Ozonolysis of 71 (85). A stream of O_3 was bubbled through a solution of **71** (0.050 g, 0.896 mmol) in MeOH (1 mL) and CH_2Cl_2 (4 mL) at −78 °C until a blue color persisted. The excess O_3 was then removed with a stream of Ar, and Me_2S (2 mL) was added. This solution was allowed to warm to room temperature and maintained for 0.5 h. At this time, HCl (1.4 mL of a 1.4 M solution in absolute MeOH, 1.4 mmol) was added, and the resulting solution was maintained at room temperature for 0.5 h. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the mixture was extracted with Et_2O. The combined organic extracts were dried (K_2CO_3) and concentrated. The crude material was purified on silica gel (3:1:.01 hexane–EtOAc–Et_3N) to give 0.027 g (57%) of **85** as a slightly yellow oil: ^1H NMR (500 MHz, $CDCl_3$) 3.48 (m, 1 H), 3.40–3.30 (m, 2 H), 3.35 (s, OMe), 2.28 (dd, J = 14.0, 7.3 Hz, 1 H), 2.05 (m, 1 H), 2.00–1.85 (m, 3 H), 1.81 (ddd, J = 12.5, 7.2, 5.5 Hz, 1 H), 1.70–1.60 (m, 2 H), 1.46 (m, 1 H), 1.32 (app dq, J = 12.8, 7.4 Hz, 1 H), 1.18 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) 156.0, 112.4, 69.2, 50.7, 49.9, 45.1, 35.6, 31.3, 29.0, 28.5, 26.1 ppm; IR (film) 2954, 1725, 1272, 1067, 690 cm^{-1}; MS (CI) m/e 212 (MH^+, 100); MS (EI) m/e 211.1203 (211.1208 calcd for $C_{11}H_{17}NO_3$, 5), 137 (100).

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Supplementary Material Available: Preparations of **16–19**, **21–25**, **27**, **33–37**, **39–51**, **53–61** and related spectra (58 pages). Ordering information is given on any current masthead page.

Polyazapolycyclics by Condensation of Aldehydes with Amines. 2. Formation of 2,4,6,8,10,12-Hexabenzyl-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0^{5,9}.0^{3,11}]dodecanes from Glyoxal and Benzylamines[1,2]

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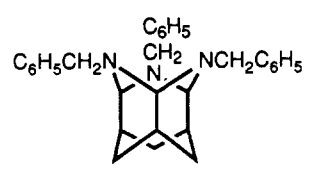
The condensation of glyoxal with benzylamine leads to 2,4,6,8,10,12-hexabenzyl-2,4,6,8,10,12-tetraazatetracyclo[5.5.0.0^{5,9}.0^{3,11}]dodecane (**2a**) in solvents such as acetonitrile or methanol with formic acid catalyst. Six phenyl-substituted derivatives of **2a** have been prepared and the scope of the reaction has been examined. Intermediates 1,2,-bis(benzylamino)-1,2-ethanediol (**6**) and *N,N'*-dibenzyl-1,2-ethanediimine (**7**) have been prepared and the mechanism of their conversion to **2a** is discussed. In the absence of acid catalysts, the glyoxal hemiacetal derivative 2,3-dihydroxy-1,4-dioxane reacts with benzylamine or 4-pyridylmethylamine in acetonitrile solvent to produce 9,10-bis(arylmethyl)-9,10-diaza-1,4,5,8-tetraoxaperhydroanthracenes **13a,b**.

The condensation of aldehydes with amines or ammonia is a valuable synthetic method leading to polyazapolycyclics, including cage compounds. The reaction of formaldehyde with ammonia to produce hexamethylenetetraamine is an important example.[3] Recently, as part of a program to synthesize polyazapolycyclics by condensation of aldehydes with amines, we reported the synthesis of 3,5,12-triazawurtzitanes (3,5,12-triazatetracyclo[5.3.1.1^{2,6}.0^{4,9}]dodecanes), including the 3,5,12-tribenzyl derivative **1**, by condensation of 1,3,5-triformylcyclohexane with selected primary amines.[1]



1

In this report we describe a facile condensation of glyoxal with benzylamine to produce a new polyazapolycyclic ring system, 2,4,6,8,10,12-hexabenzyl-2,4,6,8,10,12-hexaazatetracyclo[5.5.0.0^{5,9}.0^{3,11}]dodecane (hexabenzylhexaazaisowurtzitane, **2a**). The reaction is also successful with phenyl-substituted benzylamines leading to derivatives **2b–g**. The caged product is unusual in that all of the endocyclic nitrogens are at bridges, with none at bridgeheads as in hexamethylenetetraamine. We ascribe the name isowurtzitane to the new cage system **2** owing to its close relationship to wurtzitane, tetracyclo[5.3.1.1^{2,6}.0^{4,9}]-dodecane (see **1**).[4,5] These isomeric cages have the same adjacent groupings of atoms (six methylene bridges, six methines at bridgeheads, and three CHCH groups bonded through the methylenes). The hydrocarbon wurtzitane is known (**1**, $NCH_2C_6H_5 = CH_2$),[4] but the parent hydrocarbon isowurtzitane (tetracyclo[5.5.0.0^{5,9}.0^{3,11}]dodecane (**2**, $NCH_2Ar = CH_2$) apparently is not.

The new condensation reactions of amines with glyoxal to yield hexaazaisowurtzitane derivatives **2** appears to be limited to benzylamine and certain phenyl-substituted

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(2) Presented, in part, at 192nd National Meeting of the American Chemical Society, Anaheim, CA, Sept 12, 1986; paper No. ORGN-299.
(3) Nielsen, A. T.; Moore, D. W.; Ogan, M. C.; Atkins, R. L. *J. Org. Chem.* **1979**, *44*, 1678.
(4) Cupas, C. A.; Hodakowski, L. *J. Am. Chem. Soc.* **1974**, *96*, 4668.
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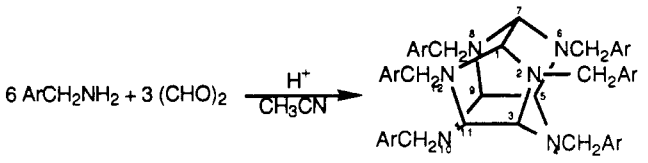


2a: Ar = C_6H_5
2b: Ar = 4-$CH_3C_6H_4$
2c: Ar = 4-(i-C_3H_7)C_6H_4
2d: Ar = 4-$CH_3OC_6H_4$
2e: Ar = 3,4-$(CH_3O)_2C_6H_3$
2f: Ar = 2-ClC_6H_4
2g: Ar = 4-ClC_6H_4

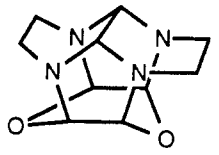
benzylamines. Primary aliphatic amines and anilines usually form dicarbinolamines **3** or diimines **4**.[6-10] With certain arylamines, such as 2-chloroaniline or aniline itself, one may obtain **3** or 1,1′,2,2′-tetrakis(arylamino)ethanes.[7] The condensation of benzylamine with glyoxal has apparently not been described previously. However, condensations of α-methylbenzylamine and α,α-dimethylbenzylamine with glyoxal produce diimines (**4**, R = $C_6H_5CH(CH_3)$ and $C_6H_5C(CH_3)_2$, respectively).[9,10]

$$2RNH_2 + OCHCHO \rightarrow$$

$$\underset{\mathbf{3}}{RNHCHOHCHOHNHR} \xrightarrow{-2H_2O} \underset{\mathbf{4}}{RN{=}CHCH{=}NR}$$

(R = alkyl or aryl)

