Pergamon

Tetrahedron 54 (1998) 15371–15384

TETRAHEDRON

Chemoselectivity and Stereoselectivity in the Condensation Reactions of 4,4'-Diethyl-2,2'-perhydrobipyrimidine

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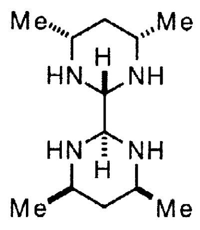
Received 25 August 1998; revised 2 October 1998; accepted 14 October 1998

Abstract. *Rac* 1,3-pentanediamine reacts with glyoxal to give a 1:1 mixture of diastereomers from which can be isolated (2*R**,2'*S**,4*S**,4'*R**)-4,4'-diethylperhydro-2,2'-bipyrimidine. Subsequent treatment with HCHO, MeCHO, EtCHO, and *i*-PrCHO gives *cis* and to a lesser extent *trans* fused 1:1 condensation products, which are 4a,4b-*cis*-3,6-diethylperhydro-4,5,8a,9a-tetraazafluorene and 4a,4b-*trans*-1,6-diethylperhydro-4,5,8a,9a-tetraazafluorene derivatives, or tetracyclic *cis* fused 1:2 condensation products, 8b,8c-*cis*-3,5-diethylperhydro-3a,4a,7a,8a-tetraazacyclopentano[def]-fluorenes, respectively, depending on conditions. 2-Phenylacetaldehyde reacts to give *cis* and *trans* 2-benzyl-4-ethylhexahydropyrimidine. The effects of aldehyde and solvent upon the outcome are discussed. © 1998 Elsevier Science Ltd. All rights reserved.

The study of highly reduced nitrogen heterocycles obtained through amine-aldehyde condensations continues to attract attention.[1] One of the challenges in the synthetic field is to be able to control the regiochemical and stereochemical outcome of these condensation reactions. Since many of the products contain aminal or amino ether groups that can readily lead to tautomerism and or rearrangement, the products are often found to be the result of thermodynamic control, although sometimes stunning in their complexity.[2-4] However, some form of kinetic control, either steric or electronic, is frequently desirable. In this context, we had developed[5,6] syntheses of two parallel series of stable, rigid, diastereomeric *trans*-tetraazafluorene ligands from perhydrobipyrimidines and sought access to the corresponding, less stable *cis* isomers, for comparison.

We have previously reported the synthesis and crystal structures of compounds **1** and **2** as part of a general program of research into the synthesis, stereochemistry and reactivity of nitrogen heterocycles derived from perhydrobipyrimidines.[7] Perhydrobipyrimidines, including **1**, react in a general way with aldehydes to yield *trans* tricycles whose structures have been dealt with in detail.[5,6] Compound **1** was found to require significantly higher temperatures than other compounds of its type in order to react with HCHO.[6] This observation led us to suspect that compound **2** and its congeners, the chemistry of which has not been investigated, might react with aldehydes in a slightly different way. In particular, we were intrigued by the possibility that the less sterically encumbered nitrogens of **2** might react regioselectively to yield the normally inaccessible *cis* tricycles. Preliminary experiments with **2** suggested that this might be the case but limited amounts of **2** made further studies impracticable.

PII: S0040-4020(98)00961-2



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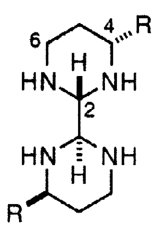
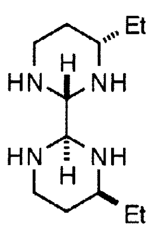


2 R = Me
3 R = Et



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In this paper, the synthesis of compound **3**, a more readily accessible homologue of **2**, and its condensation with a range of aldehydes are reported.

RESULTS AND DISCUSSION

Following established methods,[7] the condensation of 1,3-pentanediamine with glyoxal proceeded smoothly to give equal amounts of two diastereomeric 2,2'-perhydrobipyrimidines **3** and **4** in up to 95% yield. The isomers were evident in the ^{1}H NMR spectrum of the mixture through the appearance of two singlets at δ 3.48 and 3.49 and two partially overlapping multiplets at δ 2.74 and 2.76 due to the H2 and $H_{ax}6$ protons respectively. Fractional crystallization of the mixture from light petroleum gave a pure sample of the *meso* isomer **3** in 12% overall yield. The configuration of tetraamine **3** was assigned on the basis of ^{1}H and ^{13}C NMR chemical shift comparisons with those of compound **2**.

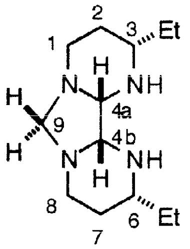
Reactions of tetramine 3 with HCHO

The *meso* compound **3** was treated with 1 mol equiv of aqueous HCHO (formalin) in MeOH under conditions adopted previously for the condensation of perhydrobipyrimidines with aldehydes.[6] The reaction gave relatively clean conversion of **3** into the oily, symmetrical *cis* tricycle **5** (*m/z* 238) in 37% yield after distillation. The *cis* geometry of the compound was evident from the non-equivalence of its C9 methylene proton signals (δ (C_6D_6) 3.47 and 3.66), signals that correlated with the C9 carbon-13 signal at δ 71.1, and equivalence of its bridgehead protons H4a and H4b (δ 3.79), a signal that correlated with the C4a and C4b carbon-13 signal at δ 77.1 (see Tables 2 and 3). The number of proton and carbon-13 NMR signals clearly pointed to a symmetrical structure but was insufficient evidence to rule out the less likely but mechanistically feasible *cis* tricycle **6**. Analysis of the NOESY spectrum in deuterobenzene, especially correlations between signals at δ 2.59 ($H_{ax}1$) and 3.47 (H9) and those at 3.47 (H9) and 3.79 (H4a/H4b), which could only have arisen from isomer **5**, allowed the position of the methylene bridge away from the two ethyl substituents to be established unambiguously. These correlations also assisted in the assignment of the signal at δ 3.47 to the proton *cis* to the bridgehead, namely $H_\beta 9$.

None of the *trans* isomer **7** could be clearly identified from analysis of the ^{1}H NMR spectrum of the crude reaction product although about 10% of a substance that might have been **7** (methylene doublets at δ 3.44 and 3.70 and bridgehead doublets at δ 3.82 and 4.01) and traces of tetracyclic products, *e.g.* **8** and **9** (δ 4.75-4.86 in the region expected for tetracyclic signals from H8b and H8c) were evident.

