Reactions of Perhydro-2,2′-bipyrimidines with Carbonyl Compounds Bearing α-Carbonyl Functionality

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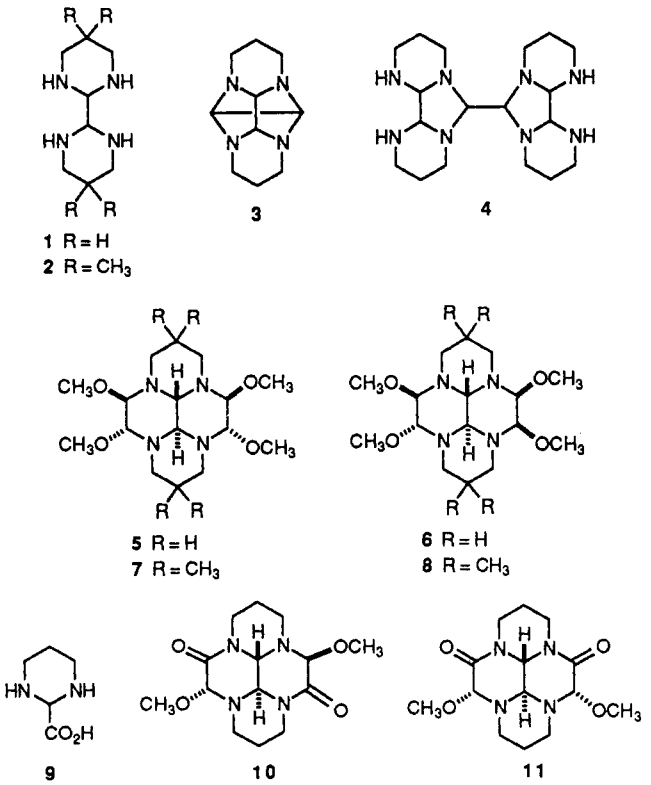
Treatment of perhydro-2,2′-bipyrimidine (1) with glyoxal, glyoxylic acid, and ethyl glyoxylate in MeOH yields 10b,10c-*trans*-4,5,9,10-tetramethoxyperhydro-3a,5a,8a,10a-tetraazapyrene (5), 1,3-diazacyclohexane-2-carboxylic acid (9) and 10b,10c-*trans*-5,10-dimethoxyperhydro-3a,5a,8a,10a-tetraazapyrene-4,9-dione (10), respectively, while similar treatment of 5,5,5′,5′-tetramethylperhydro-2,2′-bipyrimidine (2) with glyoxal gives an inseparable mixture of 10b,10c-*trans*-4,5,9,10-tetramethoxy-2,2,7,7-tetramethylperhydro-3a,5a,8a,10a-tetraazapyrene (7) and an isomeric substance and reaction with diethyl oxomalonate gives ethyl 4a,4b-*trans*-9-hydroxy-10-oxoperhydro-4,5,8a,10a-tetraazaphenanthrene-9-carboxylate (12) or an unequal mixture of diethyl 10b,10c-*trans*-4,9-dihydroxy-5,10-dioxoperhydro-3a,5a,8a,10a-tetraazapyrene-4,9-dicarboxylate (13) and diethyl 10b,10c-*trans*-4,10-dihydroxy-5,9-dioxoperhydro-3a,5a,8a,10a-tetraazapyrene-4,10-dicarboxylate (14), respectively, depending upon reaction conditions. The relative configuration of substituents in 5 is determined by NOE difference experiments, and the structure of 10 is confirmed by X-ray crystallography. Formation of these compounds represents a departure from the mode of condensation of perhydro-2,2′-bipyrimidines with simple aldehydes and ketones.

Introduction

The condensation of perhydro-2,2′-bipyrimidines, e.g. 1 or 2, with aliphatic aldehydes is an efficient, general route to tricyclic and tetracyclic tetraamines, namely, perhydro-4,5,8a,9a-tetraazafluorenes and perhydro-3a,4a,7a,8a-tetraazacyclopentano[*def*]fluorenes.[1-3] The reaction is analogous to the condensation of simple 1,2-, 1,3-, and 1,4-alkanediamines with aldehydes and ketones[4-8] in that it leads to the formation of new 1,3-cycloalkane diazine rings, in this case imidazolidine rings, exclusively. Our attention has turned recently to the design of new materials, especially rigid, nitrogen heterocyclic templates for use in metal complexation, that might be prepared through the condensation of perhydro-2,2′-bipyrimidines with dialdehydes, in particular with glyoxal. Jazwinski and Kolinski[10] have observed that perhydro-2,2′-bipyrimidine (1) undergoes condensation with glyoxal under reducing conditions with $NaBH_4$ to yield *trans*-perhydro-3a,5a,8a,10a-tetraazapyrene. Here glyoxal has taken a different course to that mentioned earlier. Reaction occurs in a "fusion" mode (each new ring that is formed contains both glyoxal carbons) rather than in a "bridging" mode (one or two new rings are formed, each containing only one of the glyoxal carbons). Ethane-1,2-diamine derivatives can behave similarly with glyoxal but the ratio of fusion to bridging products is dependent upon the nature of the nitrogen substituents.[11] In another context we have also discovered that tris(aminomethyl)ethane reacts with glyoxal, presumably through the intermediacy of a perhydrobipyrimidine, to give a caged heterocycle in which glyoxal has undergone a ring fusion reaction leading to new 1,4-pyridazine rings.[12] We were intrigued by the possibilities offered by this change in selectivity and wish to report in this paper that the formation of ring fusion



