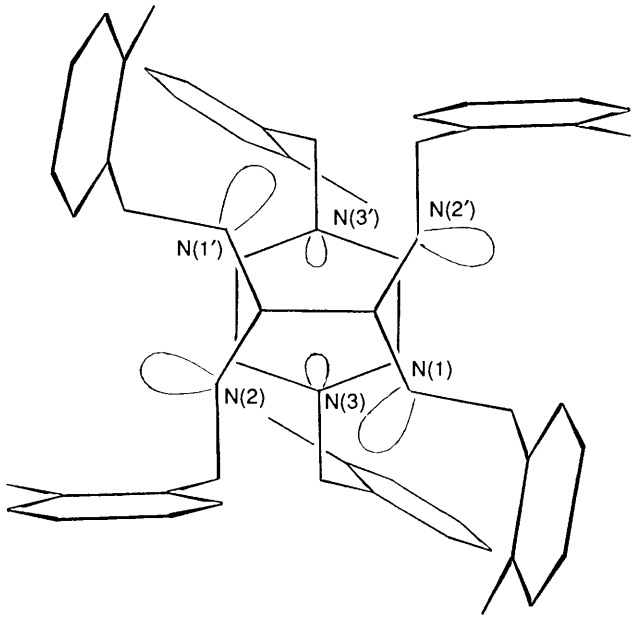

Fig. 5 The structure of **8** viewed down the twofold axis showing the orientation of nitrogen lone pairs

powder (69% yield). Owing to its insolubility recrystallisation was not readily achieved, but a pure sample was obtained from acetonitrile by an exhaustive recrystallisation under vacuum (similar to a soxhlet extraction under vacuum).[7] The pure product was obtained as colourless needles, m.p. 180–182 °C (Found: C, 72.1; H, 6.7; N, 21.0. Calc. for $C_{16}H_{18}N_4$: C, 72.18; H, 6.76; N, 21.05%).

Attempted Preparation of the Diimine **5**.—The procedure for the formation of **6** was repeated except that the 2-aminobenzylamine was dissolved in aqueous ethanol (50:50 v/v) and the aqueous glyoxal was added over a 10 min period while keeping the reaction mixture at 0 °C. Within 5 min a gummy white solid precipitated which was filtered off and cooled to dry-ice temperature. This solid was found to be very reactive. Dissolution in acetonitrile resulted in the precipitation of **6** as a white solid. Owing to the reactive nature of the initial product it was not possible to characterise it.

N,N,N′,N′-*Tetraacetyl*-2,2′-*bi*(1,2,3,4-*tetrahydroquinazoline*) **7**.—Compound **6** (4 g, 0.015 mol) was gently heated in acetic anhydride (50 cm^3) for 2 h. Cubic off-white crystals of **7** separated out and were isolated by filtration. The dark brown mother liquor was evaporated under vacuum at 50 °C to give a brown sticky residue. Addition of the brown solid to ice–water (100 cm^3) gave a fine brown precipitate. This was decolourised with charcoal in boiling aqueous ethanol (50:50 v/v). The filtrate deposited a further crop of crystalline **7**. The overall yield was 74%. The mass spectrum (chemical

Table 2 Summary of data collection, structure solution and refinement details

	Compound **6**	Compound **8**
Crystal data		
Empirical formula	$C_{16}H_{16}N_4$ + solvent	$C_{50}H_{60}N_6$
M_r	264.3 + solvent	793.1
Colour, habit	Colourless, needle	Colourless, prism
Crystal size/mm	0.10 × 0.20 × 0.45	0.34 × 0.35 × 0.56
Crystal system	Trigonal	Monoclinic
a/Å	39.027(19)	16.996(4)
b/Å	39.027(19)	14.201(3)
c/Å	4.965(3)	19.845(5)
α/°	90	90
β/°	90	103.11(2)
γ/°	120	90
V/Å^3	6549(7)	4665(2)
Space group	$R\bar{3}$	$C2/c$
Z	18	4
$F(000)$	2520 + solv	1704
d_{calc}/g cm^{-3}	1.21	1.13
μ/mm^{-1}	0.08	0.07
Data Collection		
Diffractometer	Rigaku AFC6S	Siemens R3m/V
Radiation	Mo-Kα	Mo-Kα
T/°C	20	20
Scan mode	$\theta/2\theta$	Wyckoff (limited ω)
Max 2θ/°	55	48
Refl. measured	3822	3584
Unique refl.	3351	3129
Refl. used	1353[a]	2090[b]
Structure solution and refinement[8]		
k in $w = 1/(\sigma^2F + kF^2)$	0.0008	0.0003
R	0.088	0.061
R_w	0.087	0.072
GOF	1.69	2.50
Max residual peak/e Å^{-3}	0.32	0.21

[a] $F > 2.5\sigma(F)$. [b] $I > 2\sigma(I)$.

ionisation) gave a large peak at m/z 435 corresponding to the M + 1 cation of **7**.

2,4,6,8,10,12-*Hexakis*(o-*tolyl*)-2,4,6,8,10,12-*hexaazaisowurtzitane* was prepared as reported previously.[2]

Crystal-structure Analysis.—Details of the crystal data, data acquisition and refinement are concisely summarised in Table 2. The structure of **6** was solved from a relatively poor data set reflecting the difficulty of obtaining a suitable crystal. However all non-hydrogen atoms were successfully refined with anisotropic displacement parameters. Hydrogen atoms were included at calculated positions and allowed refinement into riding mode. Difference electron density maps suggested highly disordered solvent molecules in the cavities of the $R\bar{3}$ lattice around the C_3 axis. This was assumed to be acetonitrile but could not be modelled or refined conclusively. Inclusion of some solvent carbon atoms reduced the residual cavity density to ±0.3 e Å^{-3}.

For structures **6** and **8**, the final fractional atomic coordinates together with other data tables (bond lengths and angles, anisotropic parameters and calculated hydrogen coordinates) have been deposited.

Acknowledgements

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