Treatment of the *meso* compound **3** with 4 mol equivalents of formalin (aqueous formaldehyde) in MeOH gave a roughly equal mixture of two tetracycles, **8** and possibly **9**, in 60% yield, from which compound **8** was isolated by chromatography in 20% yield. The ^1H and ^{13}C NMR spectra (see Experimental) of the isolated product were consistent with a tetracycle bearing a single plane of symmetry. Most telling were the appearance in C_6D_6 solution of only eight carbon-13 signals and two pairs of mutually coupled doublets at δ 3.76 and 3.78 for non-equivalent $H_\alpha 4$ and $H_\beta 4$, and δ 3.83 and 3.98 for non-equivalent $H_\beta 8$ and $H_\alpha 8$ nuclei. The second product could not be isolated pure but it gave in its ^1H NMR spectrum a pair of doublets (δ (C_6D_6) 4.77 and 4.83, J 4.5 Hz) in the region expected for signals from H8b and H8c. These indicated that the product contained unlike hexahydropyrimidine rings and was likely to be tetracycle **9**, a structure reminiscent of the unsymmetrical tetracycles reported in earlier work.[6,8]

The condensation of compound **3** with formalin was strongly influenced by solvent. In order to obtain a direct comparison of the results, reactions were performed in solvents of increasing polarity for one hour and at room temperature, and the reaction workup was modified to include only removal of volatile material at room temperature under rotary pump vacuum. The extent of reaction was estimated by measuring the mass recovery and the composition was determined from the ^1H NMR spectra of the crude products. In most cases a complex mixture of tricyclic and tetracyclic compounds was evident (Table 1).



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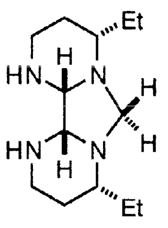

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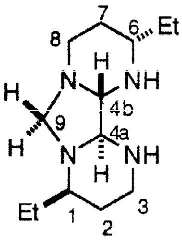

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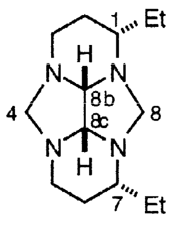

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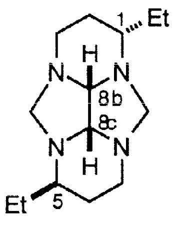

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Table 1. Product ratios and yields from reactions between tetramine **3** and formalin in various solvents.

Solvent	Tricycle/Tetracycle **5+7/8+9**	*cis/trans*-Tricycle **5/7**	Mass Recovery[a] %
toluene	88:12	81:19	94
diethyl ether	95:5	73:27	98
THF	95:5	40:60	99
MeCN	94:6	33:67	95
MeOH	85:15	90:10	98

[a] Percentage of product mass divided by the total mass of amine plus aldehyde used.

As shown in Table 1, the ratio of *cis* tricycle **5** to what was believed to be *trans* tricycle **7** showed considerable variation. The ratio did not follow any consistent trend with solvent polarity, but instead was highest in MeOH (90:10) and lowest in MeCN (33:67). Of possible significance, the trend was inversely proportional to the ratio of total tricycle to total tetracycle.

Table 2. ^{1}H NMR data for 9-R substituted 4a,4b-*cis*-3,6-diethyl-4,5,8a,9a-tetraazafluorenes

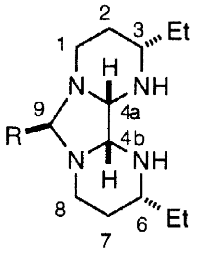
Atom	**5** (R = H)		**10** (R = Me)	**11** (R = Et)	**12** (R = *i*-Pr)
	($CDCl_3$)	(C_6D_6)	($CDCl_3$)	($CDCl_3$)	($CDCl_3$)
$H_{ax}1$	2.70, ddd, 12.3, 12.3, 3.1	2.59, ddd, 12.3, 12.3, 3.6	2.88, ddd, 12.5, 11.8, 3.1	2.86, ddd, 12.6, 12.1, 3.1	2.91, ddd, 12.6, 11.5, 3.3
$H_{eq}1$	2.96, ddd, 12.4, 4.2, 1.9	2.80, ddd, 12.6, 4.4, 2.6	2.97, ddd, 12.8, 5.1, 2.3	2.96, ddd, 12.6, 4.6, 2.6	3.01, ddd, 12.6, 4.9, 2.6
$H_{ax}2$	1.13-1.30, m	0.95-1.20, m	1.15-1.30, m	1.16, ddd, 12.0, 11.5, 11.5, 4.6	
$H_{eq}2$	1.35-1.50, m		1.40-1.60, m	1.37-1.50, m	
H3	2.46, m	2.34, m	2.48, m	2.41, m	2.60, m
H4a	3.30, s	3.79, s	3.89, s	3.84, s	3.94, s
$H_\alpha 9$	3.67, d, 4.0	3.66, d, 3.6	4.10, q, 5.7	3.82, t, *c* 6.5	3.82, d, 2.0
$H_\beta 9$	3.48, d, 4.0	3.47, d, 3.6	—	—	—
Other	—	—	1.05, d, 5.9, 9-CH_3	0.86, t, 7.4, 9-$CH_2C\underline{H}_3$ 0.87, t, 7.7, 3/6-$CH_2C\underline{H}_3$ 1.13, m, 3-$C\underline{H}_aH_bCH_3$ 1.37-1.50, m	1.84, sept, 6.9, 2.6

Table 3. ^{13}C NMR data for 9-R substituted 4a,4b-*cis*-3,6-diethyl-4,5,8a,9a-tetraazafluorenes

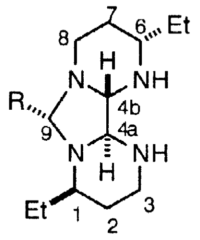
Atom	**5** (R = H) (C_6D_6) ($^1J_{C-H}$)	**10** (R = Me) ($CDCl_3$)	**11** (R = Et) ($CDCl_3$) ($^1J_{C-H}$)	**12** (R = *i*-Pr) ($CDCl_3$)
C1	48.9	44.9	45.4	45.6
C2	31.3	29.9	30.1	30.0
C3	56.6 (131)	56.2	55.9 (129.0)	55.8
C4a	77.1 (150)	74.5	74.3 (149.6)	74.1
C9	71.1	71.9	77.0 (143.8)	79.8
Other	11.4, $CH_2\underline{C}H_3$ 31.1, $\underline{C}H_2CH_3$	10.4, $CH_2\underline{C}H_3$ 17.1, 9-$\underline{C}H_3$ 29.9, $\underline{C}H_2CH_3$	10.3, 3- and 6-$CH_2\underline{C}H_3$ 10.5, 9-$CH_2\underline{C}H_3$ 25.6, 9-$\underline{C}H_2CH_3$ 29.9, 3- and 6-$\underline{C}H_2CH_3$	10.3, $CH_2\underline{C}H_3$ 19.1, 9-$CH(\underline{C}H_3)_2$ 30.3, 3- and 6-$\underline{C}H_2CH_3$ 32.0, 9-$\underline{C}H(CH_3)_2$

Reactions of tetramine 3 with aldehydes other than HCHO

The study was next extended to condensations of tetramine **3** with one mol equivalent of MeCHO, EtCHO and *i*-PrCHO, respectively, in MeOH for 1 h. Workup through solvent evaporation and vacuum distillation gave near quantitative yields of tricyclic compounds admixed with some tetramine **3** and with traces of tetracyclic material (Table 4). In each case efforts were made to separate the more crystalline *trans* tricycles, which appeared essentially as one isomer, by fractional crystallization and the *cis* isomers by repetitive distillation of the crystallization residues, in order to complete characterization; substantial losses were incurred during purification.