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products is a general phenomenon when reactions are carried out on perhydro-2,2′-bipyrimidines with a range of carbonyl compounds bearing α-carbonyl functionality.

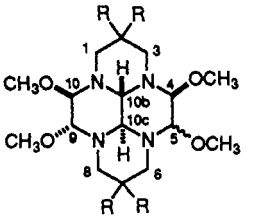
Results and Discussion

Our initial purpose in doing this work was to examine the possibility that caged or bridged heterocycles such as **3** or **4**, respectively, might be formed through the condensation of perhydro-2,2′-bipyrimidines with glyoxal. Thus, half an equivalent of glyoxal was made to react separately with perhydrobipyrimidines **1** and **2** in MeOH. The former reaction gave traces of highly insoluble crystalline material which appeared from its insolubility and broad NMR signals to be polymeric. Removal of solvent from the remainder gave a gummy residue which contained perhydrobipyrimidine **1** and one other distinguishable condensation product in the ratio 3:1 respectively. The second compound could not be identified because of the complexity of its ^{1}H NMR spectrum and the overlap of signals. It also decomposed upon attempted purification by extraction into petroleum ether. In contrast, the reaction with **2** gave a white precipitate, which was easily isolated by filtration from the MeOH solution. The solid was obtained in 15% yield based on **2**, and identified as a 1:1 mixture of tetramethoxylated tetracycles **7** and **8** (see later). The remaining soluble residue comprised mainly unreacted bipyrimidine **2**.

When 2 equiv of glyoxal were intentionally used and the mixture stirred overnight at ambient temperature in MeOH, bipyrimidine **1** gave a 70:30 mixture of tetramethoxy-substituted tetracycle **5** and an isomeric substance **6** as a white crystalline solid in 35% yield. Recrystallization of the solid twice from MeOH afforded the isomerically pure tetracycle **5**. The simplicity of its ^{13}C NMR spectrum (Table I) confirmed the high symmetry of **5** while the absence of dynamic behavior in the ^{1}H NMR spectrum at rt was taken as an indication that the hydrogens at its central ring junction were in a trans arrangement. Difference NOE experiments confirmed the all-axial arrangement of the methoxy groups and thereby demonstrated their configuration relative to the bridgehead protons (see Table II). Subtraction of the signals for **5** from the proton spectrum of the isomeric mixture did not allow the structure of the isomer to be assigned although distinct signals were visible, e.g. δ 3.40 (s, 3H), 3.42 (s, 3H), 3.43–3.47 (m, 3H), 3.75 (d, J = 7.5 Hz, 1H), 3.81 (d, J = 2.3 Hz, 1H), 3.85 (d, J = 2.3 Hz, 1H), 4.28 (dd, J = 11.4, 2.5 Hz, 1H). Notably, none of these signals could be correlated with the signals from the product of the earlier reaction with **1**. In contrast, the ^{13}C NMR spectroscopic data (Table I) were consistent with a diastereoisomeric structure which lacked symmetry. The most likely possibility was that of **6** in which the configuration of one methoxy group differed from that in **5**. Alternative structures in which the configuration of two methoxy groups differed would have contained a measurable degree of symmetry.

Treatment of bipyrimidine **2** with 2 equiv of glyoxal gave complete reaction within 4–6 h at ambient temperature. The product was again isolated as an isomeric mixture identical to that from reaction with 0.5 equiv of glyoxal, in 66% yield based upon **2**. Repeated crystallization from $CHCl_3$–MeOH gave no change in the isomer ratio although the melting point of the substance was increased. The mixture was remarkably insoluble in MeOH and attempted fractional crystallization from MeOH or from toluene gave products which were not pure and had quite different NMR spectra to those of the original mixture. The symmetrical tetracycle **7** was readily identified using ^{1}H and ^{13}C NMR data from the mixture by comparison with those of **5**. The remaining ^{1}H NMR signals from the mixture were again too complex to enable the isomer to be identified but those visible, δ 0.86, 0.87 (obscured) (2 × s, 3H each), 1.15, 1.16 (2 × s, 3H each), 2.25 (partially obscured d, J = 10.5 Hz, 1H), 2.56 (severely obscured d, J = 10.5 Hz, 1H), 2.60 (partially obscured dd, J = 10.7, 6.1 Hz, 1H), 3.35 (obscured), 3.36, 3.38, 3.39 (4 × s, 3H each), 3.38 (d, J = 7.2 Hz, 1H), 3.47 (br s, 2H), 3.48–3.50 (m, 2H), 3.67 (d, J = 7.6 Hz, 1H), 4.24 (dd, J =