The reactions of ethylenediamine and N,N′-disubstituted ethylenediamines with glyoxal lead to other products, including *cis*- and *trans*-1,4,5,8-tetraazadecalins and 2,2′-biimidazolidines.[11-13] In one example, condensation of glyoxal with ethylenediamine led to a tetraazadioxa caged polycyclic compound (**5**), also an isowurtzitane derivative.[14,15]



5

Hexabenzylhexaazaisowurtzitane (**2a**) is prepared in a very facile manner by condensation of nearly stoichiometric quantities of benzylamine with 40% aqueous glyoxal in aqueous acetonitrile solvent (15% total water) at 25 °C. An acid catalyst (formic acid, 0.1 molar % of the amine) is required. The reaction is rapid and nearly complete within a few hours. Crystalline **2a** separates from the reactiom mixture and is recovered by filtration and washing. Best yields (75–80%) are obtained by addition of the glyoxal solution over a 1-h period. Six phenyl-substituted derivatives of **2a** were prepared by this same procedure (A). Substituents included 4-methyl, 4-isopropyl, 4-methoxy, 3,4-dimethoxy, 2-chloro, and 4-chloro

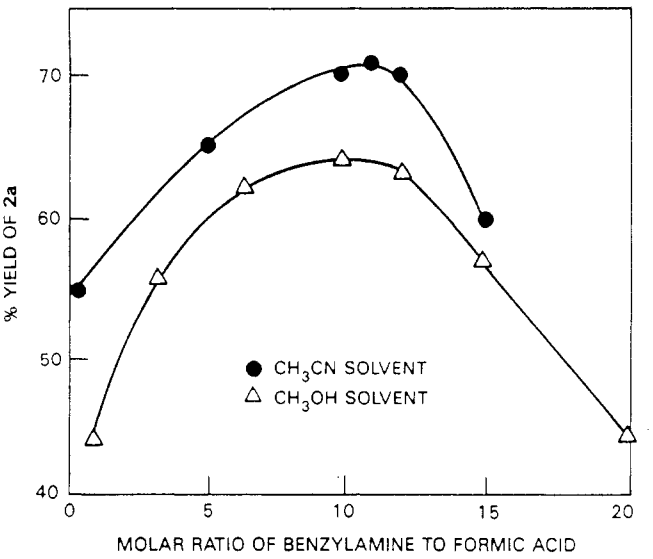


Figure 1. Percent yield of **2a** vs molar ratio of benzylamine to formic acid; conditions not optimum (see text).

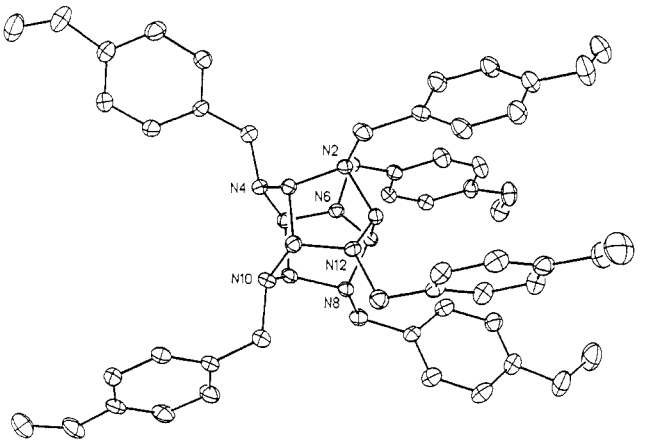


Figure 2. Computer-generated perspective drawing of final X-ray model of 2,4,6,8,10,12-hexakis(4-methoxybenzyl)-2,4,6,8,10,12-hexaazaisowurtzitane (**2d**). Hydrogen atoms are omitted for clarity.

to produce good yields of phenyl-substituted derivatives **2b–g** (Table I). Aqueous methanol may also be employed as a solvent in the reaction (procedure B), but yields of **2a–g** are usually lower. The yields by procedure B listed in Table I are for an unoptimized modification in which all the reactants are mixed at once rather than adding the glyoxal slowly. The reaction is much slower in methanol than in acetonitrile, requiring several days instead of a few hours to reach completion.

Parametric studies were made of the reaction conditions leading to **2a** by procedures A and B. Yields are very sensitive to reaction conditions. Factors studied include solvent, stoichiometry of reactants, reactant concentration, rate of mixing, reaction temperature, and time. Details are discussed in the Experimental Section. Yields are higher in aqueous solvents (10–20% water). Of major importance is the molar ratio of amine to formic acid catalyst. Yields of **2a** maximize at an acid/amine molar ratio of about 0.1 in either acetonitrile or methanol solvent (Figure 1). The solution reaches a pH of about 9.5 at this point. The yield appears to be independent of the carboxylic acid catalyst employed if the pH is optimum.

The hexaazaisowurtzitane ring system **2** is considerably more stable toward acids than is the related triazawurtzitane **1**, which undergoes very facile ring opening in the

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Table I. Synthesis of Hexabenzylhexaazaisowurtzitanes 2

			yield, %[a]				elemental analysis					
							calcd			found		
compd	phenyl substttn	mp, °C[b]	proc A	proc B	mol form.	M_r	C	H	N	C	H	N
2a	H	154–155	80	64	$C_{48}H_{48}N_6$	708.91	81.32	6.83	11.86	81.34	6.91	11.84
2b	4-CH_3	172–174	68	49	$C_{54}H_{60}N_6$	793.11	81.78	7.63	10.60	81.74	7.69	10.63
2c	4-*i*-C_3H_7	144–145[c]	24	52	$C_{66}H_{84}N_6$	961.44	82.45	8.81	8.74	82.43	8.91	8.63
2d	4-CH_3O	148–150	60	35	$C_{54}H_{60}N_6O_6$	889.11	72.95	6.80	9.45	72.76	6.78	9.26
2e	3,4-$(CH_3O)_2$	160–161[d]	50	11	$C_{60}H_{72}N_6O_{12}$	1069.28	67.40	6.79	7.86	67.49	6.81	7.81
2f	2-Cl	208–211[e]	68	15	$C_{48}H_{42}Cl_6N_6$[f]	915.63	62.97	4.62	9.18	62.73	4.82	9.16
2g	4-Cl	212–214	46	15	$C_{48}H_{42}Cl_6N_6$[g]	915.63	62.97	4.62	9.18	63.07	4.55	9.07

[a] See Experimental Section for procedure details. A modified procedure B was employed (except for **2a**) in which all of the reactants are mixed at once. [b] Melting point of analytical samples recrystallized from acetonitrile. [c] Clusters of flat prisms, mp 123–125 °C, changing to clusters of needles, mp 144–145 °C. [d] Clusters of chunky crystals, mp 137–140 °C, changing to small crystals, mp 160–161 °C. In another run where 95% methanol was employed as solvent, another polymorph of **2e** was isolated as clusters of fine needles, mp 186–188 °C (1.5% yield). The ^1H and ^{13}C NMR spectra of these samples are identical; see Tables II and III. [e] Recrystallized from dimethyl sulfoxide. [f] For **2f**, calcd percent of Cl 23.23; found 23.39. [g] For **2g**, calcd percent of Cl 23.23; found 23.56.