10 R = Me
11 R = Et
12 R = *i*-Pr



13 R = Me
14 R = Et
15 R = *i*-Pr

Table 4. Summary of tricycle yields from reactions of tetramine **3** with aldehydes in methanol

Reactant aldehyde	Tricycle Ratio (*cis*/*trans*)	Isolated Products (Yields %) *cis*	*trans*
HCHO	90:10	**5** (37)	**7** (–)
MeCHO	65:35	**10** (30)	**13** (15)
EtCHO	47:53	**11** (48)	**14** (3)
*i*PrCHO	35:65	**12** (–)	**15** (2)

The structures of *cis* tricycles **10-12** were readily assigned by comparing chemical shift and spin coupling data with values for compound **5** (Tables 2 and 3). In contrast, the detailed structures of the isomeric *trans* tricycles **13-15** and their parent, **7**, were more difficult to determine.

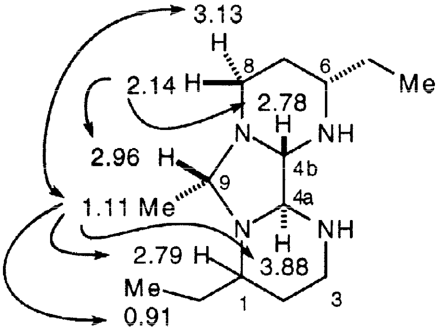


Figure 1. Selected NOESY correlations for *trans*-tricycle **13**

The *trans* nature of the tricycles was evident from the appearance of mutually spin-coupled pairs of doublets for H4a and H4b in their ^1H NMR spectra (Table 5). Moreover, the magnitude of the spin couplings (6.4-8.5 Hz) were fully in accord with *trans* protons and significantly larger than values expected for *cis* protons (4-5 Hz).[9] The location of the ethyl substituents at positions 1 and 6 on the tricycles was established by NOESY correlation experiments that revealed associations between the methyl and hydrogen at C9 with one ethyl group and one set of neighbouring methylene protons, as illustrated for compound **13** in Figure 1. Furthermore, the ethyl group at position 6 in **13** was equatorial since the methine proton H6 showed distinct axial-axial and axial-equatorial spin coupling, *J* 14 and 7 Hz, respectively, to its neighbours at C7. Similarly, the C9-methyl signal correlated with the bridgehead proton signal at δ 3.88 and not the signal at δ 2.78. This identified the signal at δ 3.88 as coming from H4a and demonstrated that the C9-methyl group resided away from and therefore *trans* to H4b.

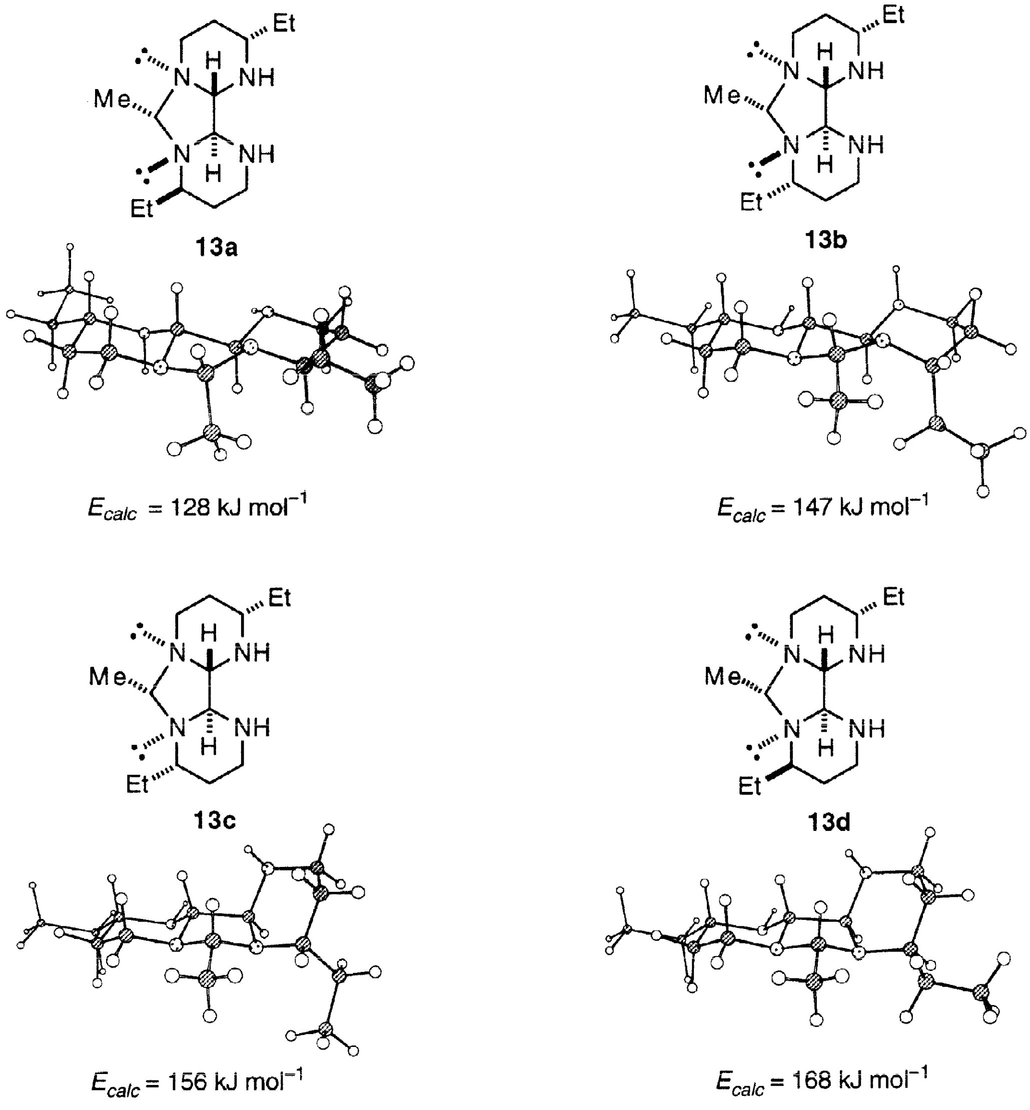
Table 5. ^1H NMR data for 9-R substituted 4a,4b-*trans*-3,6-diethyl-4,5,8a,9a-tetraazafluorenes