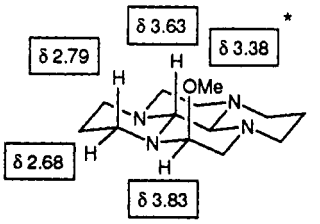
Table I. ^{13}C NMR Chemical Shift Data for Tetracycles 5–8 in $CDCl_3$



carbon[a]	5, R = H 5α-OMe	6, R = H 5β-OMe	7, R = Me 5α-OMe	8, R = Me 5β-OMe
1	48.05	48.29	59.65	59.83
2	24.26	24.26[b]	30.28	30.2
3	48.05	48.29	59.65	59.83
4	91.46	81.75	91.83	82.04
5	91.46	77.3	91.83	77.25
6	48.05	47.83	59.65	59.35
7	24.26	24.06	30.28	30.1
8	48.05	47.90	59.65	59.42
9	91.46	93.53	91.83	93.72
10	91.46	91.23	91.83	91.75
10b	68.74	68.98	67.16	67.82
10c	68.74	68.36	67.16	68.31
4-OMe	58.19	58.16[b]	57.55	57.44
5-OMe	58.19	58.58	57.55	58.04
9-OMe	58.19	57.96	57.55	57.94
10-OMe	58.19	58.16[b]	57.55	57.55[b]
2-eq-Me	–	–	24.54	24.42
2-ax-Me	–	–	26.57	26.73
7-eq-Me	–	–	24.54	24.10
7-ax-Me	–	–	26.57	26.73

[a] Numbering as shown in structural diagram. [b] Chemical shifts uncertain, signals obscured by those of symmetrical isomer.

Table II. NOE Difference Experiments Using Tetracycle 5



* three methoxy groups omitted for clarity

irr	obsd	% enhancement
3.38	2.79	1
	3.63	0.2
	3.83	5
3.63	2.68	1
	2.79	5
	3.38	4
	3.83	2
3.83	2.68	6
	2.79	0.5
	3.38	13
	3.63	1

11.4, 2.5 Hz, 1H), were reminiscent of those from **6**. The ^{13}C NMR spectrum (Table I) also showed signals consistent with a diastereoisomeric tetracyclic structure similar to **6**, with two different hexahydropyrimidine rings; therefore the isomer was tentatively assigned structure **8**.

From these results it appeared that the desired reactions to give compounds **3** or **4** had not taken place, and that there was a preference for condensation in a fusion mode with 2 equiv of glyoxal.

Reaction of perhydro-2,2'-bipyrimidine (**1**) in MeOH with 1 equiv of an analogous aldehydic component, glyoxylic acid, gave a single compound for which a satisfactory elemental analysis could not be obtained. The substance gave an infrared spectrum which showed a broad absorption at 3100–2300 cm^{-1} and a carbonyl stretch at 1628 cm^{-1}. The compound therefore contained the carboxylic acid group but it probably existed as a zwitterion with one of the amine groups of the heterocycle. The compound was not soluble in $CDCl_3$ but dissolved readily in D_2O. Its ^1H NMR spectrum showed four major signals (δ 1.79, m, 2H; 3.07, m, 2H; 3.35, dt, J = 13.3 Hz, J = 3.8 Hz, 2H; 4.40, s, 1H). The spectrum lacked the pair of doublets expected for the bridgehead protons and was not at all consistent with a tricyclic structure. It was in fact more in keeping with a hexahydropyrimidine ring, and this concept was supported by the ^{13}C NMR spectrum which showed only four signals (δ 23.33, 43.92, 76.67, and 172.44), the most deshielded of which corresponded to the carbon of a carboxylic acid. From this information the product was assigned structure **9**. This assignment was confirmed by comparison of the physical and spectroscopic properties of the substance with those of an authentic sample prepared from reaction of propane-1,3-diamine with glyoxylic acid. It appeared that the preferred reaction pathway was one of expulsion of the glyoxal-derived carbons from **1** rather than of tricyclic formation.

Treatment of perhydro-2,2'-bipyrimidine (**1**) with ethyl glyoxylate, in which there is an ester group adjacent to the aldehyde, was of interest especially in light of the results with glyoxylic acid.