Table II. ^1H NMR Spectral Data of Hexabenzylhexaazaisowurtzitanes 2 (30 °C, Tetramethylsilane Internal Standard)

compd	phenyl substttn	solvent	phenyl protons[a]	benzyl CH_2 (s)	cage ring, CH (s)	phenyl substit signals
2a	none	$CDCl_3$	7.20–7.24	4.16 (4 H)	3.59 (2 H)	
				4.09 (8 H)	4.03 (4 H)	
2b	4-CH_3	CD_2Cl_2	7.10–7.27	4.17 (4 H)	3.54 (2 H)	CH_3 2.39 s (18 H)
				4.10 (8 H)	4.06 (4 H)	
2c	4-*i*-C_3H_7	CD_2Cl_2	7.23–7.28	4.28 (4 H)	3.53 (2 H)	CH 3.01 septet, J = 6.9 Hz, (6 H)
				4.16 (8 H)	4.22 (4 H)	CH_3 1.37 d, J = 6.9 Hz (36 H)
2d	4-CH_3O	$CDCl_3$	6.71–7.19	4.08 (4 H)	3.52 (2 H)	CH_3 3.78 s (18 H)
				3.99 (8 H)	3.93 (4 H)	
2e	3,4-$(CH_3O)_2$	$CDCl_3$	6.76–6.93	4.17 (4 H)	3.56 (2 H)	CH_3 3.84, 3.80 s (36 H)
				4.06 (8 H)	3.91 (4 H)	
2f	2-Cl	$(CD_3)_2CO$	7.03–7.42	4.38 (4 H)	3.79 (2 H)	
				4.25 (8 H)	4.24 (4 H)	
2g	4-Cl	$CDCl_3$	6.92–7.31	4.06 (4 H)	3.56 (2 H)	
				3.98 (8 H)	3.88 (4 H)	

[a] Range of peak chemical shifts.

Table III. ^{13}C NMR Spectral Data of Hexabenzylhexaazaisowurtzitanes 2 ($(CD_3)_2CO$ Solvent, 30 °C)

compd	phenyl substttn	phenyl carbons	benzyl CH_2 carbons[a]	ring cage CH carbons[b]	phenyl substit signals
2a	none	127.11, 128.51, 128.82, 129.67, 141.34	57.29 (2 C), 56.62 (4 C)	80.94 (2 C), 77.53 (4 C)	
2b	4-CH_3	128.89, 129.19, 129.70, 136.56, 136.68, 138.51	57.13 (2 C), 56.40 (4 C)	81.05 (2 C), 77.53 (4 C)	CH_3 21.30
2c	4-*i*-C_3H_7	126.59, 128.99, 129.86, 138.96, 139.05, 147.81, 147.87	57.25 (2 C), 56.49 (4 C)	80.31 (2 C), 78.02 (4 C)	CH 51.10, 52.45, 53.80, 55.15, 56.49 CH_3 24.49, 34.43
2d	4-CH_3O	113.95, 129.89, 130.71, 133.44, 133.66, 159.18	56.71 (2 C), 55.97 (4 C)	80.86 (2 C), 77.26 (4 C)	CH_3 55.68
2e[b]	3,4-$(CH_3O)_2$	112.09, 112.75, 113.67, 120.87, 121.83, 134.31, 134.10, 148.90, 149.74, 149.91	57.12 (2 C), 56.38 (4 C)	80.93 (2 C), 77.45 (4 C)	CH_3 56.43, 56.28
2g	4-Cl	128.35, 128.51, 129.41, 130.41, 132.75, 132.95, 138.54, 138.69	56.27 (2 C), 55.67 (4 C)	81.29 (2 C), 76.64 (4 C)	

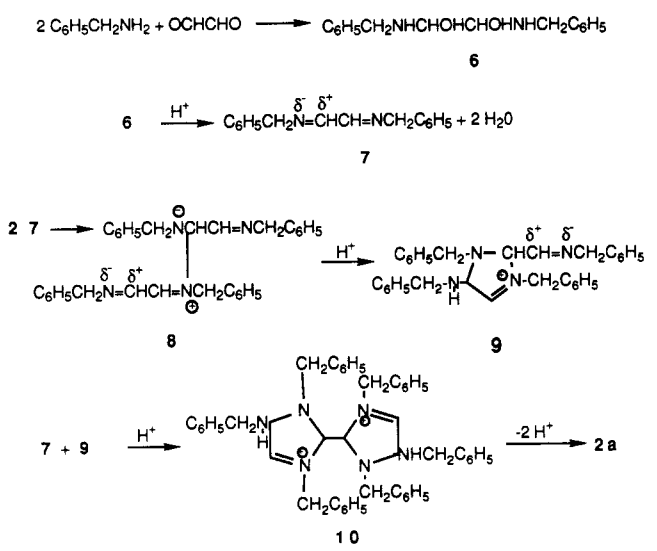
[a] Assignments confirmed from coupled spectra and/or distortionless enhancement by polarization transfer (DEPT) spectra. [b] Measurement in CD_2Cl_2 solvent.

presence of acid catalysts, even weak ones. Also, in aprotic solvents such as chloroform-*d* and acetonitrile-d_3 **1** is in equilibrium with its monocyclic triimine form. On the other hand, hexabenzylhexaazaisowurtzitanes **2a–g** show no evidence of decomposition in aprotic solvents by NMR assay. Furthermore, they are rather stable toward acids in aprotic solvents. The hexabenzyl compound **2a**, for example, forms stable hydrochloride and hydrobromide salts in benzene, from which **2a** may be regenerated by treatment with sodium hydroxide. However, **2a** is completely decomposed by being heated in acetic acid at 50 °C for an hour or by treatment with 10% acetic acid in methylene chloride for several hours at 25 °C. The decomposition products are unidentified oils.

The structure of the 4-(methoxybenzyl)hexaaxaisowurtzitane derivative **2d** was established by X-ray crystallography (Figure 2). (The crystals obtained for the benzyl derivative **2a** were twinned and less suitable for crystallographic analysis.) The benzyl methylene groups at N-4 and N-10 in crystalline **2d** are exocyclic to the six-membered rings. In the five-membered rings, two of the methylene groups are exocyclic to the five-membered rings (at N-6 and N-12) and two are endocyclic (at N-2 and N-8). In **2a–g** in solution only two types of benzyl methylenes are seen, corresponding to those attached to the five- and six-membered rings (NMR data).

All of the isolated isowurtzitanes **2a–g** show similar ^1H and ^{13}C NMR spectra (acetone-d_6 solvent; Tables II and III). Characteristic of the proton spectra are two singlets for the two types of ring cage methine protons (six total) observed in 4:2 ratio near δ 4.0 and 3.5, respectively (Table II). Also seen in a 2:1 ratio are the signals for the 12 adjacent benzyl methylene protons that appear near δ 4.0. The ^{13}C NMR spectra reveal two signals for the carbons

Scheme I



of the isowurtzitane ring in a 2:1 ratio near 77.5 and 81 ppm (Table III). Because of extremely low solubility in NMR solvents, it was not possible to obtain a ^{13}C NMR spectrum for the 2-chloro derivative **2f**.

A molecular ion peak (M + 1) is seen in the chemical ionization mass spectrum of **2a**. The 100% peak, m/z = 237, is believed to be the M + 1 ion of *N,N'*-dibenzyl-1,2-ethanediimine (**7**).

The mechanism of formation of hexabenzylhexaazaisowurtzitane (**2a**) is believed to involve a trimerization of diimine **7** (Scheme I). The dicarbinolamine precursor **6** was prepared by reaction of benzylamine with glyoxal in 50% aqueous ethanol or tetrahydrofuran, containing formic acid catalyst, at 0 °C; the reaction is complete within a few minutes. The diol is isolated as a white, crystalline solid, mp 48–58 °C, containing much water of solvation (40–50% by weight). The diimine, *N,N'*-dibenzyl-1,2-ethanediimine (**7**) is obtained by simply dehydrating the hydrated diol by pumping at 0.1 mm (25 °C) for about an hour. Sufficient formic acid remains in the solvate to assure rapid and complete dehydration of the diol to the diimine. The diol **6** and diimine **7** may readily be distinguished by differences in their ^1H NMR spectra. The diimine reveals a characteristic vinyl CH signal near δ 8.08 in $CDCl_3$. The benzyl methylene signals appear at δ 4.63 and 4.78 for **6** and **7**, respectively. The samples of **6** isolated are rather pure, except for the presence of water and some tetrahydrofuran or ethanol solvent. The diimine samples also contain water, in addition to some oligomers of **7** (^1H NMR assay).