Atom	**13** (R = Me) ($CDCl_3$)	**14** (R = Et) ($CDCl_3$)	**15** (R = *i*-Pr) ($CDCl_3$)
$H_{ax}1$	2.79, m	2.74, ddd, 9.5, 7.2, 6.5	2.59, m
$H_{ax}2$	1.30, m	1.24-1.42, m	1.15-1.42, m
$H_{eq}2$	1.89, dddd, 13.1, 8.0, 5.1, 3.0	1.82, dddd, 13.1, 6.2, 4.9, 3.1	1.40-1.70, m
$H_{ax}3$	2.42, ddd, 11.0, 11.0, 3.1	2.52, ddd, 11.5, 11.3, 2.8	2.64, ddd, 12.0, 11.0, 3.1
$H_{eq}3$	2.97, m	2.98, ddd, 11.0, 4.1, 4.1	2.93, ddd, 11.0, 3.8, 3.6
H4a	3.88, d, 6.4	3.83, d, 7.2	3.70, d, 8.5
H4b	2.78, d, 6.7	2.97, d, 7.2	3.29, d, 8.5
H6	2.49, dddd, *c* 14, *c* 7, *c* 6, 3.0	2.47, m	2.42, m
$H_{ax}7$	1.30, m	1.24-1.42, m	1.15-1.42, m
$H_{eq}7$	1.63, m	1.64, dddd, 13.1, 3.0, 2.8, 2.6	1.40-1.70, m
$H_{ax}8$	2.14, ddd, 11.5, 10.5, 2.8	2.22, ddd, 11.8, 10.8, 3.1	2.31, ddd, 11.8, 10.8, 2.8
$H_{eq}8$	3.13, ddd, 10.5, 4.6, 2.3	3.12, ddd, 10.5, 4.9, 2.3	3.09, ddd, 10.5, 4.6, 2.3
H9	2.96, q, 5.4	2.91, dd, 4.9, 3.6	2.77, d, 4.4
Other	1.11, d, 5.4 0.88, t, 7.2 0.91, t, 7.4	0.90, t, 7.4 0.91, t, 7.4 0.92, t, 7.4	0.89, t, 7.4 0.905, d, 6.9 0.910, d, 6.9 0.910, t, 7.4

Table 6. ^{13}C NMR data for 9-R substituted 4a,4b-*trans*-3,6-diethyl-4,5,8a,9a-tetraazafluorenes

Atom	**13** (R = Me) ($CDCl_3$) ($^1J_{C-H}$)	**14** (R = Et) ($CDCl_3$) ($^1J_{C-H}$)	**15** (R = *i*-Pr) ($CDCl_3$) ($^1J_{C-H}$)
C1	51.5 (134)	51.4	51.2
C2	28.5	29.0	29.3
C3	42.1	45.3	50.4 (133)
C4a	70.7 (156)	71.5 (155)	73.3 (150)
C4b	83.1 (137)	83.4 (134)	88.7 (138)
C6	57.2 (134)	57.2 (132)	57.3 (129)
C7	31.4	31.6	32.3
C8	47.5	48.3	50.9
C9	77.4 (134)	80.2 (136.6)	75.6 (133.2)
Other	10.4, $CH_2\underline{C}H_3$ 10.7, $CH_2\underline{C}H_3$ 17.1, 9-$\underline{C}H_3$ 28.9, $\underline{C}H_2CH_3$ 29.3, $\underline{C}H_2CH_3$	9.0, 9-$CH_2\underline{C}H_3$ 10.5, $CH_2\underline{C}H_3$ 10.6, $CH_2\underline{C}H_3$ 25.0, 9-$\underline{C}H_2CH_3$ 29.4, 2x$\underline{C}H_2CH_3$	10.3, 1- or 6-$CH_2\underline{C}H_3$ 10.5, 1- or 6-$CH_2\underline{C}H_3$ 17.6, 9-$CH(\underline{C}H_3)_2$ 18.9, 9-$CH(\underline{C}H_3)_2$ 29.5, 1- or 6-$\underline{C}H_2CH_3$ 30.8, 1- or 6-$\underline{C}H_2CH_3$ 32.1, 9-$\underline{C}H(CH_3)_2$

The configuration of the second ethyl substituent in **13** and its congeners was much more difficult to assign. In each case the spin coupling pattern of the H1 signal could not be deciphered because of severe overlap of the H1 and H2 signals with each other and with nearby other resonances. However, significant NOESY correlations between the 9-methyl signal and that for H1 and the methyl group of the 1-ethyl substituent of **10** (Fig. 1) indicated that the peripheral 9-methyl group was close in space to both H1 and the 1-ethyl group. This arrangement is most consistent with structures **13a** and **13d** of the four possible configurational isomers **13a-13d** although only **13a** and **13c** retain the relative configuration of stereogenic centres associated with the original perhydrobipyrimidine **3**.



13a

E_{calc} = 128 kJ mol^{-1}

13b

E_{calc} = 147 kJ mol^{-1}

13c

E_{calc} = 156 kJ mol^{-1}

13d

E_{calc} = 168 kJ mol^{-1}

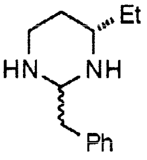
Figure 2. Conformational minima of configurational isomers **13a-13d** and their total steric energies as calculated using MacroModel BatchMin Version 4.5[11]

In previous studies, the one-bond spin couplings between the protons and carbons at bridgehead positions 4a and 4b were found to be extremely useful in establishing the nitrogen configurations of such heterocycles in solution.[8,10] Accordingly, the relevant C4a, C4b and C9 signals from *trans* tricycles **13-15** were identified and their $^1J_{C-H}$ measured (Table 6). The C4b signals consistently gave relatively small one-bond coupling constants that were in accord with an antiperiplanar arrangement of H4b and non-bonded electrons on N8a. Much larger $^1J_{C-H}$ values for the C4a signal, similar to the values for the corresponding carbons of *cis* tricycles **5** and **11** (Table 3), were observed. The higher values could be explained by a nearly eclipsed arrangement of H4a and the adjacent tertiary nitrogen lone pair of electrons, as found when these groups are *cis*, as in **13c** and **13d**. However, molecular mechanics calculations[11] do not support such structures and reveal that configurations **13b** - **13d** have much higher steric energy than **13a** (Fig. 2).

Tricycles **13-15** were therefore assigned structures similar to **13a** in which the relative configuration of substituents in the perhydrobipyrimidine-derived portion is retained. This does not account for the disparate C–H couplings of C4a and C4b; the unexpectedly high $^1J_{C-H}$ values for C4a remain anomolous and will be the subject of further investigation.

Reaction of tetramine 3 with PhCH₂CHO

When the tetramine **3** was treated in MeOH with one equivalent of $PhCH_2CHO$, the reaction took a different course and gave a stereoisomeric mixture of 2-benzyl-3-ethyltetrahydropyrimidines **16**, a result that was reproducible and confirmed by unambiguous synthesis of **16** from 1,3-pentanediamine and $PhCH_2CHO$.