Treatment of perhydrobipyrimidine **1** with 2 equiv of ethyl glyoxylate for 3.5 h in MeOH at 60–65 °C gave a low yield of the tetracycle **10** as a crystalline substance. The product after recrystallization was shown from elemental analysis and mass spectrometry (m/z 310) to have the molecular formula, $C_{14}H_{22}N_4O_4$. The ^1H NMR spectrum indicated that the ethoxy group of the ester had been lost. In place of its signals was a single methoxy resonance at δ 3.57 corresponding to six protons. The central bridgehead protons appeared as a singlet (δ 4.22, 2H) somewhat downfield of the normal position, while there was another singlet of equal intensity which appeared at δ 4.38. From the intensities of the signals and from the molecular formula, two molecules of ethyl glyoxylate must have reacted with **1**, but the methoxy signal occurred at lower chemical shift than expected for a methyl ester. The compound was therefore assigned structure **10** in which a mode of condensation similar to that with glyoxal had taken place. The symmetry of the molecule and its structural assignment were supported by the ^{13}C NMR spectrum which showed seven signals. An alternative structure **11**, in which there was a plane of symmetry, was easily ruled out since its bridgehead protons should have been nonequivalent thus giving rise to nine and not seven carbon signals.

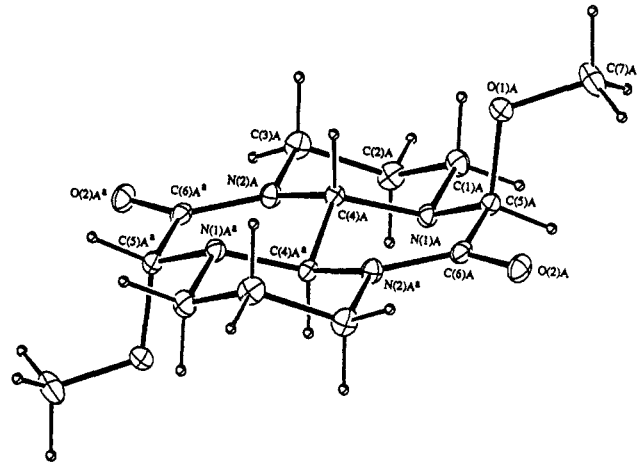
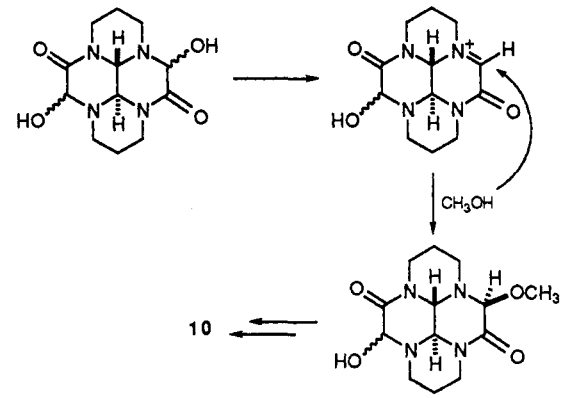


Figure 1. ORTEP diagram of compound **10** (molecule A).

Scheme I

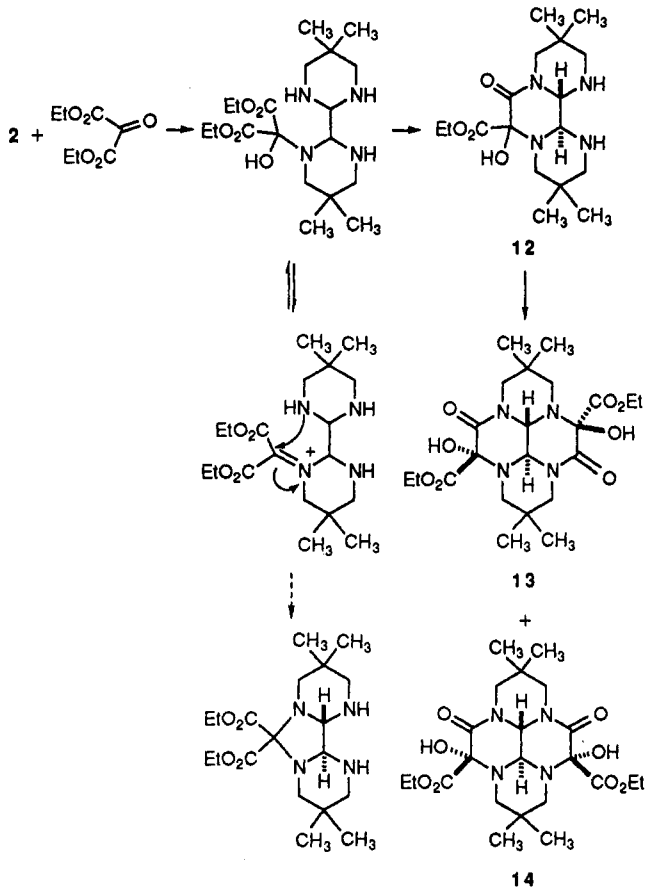


The configuration of the methoxy groups relative to the bridgehead positions in **10** could not be determined from the routine spectroscopic data. Nuclear Overhauser experiments were not performed but single crystal X-ray crystallographic analysis supported the gross structural assignment. The crystal structure consisted of three independent but geometrically similar molecules located on crystallographic centers of symmetry, making the asymmetric unit three half molecules. The structure and atom numbering scheme for one of the molecules is shown in Figure 1. The centers of symmetry were located at the midpoints of the central C–C bonds and, as found in compound **5**, the methoxy groups occupied axial positions which bore a cis relationship with respect to the central bridgehead protons. As can be seen from Figure 1, the bridgehead protons themselves were trans to one another, in agreement with the rigid, nondynamic behavior of the molecule, and definitely trans with respect to the neighboring amine nitrogen.