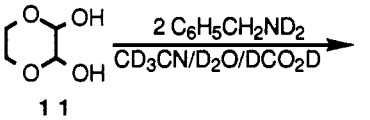
Diol **6** and diimine **7** are very reactive, unstable substances. At ambient temperature they rapidly change to brown gums within a few days; a low yield (3–5%) of **2a** may be isolated from the gums. However, in solution in acetonitrile solvent containing a small amount of formic acid, both **6** and **7** rapidly produce **2a** (50–60% yield). The diol reacts more slowly than the diimine, indicating dehydration of the diol to **7** to be slower than trimerization of **7** to form **2a**. Of the total **2a** formed within 17 h, 92% of it is formed within the first 0.5 h from diimine **7**, but only 75% from diol **6** during this same time period under the same reaction conditions. The principal side reaction appears to be polymerization of **7**. Most diimines **4** isolated from other amines and glyoxal are stable materials; they do not polymerize readily nor do they self-react to produce isowurtzitanes. Dibenzyl diimines appear to be unusual in their very reactive behavior to produce **2**.

The diimine trimerization to yield **2a** is one of addition of a 1,2-dipole to itself (Scheme I). The acyclic dimer of a diimine is a dipole (**8**), which can cyclize and protonate most readily to form a five-membered ring monocyclic dimer (cation **9**). Reaction of **9** with diimine **7** and protonation should lead to the bicyclic trimer **10**, a dication. Intramolecular cyclization of **10** leads to **2a** after loss of two protons.

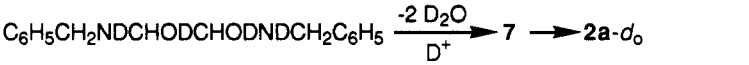
Monoimines derived from most aldehydes and ammonia undergo a related, extremely rapid trimerization to produce 2,4,6-trisubstituted-1,3,5-hexahydrotriazines. These reactions also proceed by additions of an imine 1,2-dipole to itself.[16,17] The reaction of amines with aldehydes to form N,N,N-trisubstituted 1,3,5 hexahydrotriazines has also been observed; amines include anilines and benzylamine. However, with most amines the reaction is limited to reactions with formaldehyde.[18–21] Only methylamine and allylamine have been observed to produce 1,2,3,4,5,6-hexasubstituted-1,3,5-hexahydrotriazines, and only when reacting with acetaldehyde.[19–23] Other amines react with aldehydes to produce imines RCH=NR' that do not cyclize to hexahydrotriazines. Diimine **7** is such an imine.

In the reactions of anilines with aromatic aldehydes to form Schiff bases, the rate-limiting step at neutral or slightly alkaline pH is dehydration of the carbinolamine intermediate ArNHCHOHAr'.[24] The rate of Schiff base formation is slower for electronegatively substituted anilines.[25] It has been observed in the condensation of benzylamines with glyoxal to form phenyl-substituted hexabenzylhexaazaisowurtzitanes that the rate is much slower with benzylamines bearing electronegative substituents (2-Cl, 4-Cl, 4-CH_3O, 3,4-di-CH_3O) than those with electron-releasing substituents (H, CH_3, i-C_3H_7). Nitro-substituted anilines react with glyoxal to form dicarbinolamines (**3**, R = 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$) of very great stability.[7]

To determine the effect of deuterium substitution on formation of **2a**, another method was employed to generate glyoxal. 2,3-Dihydroxy-1,4-dioxane (**11**), a hemiacetal derivative of glyoxal, is a very useful precursor to it that does not require the 40% aqueous solution.[26] A mixture of **11** and benzylamine-*N,N*-d_2 in CD_3CN/D_2O with formic acid-d_2 as catalyst produced **2a** containing no deuterium.



11



12

The yield of **2a** was only 30% after 22 h, compared to 61%

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when the reaction was conducted in the same manner and the same concentrations with benzylamine, CH_3CN/H_2O, and formic acid catalyst (18-h reaction time). The reaction is roughly twice as slow in the deuterated medium, suggesting a proton transfer from the deuterated dicarbinolamine **12** in the rate-limiting step. The protonation of the intermediate anions from the 1,2-dipole self-reaction (**8**, Scheme I, for example) would be expected to occur at or near the encounter rate. Thus, the observed deuterium isotope effect in the formation of **2a** suggests a rate-limiting step of dicarbinolamine dehydration. In related experiments, the diimine **7** was self-condensed in $CH_3CN/H_2O/HCO_2H$ and in $CD_3CN/D_2O/DCO_2D$ to yield **2a** in 59% yield in both experiments (17-h reaction time). These results also suggest that trimerization of **7** to **2a** is not rate-limiting.

The absence of deuterium in **2a** isolated from deuterated reactants and solvents discounts mechanisms that require exchange of benzyl α-methylene protons. Certain monoimines derived from benzylamine or α-substituted benzylamines undergo 1,3-dipolar addition with dipolarophiles such as styrene or methyl maleate to form substituted pyrrolidines.[27,28] These cyclizations require removal of benzyl α-methylene protons. Thus, 1,3-dipolar addition mechanisms of this type may be discounted as a route to **2a**. We have also observed that the structurally related imine benzylidenebenzylamine, $C_6H_5CH_2N{=}CHC_6H_5$, does not exchange any of its protons in $CD_3CN/D_2O/DCO_2D$.

The question arises regarding the apparent uniqueness of benzylamines in the condensation with glyoxal, which leads to hexabenzylhexaazaisowurtzitanes. The mechanism depicted in Scheme I suggests that the benzyl group is exerting its characteristic stabilizing and activating influence on ionic intermediates. Most *N*-aryl and *N*-alkyl groups are much less effective for this purpose. Those groups that are effective, such as *tert*-butyl, are too sterically hindered or perhaps not sufficiently activating. α-Substituted benzylamines yield diimines that fail to trimerize owing to steric effects, known to inhibit imine 1,2-dipole self-reactions.[9,10,16,17]

The scope of the reaction of amines with glyoxal leading to hexabenzylhexaazaisowurtzitanes **2** appears to be limited to benzylamine and certain phenyl-substituted benzylamines; it excludes α-substituted benzylamines. The published data indicate that most monoamines react with glyoxal to form diimines **4**. Our attempts to convert certain diimines other than **7** into **2** under various reaction conditions, including conditions suitable for formation of **2a**, were unsuccessful. Diimines examined include **4**, R = t-C_4H_9, i-C_3H_7, $C_6H_5CH(CH_3)$, and $(CH_3)_3CCH_2$; the diimines were recovered unreacted. Reactions of mixtures of diimines (**4**, R = t-C_4H_9, i-C_3H_7, separately) with dibenzyl diimine **7** lead only to **2a** and recovered **4**. Also, mixtures of amines (t-$C_4H_9NH_2$ and i-$C_3H_7NH_2$, separately) with benzylamine and glyoxal lead only to **2a**. Heteroarylmethylamines and allylamines might be expected to produce hexaazaisowurtzitanes. However, our efforts to extend the isowurtzitane synthesis to amines of this type have been unsuccessful. Amines examined include furfurylamine, 4-pyridylmethylamine, 1- and 2-naphthylmethylamine, 2-thiopheneylmethylamine, allylamine, cinnamylamine, as well as 2-phenylethylamine and glycine methyl and ethyl esters; most of these reactions lead not to isowurtzitanes or diimines, but to complex, mostly polymeric noncrystalline mixtures. Substitution of 2,3-dihydroxy-1,4-dioxane (**11**) for 40% aqueous glyoxal in several of the above mentioned experiments leads to similar results.