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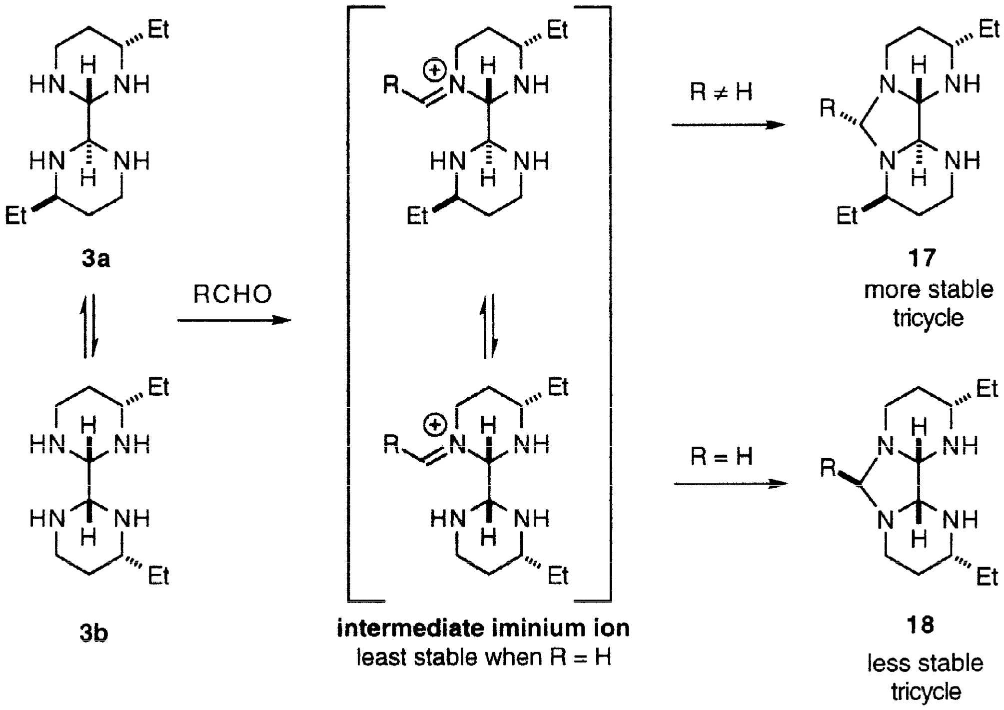
There are two possible pathways for formation of tricycles from tetramine **3** (Scheme 1). Condensation of the *trans*-like or *cis*-like conformers **3a** or **3b** through their less hindered nitrogens should provide intermediates that can cyclise to tricycles **17** or **18**. Clearly HCHO is capable of following the latter path, but as the size of the aldehyde increases the preference for the *cis* tricycle remains static or decreases. Size and steric bulk therefore must not be an important control factor in tricycle formation. It is also known from previous experiments that the *trans* tricycles are normally formed in larger amount than the corresponding *cis* tricycles. One could then assume that the *trans* tricycles are more stable than their *cis* counterparts, and this conclusion is supported by molecular mechanics calculations. The observed selectivity in this study must therefore arise from the stability of the ionic intermediate.

A distinct solvent effect was noted in the condensations with HCHO (Table 1), which was consistent with the involvement of a cationic intermediate. Unfortunately, interpretation of the effect was complicated by the fact that aqueous HCHO (40% formalin) was used in the reactions. However in no case, not even in toluene or ether solvents, were two distinct phases observed. No attempt was made to remove the water since the reactions themselves generate one mole equivalent of water.

In condensations with HCHO, the iminium ion has little stabilisation available to it and the subsequent cyclisation is expected to be relatively fast and irreversible over a short period of time. Hence ring closure takes place on the second less hindered nitrogen and the less stable *cis* tricycle is formed. With the higher aldehydes, the additional alkyl groups provide stability to the intermediate iminium ion and the ring closure is likely to occur more slowly, and perhaps reversibly (see later). Similar iminium ion stabilisation has been proposed to rationalise ring chain tautomerism observed in 2-aryl-1,3-diazolidines.[12] The latter, slower process must involve selective ring closure on to the more hindered nitrogen of the second ring thereby providing a route to the more stable *trans* tricycles. Thus a kinetic pathway appears to be followed in the condensation with HCHO.

The unusual behaviour of $PhCH_2CHO$ can similarly be explained if the intermediate iminium ion from initial condensation were to lose a proton. The resulting enamine, which would be much longer lived than intermediates from the other aldehydes, could therefore permit loss of the central carbons of the heterocycle as glyoxal.



Scheme 1

In support of this mechanistic picture, the relative configuration of the ethyl substituents in the *trans* tricycles **17** remains the same as that in perhydrobipyrimidine **3**. This contrasts with observations of reactions between HCHO and related, substituted perhydrobipyrimidines in which isomerism was demonstrated to occur, at least in part, through inversion of configuration at C4a or C4b by opening and reclosing of the respective hexahydropyrimidine rings.[6] Absence of the latter pathway in reactions of **3** is supportive of a charged intermediate, such as in Scheme 1, which is relatively stable when R ≠ H. Also, the fact that only one configurational isomer was observed at C9, in the presence of configurational stability in the hexahydropyrimidine rings, indicates the presence of a reversible process during product formation. Alkyl substitution at C9, through stabilisation of the ring-opened intermediate, should decrease the inherent kinetic stability of the 1,3-diazolidine ring system and thereby account for this observation.

Future studies will focus on the condensation reactions of racemic and homochiral analogues of **3**.

ACKNOWLEDGEMENTS

This work was supported by a grant from the Australian Research Council for which the autho grateful. Assistance by Ms T.K. O'Leary in the initial preparation of tetramine **3** is gratefully acknowled

EXPERIMENTAL SECTION

General Methods. The general methods described in this paper were essentially those describ reference 5. Force-field energy minimisation studies were performed using the MacroModel Batc version 4.5 molecular modelling computer program[11] with its MM2 basis set.