In this example, and in the earlier case with glyoxal, introduction of the methoxy groups must have resulted from an exchange process involving nucleophilic attack by solvent on iminium ion substrates. Axial approach of the solvent molecules should yield better orbital overlap but it is probable that the anomeric effect plays a major part in the final orientation of the axial methoxy substituents. This process is illustrated for compound **10** in Scheme I.

Another variation on the condensation of perhydrobipyrimidines **1** and **2** with α-dicarbonyl compounds involved the use of the highly electrophilic substance, diethyl oxomalonate. The reaction of 1 equiv of diethyl oxomalo-

Scheme II



nate with the more highly substituted perhydrobipyrimidine 2 in MeOH at ambient temperature resulted in formation of a single crystalline product in 46% yield. Elemental analysis and mass spectrometry (m/z 353) indicated molecular formula $C_{17}H_{30}N_4O_4$. The substance was therefore a tricycle. Its ^{1}H NMR spectrum contained four nonequivalent methyl signals (δ 0.81, 0.88, 0.98, and 1.01) and two mutually coupled one-proton doublets (δ 3.61 and 3.90, J = 7.3 Hz) due to the bridgehead protons, from the bipyrimidine reactant. A three-proton triplet (δ 3.10) and two one-proton doublet of quartet signals (δ 4.29 and 4.39) also showed retention of one ethyl ester group but now in a chiral environment. Two carbonyl carbons were evident in the ^{13}C NMR spectrum (δ 163.43 and 170.31) but the nonequivalence of the hexahydropyrimidine protons and carbons and the loss of one ethoxy group indicated that the compound had structure 12 (Scheme II). The magnitude of their vicinal spin coupling and again the absence of line broadening suggested that the central bridgehead protons were in a trans relationship. Meanwhile the hydroxyl groups were assigned to axial positions, in keeping with the situation in 5, 7, and 8 and in accordance with the anomeric effect.[13] This of course need not be the case since retention of the hydroxyl group and the absence of solvent exchange might indicate that equilibration has not occurred.

With 2 equiv of diethyl oxomalonate, the reaction gave two products which were isolated as a 46:54 mixture in 14% yield. Separation of the less polar minor isomer ($C_{22}H_{34}N_4O_4$, elemental analysis) was achieved by column chromatography using 95:5 CH_2Cl_2/petroleum ether as eluant (R_f 0.6). Its ^{1}H NMR spectrum showed the compound to possess a 2-fold axis of symmetry with the methyl groups of the hexahydropyrimidine rings appearing as two singlets (δ 0.96, 1.02) and the central bridgehead protons as one singlet at δ 4.59. In this case two ethyl ester groups were retained (δ 1.28, t, J = 7.1 Hz, 6H; 4.24, dq, J = 10.7, 7.1 Hz, 2H; and 4.39, dq, J = 10.7, 7.1 Hz, 2H). The symmetry of the compound was again indicated by the simplicity of its ^{13}C NMR spectrum which showed only ten signals. The spectra were therefore consistent with a tetracyclic molecule with structure 13. The trans geometry of the central bridgehead protons was proposed because the spectra contained no broad signals that might have arisen from the dynamic behavior expected for the cis isomer. Moreover, the ester groups were placed in equatorial positions to satisfy the preference due to the anomeric effect of the hydroxyl groups to reside anti with respect to the nonbonded electrons on nitrogen.

The major product from the reaction was isomeric with 13 but the number of signals in its ^{1}H NMR spectrum indicated that the compound was of different symmetry to that of the minor product. The methyl groups of the hexahydropyrimidine rings appeared as four singlets at δ 0.88, 0.98, 1.04, and 1.08, while the signals from the central bridgehead protons appeared as two one-proton doublets (J = 7.2 Hz) at δ 4.37 and 4.85. There was a total of 15 signals present in the ^{13}C NMR spectrum of the major isomer and this fact added final support for the assignment of structure 14. The compound was again assumed to have a trans relationship between the central bridgehead protons and axial orientation of the two hydroxyl groups as shown in 14.

The likely mechanism of formation of these tetraazapyrene derivatives, from the reaction of perhydrobipyrimidines with aldehydes bearing α-functionality, is outlined in Scheme II. Inspection of the products from this reaction pathway reveals a distinct preference by the second nitrogen for attack at the α-carbonyl group to form a six-membered ring over the previously observed exclusive formation of five-membered rings. The reason for this may have to do with the greater thermodynamic stability of the six-membered ring. However, it is noted that cyclization to generate the five-membered ring might involve a 5-endo-trig ring closure in which case it would be an unfavorable process according to principles outlined by Baldwin.[14] The alternative ring closure is formally 6-exo-trig and should be favored according to Baldwin's rules. Such a mechanism also explains the preponderance of isomer 14 over 13. Once formed, the amide group in 12 must reduce the nucleophilicity of the other nitrogen in the same hexahydropyrimidine ring and allow the remaining secondary nitrogen to react preferentially with a second equivalent of oxomalonate.