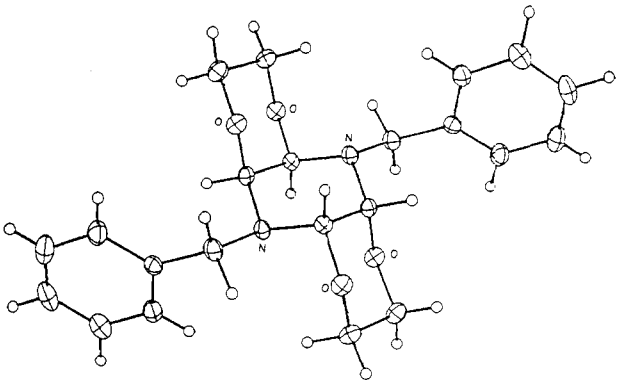
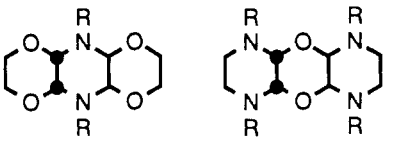


Figure 3. Computer-generated perspective drawing of final X-ray model of 9,10-dibenzyl-9,10-diaza-1,4,5,8-tetraoxaperhydroanthracene (**13a**).

The reaction of benzylamine with 2,3-dihydroxy-1,4-dioxane (**11**) in acetonitrile solvent was examined in the presence of 1 molar equiv of silver nitrate; no acid catalyst was added. The reaction took a different course. Instead of forming **2a**, **6**, or **7**, the dioxane ring remained unopened and a 9,10-diaza-1,4,5,8-tetraoxaperhydroanthracene derivative (**13a**) was obtained (42% yield). This reaction was also observed with 4-pyridylmethylamine, in the absence of either silver nitrate or acid catalyst, to yield **13b** (67% yield). The structures **13a,b** are in agreement with their spectral data. An X-ray crystal structure determination established the structure of **13a** (Figure 3). Previously, one of us (D.J.V.) had reported the preparation of related 9,10-dioxa-1,4,5,8-tetraazaperhydroanthracenes **14a–c**, obtained by condensation of substituted ethylenediamines with glyoxal in ethanol solvent (5–10% yields); the crystal structure of **14b** (R = i-C_3H_7) was determined.[13] Both **13** and **14** exhibit cis-transoid-cis ring stereochemistry.



13a: R = $C_6H_5CH_2$
13b: R = 4-$C_5H_4NCH_2$

14a: R = $C_6H_5CH_2$
14b: R = i-C_3H_7
14c: R = CH_3

Experimental Section

^1H and ^{13}C NMR spectra were recorded on an IBM NR-80 or a Nicolet NT200 spectrometer with a pulsed Fourier transform system; spectra were recorded at ambient temperature (near 30 °C) unless otherwise stated and are referenced to tetramethylsilane. Infrared spectra (IR) were determined on a Nicolet 605X instrument and mass spectra on a Hewlett Packard Model 5985 GC/MS system. Melting points were determined on a Kofler hot state apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

2,4,6,8,10,12-Hexabenzyl-2,4,6,8,10,12-hexaazatetracyclo-[5.5.0.0^{5,9}.0^{3,11}]dodecane (Hexabenzylhexaazaisowurtzitane) (2a). Procedure A. During a 1-h period, glyoxal (72.5 g, 40% aqueous solution, 0.50 mol) was added dropwise to a solution of benzylamine (117.9 g, 1.10 mol), water (100 mL), and formic acid (88%, 5.76 g, 0.110 mol) in acetonitrile (1100 mL) while keeping the temperature below 20 °C. The addition funnel was rinsed with 10 mL of water. After standing at 25 °C overnight (16–18 h), the precipitated product was removed by filtration and washed with cold acetonitrile. The crude product is resuspended twice in cold acetonitrile with stirring and filtered. The yield is 94.8

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g (80%) of hexabenzylhexaazaisowurtzitane (**2a**); mp 150–152 °C. Parallel runs gave 75–80% yields. Recrystallization from acetonitrile yields a product, mp 155–157 °C (90% recovery of colorless prisms): IR (KBr) shows absence of NH and C=O bands; mass spectrum (CI, CH_4) m/z (rel intensity) 709 (MH^+, 0.6), 618 (0.7), 473 (0.7), 237 (100); ^1H and ^{13}C NMR data are listed in Tables II and III.

The condensation of other benzylamines with glyoxal was conducted under conditions similar to that described for the preparation of **2a**. The reaction was successful with 4-methyl-, 4-isopropyl-, 4-methoxy-, 3,4-dimethoxy-, 2-chloro-, and 4-chlorobenzylamines to produce compounds **2b–g**; see summaries of data in Tables I–III. No crystalline product was isolated from the reaction of 4-(dimethylamino)benzylamine with glyoxal with use of various procedures that produce **2a**. The procedure used for preparation of **2e** from 3,4-dimethoxybenzylamine was modified slightly; 50% aqueous acetonitrile was the solvent. In the preparations of **2f** and **2g** (from 2-chloro- and 4-chlorobenzylamine, respectively), 3.3 molar equiv of amine and 0.33 molar equiv of formic acid per mole of glyoxal were employed, rather than 2.2 molar equiv of amine and 0.22 molar equiv of acid used with the other amines. The reaction with 4-chlorobenzylamine was very slow and required 7 days to attain a 46% yield of **2g**. The yield of **2c** obtained from 4-isopropylbenzylamine was lower in aqueous acetonitrile than in aqueous methanol (much gummy material was produced in this reaction); in all other examples the yields of condensation products were higher in acetonitrile (Table I).

Procedure B. During an 8-h period, a solution of glyoxal (72.5 g, 40% aqueous solution, 0.50 mol) in methanol (200 mL) was added dropwise to a solution of benzylamine (112.0 g, 1.045 mol), water (40 mL), and formic acid (99%, 5.5 g, 0.105 mol) in methanol (750 mL) while keeping the temperature below 20 °C. After standing at 25 °C for 11 days (most of the product precipitates within 5 days), the precipitated product is removed by filtration and washed with cold methanol to yield 75.9 g (64%) of **2a**, mp 150–152 °C. Recrystallization from acetonitrile raises the mp to 153–157 °C (90% recovery).

Substituted benzylamines were also condensed with glyoxal in aqueous methanol solvent to produce compounds **2b–g**; see Table I. However, the data in Table I (except for **2a**) are for a modified procedure B in which all of the reactants were mixed at once instead of adding the glyoxal slowly (reaction at 25 °C, 20 days). The yield of **2a** by this modified procedure is only 50%, compared to 64% when the glyoxal is added over an 8-h period. In the preparation of **2e**, 50% aqueous methanol was used as solvent. Similar to the preparations of **2f** and **2g** from 2-chloro- and 4-chlorobenzylamine, respectively, by procedure A, 3.0 molar equiv of amine and 30 equiv of formic acid per mole of glyoxal were employed; using a 2:1 molar ratio gave yields of **2f** and **2g** of about 8% in each case.

Procedure C. From 2,3-Dihydroxy-1,4-dioxane and Benzylamine. 2,3-Dihydroxy-1,4-dioxane (1.20 g, 0.01 mol) was added to a solution of benzylamine (2.25 g, 0.021 mol), formic acid (0.11 g of 88% formic acid, 0.0021 mol), and water (7.0 mL) in 40 mL of acetonitrile with stirring at 25 °C during a 5-min period. After standing at 25 °C for 18 h, the precipitate that formed was filtered off and washed with acetonitrile to yield 1.45 g (63%) of **2a**, mp 152–154 °C. More product precipitated on standing, which was filtered off after 4 days to yield 0.24 g of additional **2a**, mp 145–155 °C; total yield 1.69 g (73%).