Condensation of rac-*1,3-Diaminopentane with Glyoxal*

Aqueous glyoxal (23.5 mL of 40%, 0.20 mol) was added dropwise to a stirred solution of racemi diaminopentane (41.0 g, 0.40 mol) in EtOH (200 mL) at 0 °C over 20 min. The mixture was heated on a s bath (80-82 °C) for 3.5 h and then cooled and refrigerated overnight. Crystals were not deposited, but rotary evaporation of the solvent the residue became semi-solid (53.2 g, 95%). Recrystallization of the re from light petroleum afforded *(2*R**,2'*S**,4*S**,4'*R**)-4,4'-diethyl-2,2'-perhydrobipyrimidine* **3** as white p (5.42 g, 12%) m.p. 75-76°C (Found: C, 63.80; H, 11.68; N, 24.82. $C_{12}H_{26}N_4$ requires C, 63.68; H, 11.5 24.75%). ν_{max} (Nujol): 3380, 3320, 3310, 3250, 3170, 2950, 2910, 2850, 2802, 2710, 2170, 1645, 1455, 1345, 1180, 1095, 1058, 1035, 975, 918, 865, 830, 810, 645, 605 cm^{-1}. ^1H NMR δ ($CDCl_3$) (300 MHz): t, J 7.7 Hz, $CH_2C\underline{H}_3$; 1.17, m, $H_{ax}5$; 1.42, m, $C\underline{H}_a\underline{H}_bCH_3$; 1.60, br d, *J ca.* 13.3Hz, $H_{eq}5$; 1.90, br s, 2.59, m, $H_{ax}4$; 2.74, ddd, *J* 13.2, 12.6, 3.0 Hz, $H_{ax}6$; 3.20, ddd, *J* 13.3, 5.0, 1.7 Hz, $H_{eq}6$; 3.48, s, H2 NMR δ ($CDCl_3$) (75.6 MHz): 9.6, $CH_2\underline{C}H_3$; 29.8, $\underline{C}H_2CH_3$; 32.9, C5; 45.1, C6; 56.9, C4; 74.2, C2. spectrum: *m/z* 227 (M+1, 0.7%), 226 (M^+, 0.3), 225 (0.3), 149 (11), 113 (100), 83 (21), 69 (36).

Condensation Reactions of Perhydrobipyrimidine ***3***

(a) With 1 mol equiv of HCHO in MeOH Aqueous HCHO (0.38 mL of 40%, 5.1 mmol) was slowly to a stirred, ice-cooled solution of perhydrobipyrimidine **3** (1.13 g, 5.0 mmol) in MeOH (8 mL) bath was removed and stirring was continued at ambient temperature for 1 h. The solvent was evapora *vacuo* at room temperature, and the residue was Kugelrohr distilled twice to give *(3*S**,4a*S**,4b*R**,6*R**)-* cis-*3,6-diethyl-4,5,8a,9a-tetraazafluorene* **5** as a hygroscopic, colourless oil (0.44 g, 37%) b.p. 155°C/0. (Found: C, 63.20; H, 11.23; N, 22.94. $C_{13}H_{26}N_4{\bullet}0.5H_2O$[13] requires: C, 63.16; H, 10.93; N, 22.67%; F *m/z* 238.2120, 3%, $C_{13}H_{26}N_4$ requires: 238.2157). ν_{max} (film): 3400 br, 3290, 2960, 2930, 2860, 2800, 1660 br, 1465, 1450, 1430, 1380, 1340, 1265, 1215, 1175, 1140, 1090, 980, 895, 795, 745, 610 cm NMR see Table 2. ^{13}C NMR see Table 3. Mass spectrum: *m/z* 238 (M^+, 3%), 237 (2), 152 (3), 126 (76 (100), 97 (25), 69 (21). High resolution mass spectrum: Found: *m/z* 237.2084, 15%, $C_{13}H_{25}N_4$ req 237.2079; Found: *m/z* 221.1776, 3%, $C_{12}H_{21}N_4$ requires: 221.1766; Found: *m/z* 126.1142, 55%, C_7H

requires: 126.1157; Found: *m/z* 113.1078, 100%, $C_6H_{13}N_2$ requires: 113.1079; Found: *m/z* 98.0843, 8%, $C_5H_{10}N_2$ requires: 98.0844; Found: *m/z* 97.0766, 8.5%, $C_5H_9N_2$ requires: 97.0766.

NMR spectroscopic assignments were confirmed by H-H COSY, C-H correlation and NOESY experiments.

(b) With 4 mol equiv of HCHO in MeOH Aqueous HCHO (1.32 mL of 40%, 17.6 mmol) was added dropwise to a stirred ice-cooled solution of perhydrobipyrimidine **3** (1.00 g, 4.4 mmol) in MeOH (50 mL) The cooling bath was removed and the mixture was kept at ambient temperature for 3.5 h. Removal of the solvent by rotary evaporation at room temperature gave a pale yellow oil (0.9 g) which failed to crystallize from light petroleum. The mixture was chromatographed on silica gel and the fraction eluted with 1:1 of EtOAc/MeOH gave *8b,8c-*cis*-1,7-diethylperhydro-3a,4a,7a,8a-tetraazacyclopentano[*def*]fluorene* **8** as hygroscopic, white plates (0.22 g, 20%) m.p. 93-94°C (Found: C, 66.31; H, 10.00; N, 22.15. $C_{14}H_{26}N_4 \cdot 0.2H_2O$[13] requires: C, 66.21; H, 10.48; N, 22.06%; Found: *m/z* 251.2225, $C_{14}H_{27}N_4$ (M+1) requires 251.2236). ν_{max} (Nujol): 2950, 2920, 2840, 2680, 1455, 1375, 1185, 1150, 1085, 885, 650 cm^{-1}. ^1H NMR δ ($CDCl_3$): 0.97, t, *J* 7.4 Hz, $CH_2C\underline{H}_3$; 1.02, dddd, *J* 13.3, 4.1, 2.7, 2.6 Hz, $H_{eq}2$ and $H_{eq}6$; 1.39, m, $C\underline{H}_aH_bCH_3$; 1.51, m, $CH_a\underline{H}_bCH_3$; 1.65, dddd, *J* 13.3, *ca* 13, 11.7, 6.5 Hz, $H_{ax}2$ and $H_{ax}6$; 3.00, m, Hl and H7; 3.20, dd, *J ca.* 10.5, 2.6 Hz, $H_{eq}3$ and $H_{eq}5$; 3.24, dd, *J ca.* 10.5, *ca.* 10.5, 2.6 Hz, $H_{ax}3$ and $H_{ax}5$; 3.61, br d, *J* 2.7 Hz, $H_{\alpha}4$; 3.63, br d, *J* 2.4 Hz, $H_{\beta}4$; 3.72, d, *J* 2.8 Hz, $H_{\beta}8$; 3.99, d, *J* 2.6 Hz, $H_{\alpha}8$; 4.77, s, H8b and H8c. ^1H NMR δ (C_6D_6): 0.79, dddd, *J* 13.1, *J ca.* 2.5, *ca.* 2.5, *ca.* 2.5 Hz, $H_{eq}2$ and $H_{eq}6$; 1.15, t, *J* 7.3 Hz, $CH_2C\underline{H}_3$; 1.38, 7 line multiplet, *J* 7.2 Hz, $C\underline{H}_aH_bCH_3$; 1.53-1.71, m, $CH_a\underline{H}_bCH_3$ and $H_{ax}2$ and $H_{ax}6$; 2.99, m, H1 and H7; 3.18, ddd, *J ca.* 13.5, 4.4, 2.1 Hz, $H_{eq}3$ and $H_{eq}5$; 3.28, ddd, *J ca.* 13.5, 12.3, 3.1 Hz, $H_{ax}3$ and $H_{ax}5$; 3.76, d, *J* 2.3 Hz, $H_{\alpha}4$; 3.78, br s, $H_{\beta}4$; 3.83, br s, $H_{\beta}8$; 3.98, d, *J* 1.9 Hz, $H_{\alpha}8$; 5.07, s, H8b and H8c. ^{13}C NMR δ ($CDCl_3$): 10.8, $CH_2\underline{C}H_3$; 19.7, C2 and C6; 27.7, $\underline{C}H_2CH_3$; 44.8, C3 and C5; 56.7, Cl and C7; 60.0, C8; 70.9, C5; 77.9, C8b and C8c. ^{13}C NMR δ (C_6D_6): 10.8, $CH_2\underline{C}H_3$; 19.7, C2 and C6; 27.8, $\underline{C}H_2CH_3$; 44.8, C3 and C5; 56.7, Cl and C7; 60.0, C8; 71.2, C5; 77.9, C8b and C8c. Mass spectrum: *m/z* 251 (M+l, 6%), 250 (M^+, 16), 249 (55), 221 (36), 192 (24), 165 (20), 152 (19), 123 (14), 98 (38), 81 (23), 69 (65), 56 (23), 41 (100).