In summary, these simple experiments show that there are limits to the types of aldehydes or active carbonyl compounds that can be used to form perhydrotetraazafluorene heterocycles. The use of α-carbonyl reactants provides a convenient route to perhydrotetraazapyrene derivatives. Utilization of these selective reaction pathways should enable new families of rigid heterocyclic frameworks to be prepared for future study.

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Experimental Section

General Methods. The general methods used in this paper were essentially the same as described previously.[3]

Reactions of Perhydro-2,2′-bipyrimidine (1). (i) With 0.5 Equiv Glyoxal. Perhydro-2,2′-bipyrimidine (1) (0.88 g, 5.2 mmol) was dissolved in MeOH (10 mL) and the solution cooled in ice. Aqueous glyoxal (0.38 mL of 40%, 2.6 mmol) was added dropwise to the solution. When addition was complete, the mixture was stirred at 0 °C for a further 1 h and then allowed to stir at ambient temperature overnight. The mixture was filtered to remove a white powder (0.02 g) mp 250–260 °C dec. Solvent was removed under reduced pressure to yield a colorless foam (1.01 g) which could not be induced to crystallize.

(ii) With 2.0 Equiv Glyoxal. Perhydro-2,2′-bipyrimidine (1) (1.68 g, 9.9 mmol) was dissolved in MeOH (20 mL) and the solution cooled in ice. Aqueous glyoxal (2.87 mL of 40%, 19.8 mmol) was added dropwise to the solution. When addition was complete, the mixture was stirred at 0 °C for a further 30 min and then allowed to stir at ambient temperature overnight. The mixture was chilled and then filtered to yield a 70:30 mixture of diastereoisomers **5** and **6** as a white crystalline solid (1.17 g, 35%), mp 192–202 °C dec. A sample of the solid from a similar preparation was twice recrystallized from MeOH to yield **10b,10c-*trans*-4,5,9,10-tetramethoxyperhydro-3a,5a,8a,10a-tetraazapyrene (5)** as white cubes (0.38 g, 13%): mp 195 °C crystals turned yellow/orange and melted at 216–218 °C to give an orange/brown liquid; IR (Nujol) 1468, 1372, 1269, 1166, 1068, 1013, 921 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (dtt, J = 12.5, 2.9, 2.8 Hz, $H_{eq}2$ and $H_{eq}7$), 1.9 (dtt, J = 12.5, 12.5, 4.3 Hz, $H_{ax}2$ and $H_{ax}7$), 2.68 (ddd, J = 11.3, 4.3, 2.8 Hz, $H_{eq}1$, $H_{eq}3$, $H_{eq}6$ and $H_{eq}8$), 2.79 (ddd, J = 12.5, 11.3, 2.9 Hz, $H_{ax}1$, $H_{ax}3$, $H_{ax}6$ and $H_{ax}8$), 3.38 (s, 4 × OCH_3), 3.63 (s, H10b and H10c), 3.83 (s, H4, H5, H9 and H10); ^{13}C NMR see Table I; MS m/z 342 (M, 27%), 310 (64), 295 (71), 278 (100), 263 (45), 248 (61), 139 (55), 127 (51), 100 (26), 70 (30), 41 (32). Anal. Calcd for $C_{16}H_{30}N_4O_4$: C, 56.1, H, 8.8, N, 16.4. Found: C, 56.5, H, 8.7, N, 16.2.

(iii) With Glyoxylic Acid. Aqueous glyoxylic acid (0.8 g of 50%, 5.9 mmol) was added to a precooled solution of perhydro-2,2′-bipyrimidine 1 (1.0 g, 5.9 mmol) in MeOH (10 mL) at 0 °C. The mixture was allowed to stir at ambient temperature for 1 h and the solvent removed under reduced pressure at rt. The residue was dissolved in MeOH, a little Et_2O added, and the mixture refrigerated. The solid that formed was collected and found to be **1,3-diazacyclohexane-2-carboxylic acid (9)** (0.25 g, 36%): mp 122–125 °C; IR(KBr) 3460 (br H_2O), 3230, 3100–2300, 1628, 1475, 1412, 1360, 1325, 1265, 1193, 1122, 1040, 983, 919, 846, 790, 664, 375 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 1.79 (m, $(H5)_2$), 3.07 (m, $H_{ax}4$ and $H_{ax}6$), 3.35 (dt, J = 13.3, 3.8 Hz, $H_{eq}4$ and $H_{eq}6$), 4.40 (s, H2); ^{13}C NMR (D_2O with dioxane external reference taken as δ 67.8) δ 23.33 (C5), 43.92 (C4 and C6), 72.62 (C2), 172.44 (CO_2H). **Alternative Preparation of 1,3-Diazacyclohexane-2-carboxylic Acid (9).** Aqueous glyoxylic acid (10.0 g of 50%, 67.6 mmol) was added to a solution of propane-1,3-diamine (5.0 g, 67.6 mmol) in MeOH (50 mL) which was precooled in ice. The mixture was allowed to stir at ambient temperature for 1 h and the solvent was removed under reduced pressure at rt to leave a solid (10.9 g). The solid was triturated with MeOH, collected, and dried to yield **1,3-diazacyclohexane-2-carboxylic acid (9)** as a powder (8.5 g, 96%): mp 107–110 °C.