In a parallel experiment some deuterated reactants and solvents were employed. 2,3-Dihydroxy-1,4-dioxane (0.12 g, 1.0 mmol) was added to a solution of benzylamine-N-d_2 (0.24 g, 2.2 mmol, 85 atom % ND_2), formic acid-d_2 (0.015 g, 0.31 mmol, 99 atom % D), and D_2O (0.81 g of 99+ atom % D) in CD_3CN (4.0 mL of 99+ atom %). After standing at 25 °C for 21.5 h, the precipitated product was filtered off to yield 0.070 g (30%) of **2a**-d_0, mp 152–154 °C: ^1H NMR spectrum (CD_2Cl_2) identical with that of authentic **2a** prepared by procedures A or B above.

1,2-Bis(benzylamino)-1,2-ethanediol (6). Glyoxal (3.63 g of 40% aqueous solution, 0.025 mol) was added dropwise, with stirring, to a solution of benzylamine (5.88 g, 0.055 mol) and formic acid (0.0175 g of 88%, 0.0033 mol) in 30 mL of 50% aqueous tetrahydrofuran during a 5-min period, keeping the temperature at 0 °C. After stirring for an additional 5 min, the precipitated product was removed by suction filtration, washed with 20 mL of ice water, and dried by suction for a few minutes to yield 8.38 g of crude **6** containing much water of solvation, slightly gummy, small prisms, mp 48–58 °C: ^1H NMR ($CDCl_3$) δ 7.26–7.31 (m, 10 H, aryl CH), 4.66 (s, OH/NH; disappears upon addition of D_2O), 4.63 (s, 4 H, CH_2), 3.2–4.4 (m, CHCH and signals of traces of tetrahydrofuran and oligomers of **7**), 1.66 (s, br, H_2O). Also seen in the NMR spectrum are traces of the diimine **7**: δ 8.08 (s, =CH), 4.78 (s, CH_2). A similar, highly hydrated product is obtained in 50% aqueous ethanol, mp 35–55 °C (small prisms), which reveals traces of ethyl signals in its NMR spectrum; see below. These products become oily with separation of water upon standing at 25 °C for an hour; they may be stored at −70 °C for a few days without change.

***N,N'*-Dibenzyl-1,2-ethanediimine (7).** Glyoxal (3.63 g of 40% aqueous solution, 0.025 mol) was added dropwise, with stirring, to a solution of benzylamine (5.88 g, 0.055 mol) and formic acid (0.0175 g of 88%, 0.0033 mol) in 30 mL of 50% aqueous ethanol during a 5-min period, while keeping the temperature at 0 °C. After stirring for an additional 5 min, the precipitated product (principally crude diol **6**) was isolated immediately by suction filtration. After 5 min, the unwashed solid product (10.0 g) was pumped at 0.1 mm (25 °C) for an hour. White, crystalline crude **7** (6.0 g), mp 60–66 °C, containing water of hydration (about 10–20% by weight in various runs) was obtained: ^1H NMR ($CDCl_3$) δ 8.08 (s, 2 H, =CH), 7.28–7.31 (m, 10 H, aryl CH), 4.78 (s, 4 H, CH_2), 1.76 (s, br, H_2O). Signals of **6** were absent. The compound is very unstable at 25 °C, changing to a brown gum after a few hours. It may be stored in a dry ice chest for a few days without change. Diimine **7** may be obtained in a similar manner from a sample of diol **6** prepared as described above in aqueous tetrahydrofuran.

Synthesis of 2a, Procedure D. From 1,2-Bis(benzylamino)-1,2-ethanediol (6). A 2.35-g sample (ca. 0.0045 mol, based on ^1H NMR and gravimetric assay of water content) of freshly prepared hydrated diol **6** was dissolved in a solution of 88% formic acid (0.05 g) in acetonitrile (10 mL) at 25 °C. Crystals of **2a** began to precipitate immediately. After 30 min the precipitate was recovered by filtration and washed with 5 mL of acetonitrile to yield 0.484 g (47.5%) of **2a** mp 147–152 °C. More **2a** formed in the filtrate on standing at 25 °C. It was recovered at intervals; yields at various times, in minutes, were as follows (yields in parentheses): 30 (47.5), 90 (51.4), 180 (55.4), 1020 (62.9); 75% of the total **2a** was produced within 30 min.

Synthesis of 2a, Procedure E. From *N,N'*-Dibenzyl-1,2-ethanediimine (7). Another 2.35-g portion of the same sample of freshly prepared hydrated diol **6** employed in procedure D was immediately pumped at 0.1 mm (25 °C) for an hour to yield 1.65 g of crude diimine **7**, containing ca. 18% water; ^1H NMR ($CDCl_3$) revealed the absence of diol **6**. The crude diimine was immediately added to a solution of 88% formic acid (0.05 g) in 10 mL of acetonitrile. Crystals of **2a** began to separate immediately. After 30 min, the precipitate was recovered by filtration and washed with 5 mL of acetonitrile to yield 0.449 g (44%) of **2a**, mp 151–153 °C. More **2a** formed in the filtrate on standing at 25 °C. It was recovered at intervals; yields of **2a** at various times, in minutes, were as follows (yields in parentheses); 30 (44.0), 120 (44.9), 1020 (48.1); 92% of the total **2a** was produced within 30 min. The yield of **2a** varies with the purity of **7**, but the rate of **2a** formation is always more rapid from **7** than from diol **6**.

In a parallel experiment, a different sample of crude hydrated **7** (0.50 g, containing ca. 8% water, ca. 1.65 mmol), D_2O (1.6 g), and formic acid-d_2 (0.012 g, 99 atom % D, 0.25 mmol) were dissolved in CD_3CN (9.5 mL). After a few minutes a precipitate began to form. After standing at 25 °C for 17 h, the precipitate was filtered off and washed with acetonitrile to yield (0.23 g (59%) of **2a**-d_0, mp 135–150 °C; its ^1H NMR spectrum was identical with that of authentic **2a**.

In another experiment, a sample of freshly prepared, crude, hydrated **7** (ca 8% water) was allowed to stand at 25 °C in a closed container for 17 days without added solvent. It changed into a brown gum mixed with water. The separated solid material containing no water (0.52-g aliquot) was triturated with 10 mL of acetonitrile to deposit crystals of **2a**; the product was filtered off and washed with acetonitrile to yield 0.020 g (ca 3.8%) of **2a**, mp 150–152 °C. Concentration of the filtrate to dryness gave a

brown gum (0.50 g) from which no additional **2a** could be isolated; its ^{1}H NMR spectrum revealed the absence of **2a** signals.

X-ray Diffraction Analysis of 2d: $C_{54}H_{60}N_6O_6$, M_r = 889.11, monoclinic space group $P2_1/c$, a = 16.419 (2), b = 24.649 (4), and c = 12.358 (2) Å, β = 109.73 (1)°, V = 4707.8 (12) Å^3, Z = 4, d_{calcd} = 1.254 g/cm^3, λ(Cu K$_\alpha$) = 1.54178 Å, μ = 6.23 cm^{-1}, F(000) = 1896, T = 295 K.