NMR spectroscopic assignments were supported by H-H COSY and NOESY spectra in C_6D_6.

(c) With 1 mol equiv of other aldehydes in MeOH General procedure: Aldehyde (MeCHO, EtCHO, *i*-PrCHO, $PhCH_2CHO$, or PhC(Me)CHO) was added slowly to a stirred, ice-cooled solution of the perhydrobipyrimidine **3** in MeOH (7 mL per gram). The ice bath was removed and stirring was continued at ambient temperature for 1 h. The solvent was evaporated *in vacuo* at room temperature, and the residue was Kugelrohr distilled (normally twice) to give the *cis* perhydro-4,5,8a,9a-tetraazafluorene. Alternatively, the crude residue was dissolved in hexane and set aside whereupon the crystalline *trans* perhydro-4,5,8a,9a-tetraazafluorene separated. The sample was then recrystallized from the same solvent until pure.

(i) Perhydrobipyrimidine **3** (1.13 g, 5.0 mmol) and MeCHO (0.30 mL, 5.1 mmol) gave in approximately 95% isomeric purity *(3*R**,4a*R**,4b*S**,6*S**)-4a,4b-*cis*-9-methyl-3,6-diethyl-4,5,8a,9a-tetraazafluorene* ***10*** as a hygroscopic, colourless oil (0.38 g, 30%) b.p. 120°C/0.08 mm (Found: C, 64.76; H, 11.27; N, 21.68. $C_{14}H_{28}N_4 \cdot 0.4H_2O$[13] requires: C, 64.81; H, 11.11; N, 21.61%; Found: *m/z* 252.2285, 0.4%, $C_{14}H_{28}N_4$ requires: 252.2314). ν_{max} (film): 3400 br, 3300, 2980, 2940, 2860, 1650 br, 1460, 1430, 1380, 1325, 1180, 1115, 700 cm^{-1}. ^{1}H NMR see Table 2. ^{13}C NMR see Table 3. Mass spectrum: *m/z* 252 (M$^+$, trace), 251 (2%), 250 (8), 237 (19), 149 (5), 140 (25), 126 (8), 113 (100), 109 (9), 98 (9), 83 (14), 69 (16), 56 (20). High resolution mass spectrum: Found: *m/z* 251.2220, 2.8%, $C_{14}H_{27}N_4$ requires: 251.2236; Found: *m/z* 250.2207, 0.3%, $C_{14}H_{26}N_4$ requires: 250.2157; Found: *m/z* 249.2090, 1.7%, $C_{14}H_{25}N_4$ requires: 249.2079; Found: *m/z* 237.2078, 12%, $C_{13}H_{25}N_4$ requires: 237.2079; Found: *m/z* 140.1318, 100%, $C_8H_{16}N_2$ requires: 140.1313; Found: *m/z* 113.1070, 66%, $C_6H_{13}N_2$ requires: 113.1079.

The distillate gave (1R*,4aS*,4bS*,6S*)-4a,4b-trans-9-methyl-1,6-diethyl-4,5,8a,9a-tetraazafluorene **13** as hygroscopic, white needles (from hexane) (0.18 g, 15%) m.p. 60-61°C (Found: C, 66.00; H, 11.04; N, 22.36. $C_{14}H_{28}N_4{\bullet}0.1H_2O$[13] requires: C, 66.25; H, 11.12; N, 22.08%). ν_{max} (Nujol): 3295, 3225 br, 2980, 2940, 2860, 1700, 1465, 1380, 1255, 1190, 940, 830 cm^{-1}. ^{1}H NMR see Table 5. ^{13}C NMR see Table 6. Mass spectrum: *m/z* 252 (M$^+$, trace), 251 (1.5%), 237 (4.5), 208 (1.5), 140 (100), 113 (62), 98 (22), 83 (24), 69 (18), 58 (27), 56 (33).

NMR spectroscopic assignments were supported by H-H COSY, C-H correlation and NOESY experiments.

(ii) Perhydrobipyrimidine **3** (1.70 g, 7.5 mmol) and EtCHO (0.54 mL, 7.5 mmol) gave a 75:25 mixture of (3R*,4aR*,4bS*,6S*)-4a,4b-cis-3,6,9-triethyl-4,5,8a,9a-tetraazafluorene **11** and (1R*,4aS*,4bS*,6S*)-4a,4b-trans-1,6,9-triethyl-4,5,8a,9a-tetraazafluorene **14** as a pale yellow liquid (0.97 g, 48%) b.p. 150°C/0.1 mmHg which slowly solidified m.p. 44-46°C (Found: C, 67.63; H, 11.05; N, 21.28. $C_{15}H_{30}N_4$ requires C, 67.62; H, 11.35; N, 21.03%). ν_{max} (Nujol): 3330, 2970, 2930, 2860, 1460, 1425, 1335, 1270, 1260, 1180, 1125, 1095, 1000, 975, 930, 900, 810, 740 cm^{-1}. ^{1}H NMR (*cis* isomer): see Table 2. ^{13}C NMR (*cis* isomer): see Table 3. Mass spectrum: *m/z* 266 (M$^+$, absent), 265 (M–1, 1%), 237 (37), 180 (2), 154 (24), 139 (100), 122 (11), 113 (32), 95 (9), 83 (15), 69 (26), 56 (24), 41 (30). NMR spectroscopic assignments were supported by C–H correlation experiments.