(iv) With Ethyl Glyoxylate. Perhydro-2,2′-bipyrimidine (1) (2.0 g, 11.8 mmol) was dissolved in MeOH (20 mL) and the solution cooled in ice. Ethyl glyoxylate (2.4 g, 23.5 mmol) was added dropwise and then the mixture was warmed at 60–65 °C in a water bath for 3 h. The resultant solution was refrigerated overnight but gave no crystalline material. The solution was then concentrated and Et_2O added. Refrigeration gave a precipitate of **10b,10c-*trans*-5,10-dimethoxyperhydro-3a,5a,8a,10a-tetraazapyrene-4,9-dione 10** (0.2 g, 6%). Recrystallization from MeOH gave analytical quality material as colorless needles (0.1 g): mp 195–200 °C dec. Material suitable for X-ray analysis was obtained from toluene solvent as similar crystals:[15] IR (Nujol) 1673, 1437, 1353, 1291, 1162, 1152, 1066, 998, 988, 925, 762, 660, 557 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65–1.82 (m, $(H2)_2$ and $(H7)_2$), 2.52 (m, $H_{ax}3$ and $H_{ax}8$), 2.79 (ddt, J = 11.4, 1.6, 3.4 Hz, $H_{eq}1$ and $H_{eq}6$), 3.00 (m, $H_{ax}1$ and $H_{ax}6$), 3.57 (s, 5-OCH_3 and 10-OCH_3), 4.22 (s, H10b and H10c), 4.38 (s, H5 and H10), 4.41 (ddt, J = 12.9, 1.8, 3.4 Hz, $H_{eq}3$ and $H_{eq}8$); ^{13}C NMR ($CDCl_3$) δ 22.83 (t, J = 127.7 Hz, C2 and C7), 39.06 (t, J = 140.2 Hz, C1 and C6 or C3 and C8), 45.08 (t, J = 134.3 Hz, C1 and C6 or C3 and C8), 59.54 (q, J = 142.7 Hz, OCH_3), 68.64 (d, J = 155.3 Hz, C10b and C10c), 90.92 (d, J = 164.6 Hz, C5 and C10), 164.83 (s, C4 and C9); MS m/z 310 (M, 15%), 295 (46), 278 (100), 251 (31), 236 (60), 127 (91), 113 (70), 100 (91), 42 (92). Anal. Calcd for $C_{14}H_{22}N_4O_4$: C, 54.2, H, 7.1, N, 18.1. Found: C, 54.0, H, 7.4, N, 17.9.

Reactions of 5,5,5′,5′-Tetramethylperhydro-2,2′-bipyrimidine (2). (i) With 0.5 Equiv Glyoxal. Perhydro-2,2′-bipyrimidine (2) (2.28 g, 10.0 mmol) was dissolved in MeOH (40 mL) and the solution cooled in ice. Aqueous glyoxal (0.72 mL of 40%, 5.0 mmol) was added dropwise to the solution. When addition was complete, the mixture was stirred at 0 °C for a further 1 h and then allowed to stir at ambient temperature. Solid had separated after 2 h and the mixture was left to stir overnight. The solid was collected, washed with MeOH, and dried to yield a white powdery substance (0.53 g) mp 190–202 °C dec, which was identical by ^{1}H NMR spectroscopy to the product from part (ii). The mother liquors were evaporated to dryness to yield a solid which comprised mainly the starting bipyrimidine 2.