A clear colorless 0.04 × 0.22 × 0.50 mm crystal (recrystallized from octane/*N*,*N*-dimethylformamide mixed solvent) was used for data collection on an automated Nicolet R3m diffractometer with an incident beam monochromator. Lattice parameters were determined from 25 centered reflections within $40 \le 2\theta \le 57°$. The data collection range of hkl was $-17 \le h \le 16$, $0 \le k \le 26$, $0 \le l \le 13$, $\sin\theta/\lambda_{max}$ = 0.56 Å^{-1}. Three standards were monitored every 60 reflections and exhibited a maximum random variation of 2.0% during data collection. A total of 6464 reflections were measured in the $\theta/2\theta$ mode with a scan width from $[2\theta(K_{\alpha1}) - 1.0]$ to $[2\theta(K_{\alpha2}) + 1.0]°$; scan rate was a function of count rate (6°/min minimum, 30°/min maximum). There were 5793 unique reflections, R_{int} = 0.016 from merging equivalent reflections, and 4162 were observed with $F_o > 3\sigma(F_o)$. Data corrected for Lorentz and polarization effects but not for absorption.

The structure was solved by direct methods with the aid of the program SHELXTL.[29] In the blocked-cascade full-matrix least-squares, the function minimized was $\sum w(|F_o| - |F_c|)^2$ where $w = 1/[\sigma^2(|F_o|) + g(F_o)^2]$. In this work g = 0.00023. There were 614 parameters refined (in blocks of 101 parameters per cycle): atom coordinates, anisotropic thermal parameters for all non-H atoms, and isotropic thermal parameters for the hydrogens, methyl hydrogens used riding model in SHELXTL, H riding on C, C–H = 0.96 Å, U(H) = 1.2U_{eq}(C). The final residuals were R = 0.054 and R_w = 0.049 with an error for observations of unit weight of 1.39, N_o/N_p = 6.8. The largest shift to error ratio in the final refinement cycle was 0.03 and final difference Fourier excursions were 0.18 and −0.20 e Å^{-3}. Atomic scattering factors are from the International Tables for X-ray Crystallography (1974). Tables of atomic coordinates, bond distances and angles, and anisotropic thermal parameters are available as supplementary material.

Hexabenzylhexaazaisowurtzitane Dihydrochloride (2a·2HCl). A solution of hexabenzylhexaazaisowurtzitane (**2a**, 0.200 g, 2.82 mmol) in benzene (5.0 mL) was treated with concentrated hydrochloric acid (12 N, 0.70 mL, 8.4 mmol). The precipitate was filtered and washed with benzene and dried at 25 °C, 0.1 mm, to constant weight; yield 0.174 g (77%) of crude **2a** dihydrochloride hemihydrate; mp 113–115 °C dec; some decomposition of the sample occurs during drying.

Anal. Calcd for $C_{48}H_{48}N_6\cdot2HCl\cdot0.5H_2O$: C, 72.89; H, 6.50; N, 10.63; Cl, 8.96. Calcd for $C_{48}H_{48}N_6\cdot HCl$: C, 77.34; H, 6.63; N, 11.27; Cl, 4.76. Found: C, 72.87; H, 6.57; N, 10.63; Cl, 7.96.

A sample of the crude dihydrochloride salt (45 mg) was stirred for an hour with a mixture of water (5 mL), benzene (10 mL), and 10% aqueous NaOH solution (3 mL). The benzene layer was separated and the aqueous solution extracted with benzene (2 × 5 mL). The combined benzene solutions were dried with $MgSO_4$ and concentrated to yield 35 mg of recovered **2a**, mp 149–152 °C, having a ^{1}H NMR spectrum identical with that of authentic **2a**.

Hexabenzylhexaazaisowurtzitane Hydrobromide (2a·HBr). Concentrated hydrobromic acid (1.69 g, 48% HBr, 0.01 mol) was added dropwise with stirring to a solution of hexabenzylhexaazaisowurtzitane (**2a**, 7.09 g, 0.010 mol) in benzene (200 mL) at 10 °C. After standing at 10–20 °C for 2 h, the hydrobromide salt that precipitated was filtered off and washed with benzene; after drying in a desiccator over Drierite at 25 °C (0.1 mm) for 18 h, 8.61 g (99%) of the monohydrobromide salt of **2a** was obtained, solvated with one molecule of benzene; mp 127–130 °C.

Anal. Calcd for $C_{48}H_{48}N_6\cdot HBr\cdot C_6H_6$: C, 74.72; H, 6.39; Br, 9.21; N, 9.68. Found: C, 74.82, H, 6.38; Br, 9.29; N, 9.68.

9,10-Dibenzyl-1,4,5,8-tetraoxa-9,10-diazaperhydroanthracene (13a). Benzylamine (5.36 g, 50 mmol) was added to a suspension of 2,3-dihydroxy-1,4-dioxane (3.00 g, 25 mmol) in a solution of silver nitrate (4.25 g, 25 mmol) in acetonitrile (20 mL) dropwise during a 4-min period at 24 °C. Immediately, the mixture became dark and the temperature rose to 33 °C. After stirring at 25 °C for 60 h, the mixture was filtered to collect a dark grey powder. The product mixture was extracted with hot chloroform to separate the organic material from the insoluble silver residue. Removal of chloroform under reduced pressure left 2.28 g of pale yellow crystals; recrystallization from chloroform gave 1.99 g (42%) of **13a**, mp 262–263 °C: ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 10 H, aryl CH), 4.32 (s, 4 H, benzyl CH_2), 4.07, 3.77 (AB quartet, J = 13.2 Hz, 8 H, ring CH_2), 3.3–3.7 (m, 4 H, ring CH); X-ray crystal structure shown in Figure 3.

Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.20; H, 7.03; N, 7.34.

9,10-Bis(4-pyridylmethyl)-1,4,5,8-tetraoxa-9,10-diazaperhydroanthracene (13b). A solution of 4-(aminomethyl)pyridine (0.54 g, 5 mmol) in acetonitrile (2 mL) was added to a suspension of 2,3-dihydroxy-1,4-dioxane (1.20 g, 10 mmol) in acetonitrile (10 mL) at 25 °C during a 3-min period; the mixture was then stirred for 4 h. The yellow solid that formed was removed by filtration and dried under vacuum (0.81 g). Recrystallization from acetonitrile gave pale yellow needles (0.64 g, 67%) of **13b**, mp 243 °C: ^{1}H NMR ($CDCl_3$) δ 8.76 (d, J = 6 Hz, 4 H, aryl CH), 7.50 (d, J = 6 Hz, 4 H, aryl CH), 4.45 (s, 4 H, exocyclic CH_2), 3.6–4.0 (m, 8 H, ring CH_2), 3.3–3.6 (m, 4 H, ring CH).

Anal. Calcd for $C_{20}H_{24}N_4O_4$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.62; H, 6.33; N, 14.53.

X-ray Diffraction Analysis of 13a: $C_{22}H_{26}N_2O_4$, M_r = 382.4, monoclinic space group $P2_1/c$, a = 5.786 (1), b = 7.439 (1), and c = 22.519 (5) Å, β = 96.99 (2)°, V = 962.0 (3) Å^3, Z = 2 ($^1/_2$ molecule per asymmetric unit), d_{calcd} = 1.320 g/cm^3, λ(Cu K$_\alpha$) = 1.54178 Å, μ = 7.01 cm^{-1}, F(000) = 408, T = 295 K.

A clear colorless 0.18 × 0.07 × 0.30 mm crystal was used for data collection on an automated Nicolet R3m/V diffractometer with an incident beam monochromator. Lattice parameters were determined from 25 centered reflections within $32 \le 2\theta \le 85°$. The data collection range of hkl was $0 \le h \le 6$, $0 \le k \le 8$, $-24 \le l \le 24$, and $\sin(\theta/\lambda)_{max}$ = 0.56 Å^{-1}. Three standards were monitored every 100 reflections and exhibited a maximium random variation of 2.5% during data collection. A total of 1662 reflections were measured in the $\theta/2\theta$ mode with a scan width from $[2\theta(K_{\alpha1}) - 1.0]$ to $[2\theta(K_{\alpha2}) + 1.0]°$; scan rate was a function of count rate (16°/min minimum, 60°/min maximum). There were 1315 unique reflections, R_{int} = 0.010 from merging equivalent reflections, and 1179 were observed with $F_o > 3\sigma(F_o)$. Data corrected for Lorentz and polarization effects but not for absorption.