The distillate gave (1R*,4aS*,4bS*,6S*)-4a,4b-trans-1,6,9-triethyl-4,5,8a,9a-tetraazafluorene **14** as hygroscopic white cubes (from hexane) (0.06 g, 3%) m.p. 44-46°C (Found: C, 66.62; H, 11.40; N, 20.86. $C_{15}H_{30}N_4{\bullet}0.2H_2O$ requires: C, 66.75; H, 11.28; N, 21.05%). ν_{max} (Nujol): 3260, 3235, 1690 (w), 1400, 1335, 1315, 1255, 1220, 1190, 1105, 1085, 1005, 920, 890 cm^{-1}. ^{1}H NMR see Table 5. ^{13}C NMR see Table 6. Mass spectrum: *m/z* 266 (M$^+$, trace), 265 (M-1, 1%), 237 (11), 154 (19), 139 (100), 113 (58), 97 (16), 69 (16).

NMR spectroscopic assignments were supported by DQF H-H COSY and NOESY experiments.

(iii) Perhydrobipyrimidine **3** (2.26 g, 10.0 mmol) and *i*-PrCHO (0.90 mL, 10.0 mmol) gave from distillation an equimolar mixture of (3R*,4aR*,4bS*,6S*)-4a,4b-cis-3,6-diethyl-9-(1-methylethyl)-4,5,8a,9a-tetraazafluorene **12** and (1R*,4aS*,4bS*,6S*)-4a,4b-trans-1,6-diethyl-9-(1-methylethyl)-4,5,8a,9a-tetraazafluorene **15** as a colourless oil (0.97 g, 35 %) b.p. 178°C/0.5 mmHg. ^{1}H NMR (*cis* isomer): see Table 2. ^{13}C NMR (*cis* isomer): see Table 3. Mass spectrum: *m/z* 280 (M$^+$, absent), 237 (81%), 216 (3), 172 (5), 168 (16), 153 (100), 150 (11), 122 (18), 113 (66), 98 (9), 95 (12), 83 (22), 69 (54), 58 (29), 56 (49), 41 (97).

The distillate gave a small amount of (1R*,4aS*,4bS*,6S*)-4a,4b-trans-1,6-diethyl-9-(1-methylethyl)-4,5,8a,9a-tetraazafluorene **15** as colourless crystals (0.13 g, 5%) m.p. 51-52°C (hexane) (Found: C, 68.78; H, 11.42; N, 19.92. $C_{16}H_{32}N_4$ requires C, 68.57; H, 11.50; N, 19.98%). ν_{max} (Nujol): 3270, 2790, 1455, 1410, 1370, 1355, 1300, 1275, 1255, 1215, 1185, 1095, 980, 820 cm^{-1}. ^{1}H NMR see Table 5. ^{13}C NMR see Table

6. Mass spectrum: *m/z* 280 (M^+, absent), 237 (16), 168 (31), 153 (100), 140 (4), 122 (3), 113 (28), 95 (4), 84 (7), 69 (10), 56 (7).

(iv) Perhydrobipyrimidine **3** (1.70 g, 7.5 mmol) and $PhCH_2CHO$ (0.90 mL, 7.5 mmol) gave after distillation a 2:1 mixture of *cis* and *trans* 2-benzyl-4-ethylhexahydropyrimidine **16** as a pale yellow oil[13] (0.68 g, 27 %) b.p. 170°C/0.6 mmHg (Found: *m/z* 205.1700. $C_{13}H_{21}N_2$ (M+1) requires *m/z* 205.1705). ν_{max} (film): 3280 (br), 3015 (w), 2930, 1670 (w), 1640 (w), 1605 (m), 1450, 1425, 1345, 1315, 1185, 1105, 750, 690 cm^{-1}. ^1H NMR δ ($CDCl_3$) (300 MHz) (*cis* isomer): 0.83, t, *J* 7.4 Hz, 4-$CH_2C\underline{H}_3$; 1.07, m, $H_{ax}5$; 1.26-1.46, m, **4-**$C\underline{H}_a\underline{H}_bCH_3$; 1.55, dm, *J* 12.8 Hz, $H_{eq}5$; 2.51, m, H4; 2.69, ddd, *J* 12.8, 12.8, 3.1 Hz, $H_{ax}6$; 2.76, d, *J* 6.4 Hz, 2-CH_2Ph; 3.12, dm, *J* 10.3 Hz, $H_{eq}6$; 3.67, t, *J* 6.4 Hz, H2; 7.15-7.35, m, ArH. δ (*trans* isomer): 0.88, t, *J* 7.4 Hz, 4-$CH_2C\underline{H}_3$; 1.05, m, $H_{ax}5$; 1.20-1.45, m, 4-$C\underline{H}_a\underline{H}_bCH_3$; *ca.* 1.55, dm, *J* 12.8 Hz, $H_{eq}5$; *ca.* 2.52, m, H4; 2.67, ddd, overlapped with signals from the major isomer, $H_{ax}6$; 3.13, m, $H_{eq}6$; signals for H2 and 2-CH_2Ph overlapped with other signals and could not be identified; 7.15-7.35, m, ArH. ^{13}C NMR δ ($CDCl_3$) (75.6 MHz) (*cis* isomer): 9.9, 4-$CH_2\underline{C}H_3$; 30.05, 4-$\underline{C}H_2CH_3$; 32.7, C5; 43.6, 2-$\underline{C}H_2Ph$; 45.7, C6; 57.4, C4; 72.4, C2; 126.6, Ar-C4; 128.6, Ar-C3 and Ar-C5; 129.4, Ar-C2 and Ar-C6; 137.7, Ar-C1. δ (*trans* isomer): 9.9, 4-$CH_2\underline{C}H_3$; 30.10, 4-$\underline{C}H_2CH_3$; 33.3, C5; 43.6, 2-CH_2Ph; 45.5, C6; 57.3, C4; 74.6, C2; 126.6, Ar-C4; 128.6, Ar-C3 and Ar-C5; 129.4, Ar-C2 and Ar-C6; 137.7, Ar-C1. Mass spectrum: *m/z* 204 (M^+, absent), 203 (M–1, 8%), 146 (6), 132 (12), 113 (100), 104 (3), 91 (36).

Condensation of $PhCH_2CHO$ *with* rac-*pentanediamine*

$PhCH_2CHO$ (2.29 mL 19.6 mmol) was added slowly to a stirred, ice-cooled solution of *rac*-1,3-pentanediamine (2.00 g, 19.6 mmol) in MeOH (15 mL). The cooling bath was removed and stirring was continued at ambient temperature for 1 h. The solvent was evaporated in vacuum at r.t., and the residue was Kugelrohr distilled to give *trans*-2-benzyl-4-ethylhexahydropyrimidine **16** as a colourless oil (3.65 g, 92%) b.p. 140°C/0.15 mmHg with identical NMR and mass spectroscopic properties with the *trans* isomeric product from above.

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13. The condensation products were generally very hygroscopic, and in most cases gave unsatisfactory results from elemental microanalysis, despite repeated analyses, without the addition of fractional amounts of water. Free water was not evident in the ^{1}H NMR spectra of the samples. Such observations of hygroscopicity, and even deliquescence, have been noted with these compounds previously.[5]