The structure was solved by direct methods with the aid of the program SHELXTL.[29] In the full-matrix least-squares, the function minimized was $\sum w(|F_o| - |F_c|)^2$ where $w = 1/[\sigma^2(|F_o|) + g(F_o)^2]$. In this work g = 0.0002. There were 180 parameters refined: atom coordinates, anisotropic thermal parameters for all non-H atoms, and isotropic thermal parameters for the hydrogens. The secondary extinction parameter was p = 0.0065 (12) in $F_c^* = F_c/[1.0 + 0.002(p)F_o^2/\sin 2\theta]^{0.25}$. The final residuals were R = 0.051 and R_w = 0.056 with an error for observations of unit weight of 1.72, N_o/N_v = 6.6. The largest shift to error ratio in the final refinement cycle was 0.002 and final difference Fourier excursions were 0.20 and −0.20 e Å^{-3}. Atomic scattering factors are from the International Tables for X-ray Crystallography (1974). Tables of atomic coordinates, bond distances and angles, and anisotropic thermal parameters are available as supplementary material.

Reactions of Benzylidenebenzylamine in Deuterated Media. Benzylidenebenzylamine, $C_6H_5CH_2N{=}CHC_6H_5$, was prepared by reaction of benzylamine and benzaldehyde (0.1 mol of each) in ether solvent (100 mL) at 0 °C; after standing at 25 °C for 24 h, the mixture was dried with $MgSO_4$, filtered, and distilled to yield 16.8 g (86%) of the imine, bp 144 °C (5 mm); lit.[30] bp 143 °C (5 mm): ^{1}H NMR (CD_3CN) δ 8.44, (t, J = 1.36 Hz, 1 H, =CH), 7.23–7.87 (m, 10 H, aryl CH), 4.78 (d, J = 1.36 Hz, 2 H, CH_2).

A solution of the imine (0.11 g) in CD_3CN (1.0 mL) containing D_2O (0.13 g) and DO_2CD (0.010 g) was allowed to stand at 25 °C and the ^{1}H NMR spectrum determined at intervals. On standing,

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an equilibrium is rapidly attained between the imine, benzaldehyde (δ 9.97, CHO), and benzylamine (δ 4.08, CH_2). After 1.5 h, the equilibrium composition as indicated by the ^1H NMR spectrum is identical with that observed after 22 and 45 h, except that significant broadening of the methylene signal of benzylamine is seen owing to exchange of the NH_2 protons as they become more highly deuterated. No exchange of benzyl methylene protons is observed (the phenyl/CH_2 ratio remains constant at 2.5). In a parallel experiment the ^1H NMR spectrum of a solution of the imine (0.11 g) in CD_3CN (1.0 mL) and D_2O (0.11 g) and triethylamine (0.02 g) remained virtually unchanged during 24 h.

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Registry No. **2a**, 124782-15-6; **2a**·HCl, 124782-23-6; **2a**·HBr, 124782-24-7; **2b**, 124782-16-7; **2c**, 124782-17-8; **2d**, 124782-18-9; **2e**, 124782-19-0; **2f**, 124782-20-3; **2g**, 124782-21-4; **6**, 124782-22-5; **7**, 140-28-3; **13a**, 124782-25-8; **13b**, 124820-69-5; $PhCH_2NH_2$, 100-46-9; $(CHO)_2$, 107-22-2; $PhCH_2N{=}CHPh$, 780-25-6; 4-methylbenzylamine, 104-84-7; 4-isopropylbenzylamine, 4395-73-7; 4-methoxybenzylamine, 2393-23-9; 3,4-dimethoxybenzylamine, 5763-61-1; 2-chlorobenzylamine, 89-97-4; 4-chlorobenzylamine, 104-86-9; 4-(dimethylamino)benzylamine, 19293-58-4; dihydroxy-1,4-dioxane, 4845-50-5; benzylamine-*N*-d_2, 45579-94-0; benzaldehyde, 100-52-7; 4-(aminomethyl)pyridine, 3731-53-1.

Supplementary Material Available: Two figures showing full numbering used in X-ray analysis and the hydrogen atom locations and tables of (1) atom coordinates and equivalent isotropic thermal parameters for the non-hydrogen atoms, (2) anisotropic thermal parameters for non-hydrogen atoms, (3) hydrogen atom coordinates and thermal parameters, and (4) bond distances and valence angles (16 pages). Ordering information is given on any current masthead page.

Regiospecific and Highly Stereoselective Formation of Benzisochroman-6,9-quinones. Synthesis of (±)-Ventilagone and (±)-Ventiloquinone H

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An approach known to give regiospecific cycloadditions over a wide range of substrates has been applied to the synthesis of (±)-ventilagone and (±)-ventiloquinone H using a novel, electron-rich heterocyclic diene. The strategy provides for the sole formation of the natural, thermodynamically less stable diastereoisomer. As a basis for comparison of the spectral data, (±)-ventilagone 7-methyl ether was equilibrated and hydrolyzed to a mixture containing (±)-isoventilagone, a prototype of the heretofore unidentified trans series of compounds. Convenient substrates for eventual access to the more highly substituted natural products have also been obtained.

Although both cis and trans configurations are known in the case of naturally occurring benzisochroman-5,10-quinones (e.g., eleutherin and isoeleutherin), only the cis modification seems to far to have been attributed to the 6,9-isomers.[1,2] The structure of ventilagone (**1a**) is now well established from an X-ray crystallographic analysis,[3] and its NMR spectrum has been correlated to those of more recently isolated pigments.[2] However, no basis for comparison is available for isomeric materials, and this study shows that spectroscopic (mainly NMR) differences between the two diastereoisomeric series are indeed quite small in this area.

Many approaches have been proposed for the synthesis of natural benzisochroman-5,10-quinones[4a,b] but with the exception of one unsuccessful attempt[3] none has been devised for the 6,9-isomers such as ventilagone (**1a**) and ventiloquinones H (**18**) and I (**2**).[2] These juglone derivatives were nevertheless expected to be readily accessible by the Diels–Alder methodology involving halogenated quinones and electron-rich dienes[5] if an unusual heterocyclic reagent such as **7** were readily available.

A convenient route to a practical substrate is provided by two similar methods for the preparation of dihydro-γ-pyrones.[6,7] In a slight modification of the more recent of the two, methyl acetoacetate and crotonyl chloride were condensed in the presence of magnesium methylate to provide an 80% yield of 5,6-dihydro-3-(methoxycarbonyl)-2,6-dimethylpyran-4-one (**3**). Catalytic hydrogenation of a bicyclic product[6] analogous to the latter had previously shown that the 2,3 double bond was affected selectively albeit very slowly. However, when carried out on dihydropyrone **3** at 3 atm and in the presence of 10% palladized charcoal, the reaction was quite as satisfactory and far more rapid.

It was expected at this point that subsequent steps would either require a separation of isomers or have to be conducted on a mixture of substrates. However, only one product was isolated and corresponds to (±)-stereoisomer **4** in which, according to the NMR spectrum, all substituents show equatorial orientations, i.e., the methyl groups are cis to one another. Examination of the mother liquors does not reveal the presence of another epimeric product. This serendipitous result was particularly encouraging

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