(ii) With 2.0 Equiv Glyoxal. Perhydro-2,2′-bipyrimidine (2) (2.25 g, 10.0 mmol) was dissolved in MeOH (40 mL) and the solution cooled in ice. Aqueous glyoxal (3.0 mL of 40%, 25.6 mmol) was added dropwise to the solution. When addition was complete, the mixture was stirred at 0 °C for a further 1 h and then at ambient temperature for 3.5 h. Filtration gave a white crystalline material (2.61 g), mp 192–203 °C dec. The substance was identified as a mixture of which about 90% comprised an equimolar mixture of diastereoisomers of **10b,10c-*trans*-4,5,9,10-tetramethoxy-2,2,7,7-tetramethylperhydro-3a,5a,8a,10a-tetraazapyrenes 7 and 8**. The mixture could not be enriched in either isomer through recrystallization from toluene, MeOH, nor $CHCl_3$–MeOH, but recrystallization from the latter solvent gave colorless plates: mp 212–220 °C; IR (Nujol) 1468, 1385, 1365, 1280, 1252, 1195, 1165, 1065, 950, 935 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (7) 0.87 (s, 2-$(CH_3)_{eq}$ and 7-$(CH_3)_{eq}$), 1.14 (s, 2-$(CH_3)_{ax}$ and 7-$(CH_3)_{ax}$), 2.29 (d, J = 11.0 Hz, $H_{eq}1$, $H_{eq}3$, $H_{eq}6$ and $H_{eq}8$), 2.55 (d, J = 11.0 Hz, $H_{ax}1$, $H_{ax}3$, $H_{ax}6$ and $H_{ax}8$), 3.35 (s, 4 × OCH_3), 3.63 (s, H10b and H10c), 3.78 (s, H4, H5, H9 and H10); ^{1}H NMR δ (8) see Discussion; ^{13}C NMR see Table I; MS m/z 398 (M, 18%), 397 (14), 367 (31), 366 (25), 351 (12), 335 (9), 311 (14), 155 (100), 128 (25), 88 (60). Anal. Calcd for $C_{20}H_{38}N_4O_4$: C, 60.3, H, 9.6, N, 14.1. Found: C, 59.9, H, 9.5, N, 14.0.

(iii) With 1 Equiv Diethyl Oxomalonate. Diethyl oxomalonate (1.3 g, 8.8 mmol) was added dropwise to a stirred solution of 5,5,5′,5′-tetramethylperhydro-2,2′-bipyrimidine (2) (2.0 g, 8.8 mmol) in MeOH (24 mL) which had been precooled to 0 °C. When addition was complete the mixture was allowed to stir at ambient temperature for 1 h. The solvent was removed under reduced pressure at rt and the residue taken up in Et_2O/petroleum ether and refrigerated. The solid that formed was collected (2.6 g) and recrystallized from CH_2Cl_2 to give **ethyl 4a,4b-*trans*-9-hydroxy-10-oxoperhydro-4,5,8a,10a-tetraazaphenanthrene-9-carboxylate (12)** as white prisms (1.4 g, 46%): mp 142–146 °C; IR (Nujol) 3343, 3308, 3179 br, 1752, 1664, 1464, 1381, 1313, 1245, 1183, 1099, 1068, 930, 864, 726, 599 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81, 0.88, 0.98, 1.01 (4 × s, $(2\text{-}CH_3)_2$ and $(7\text{-}CH_3)_2$), 1.30 (t, J = 7.1 Hz, $CO_2CH_2CH_3$), 2.03 (dd, J = 11.2, 2.4 Hz, $H_{eq}1$), 2.45 (d (partially obscured), J = 13.0 Hz, $H_{ax}8$), 2.47 (d (partially obscured), J = 13.5 Hz, $H_{ax}3$), 2.58 (d, J = 11.3 Hz, $H_{ax}1$), 2.61 (d, J = 13.7 Hz, $H_{ax}6$), 2.65 (dd, J = 13.5, 2.4 Hz, $H_{eq}3$), 2.71 (dd, J = 13.7, 2.7 Hz, $H_{eq}6$), 3.61 (d, J = 7.3 Hz, H4b), 3.90 (d, J = 7.3 Hz, H4a), 4.22 (dd, J = 13.0, 2.7 Hz, $H_{eq}8$), 4.29 (dq, J = 10.7, 7.1 Hz, $CO_2CH_aH_bCH_3$), 4.39 (dq, J = 10.7, 7.1 Hz, CO_2CH_a-$H_b$$CH_3$); ^{13}C NMR ($CDCl_3$) δ 13.97 ($CO_2CH_2CH_3$), 21.92 (CH_3), 23.01 (CH_3), 25.35 (CH_3), 29.76 (C2 or C7), 30.76 (C2 or C7), 51.53, 55.85, 56.59, and 56.98 (C1, C3, C6, and C8), 63.22 ($CO_2CH_2CH_3$), 71.27 (C4a or C4b), 73.56 (C4a or C4b), 86.89 (C9), 163.43 (C10), 170.31 ($CO_2CH_2CH_3$); MS m/z 354 (M, absent),

(15) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

353 (1 %), 281 (16), 205 (10), 113 (100). Anal. Calcd for $C_{17}H_{30}N_4O_4$: C, 57.6, H, 8.5, N, 15.8. Found: C, 58.0, H, 8.9, N, 15.7.

(iv) With 2 Equiv Diethyl Oxomalonate. Diethyl oxomalonate (2.6 g, 15.0 mmol) was added to a solution of 5,5,5′,5′-tetramethylperhydro-2,2′-bipyrimidine (**2**) (1.7 g, 7.5 mmol) in MeOH (20 mL), and the mixture was allowed to stir at ambient temperature overnight. The solvent was removed by rotary evaporation, the residue taken up in a little Et_2O and diluted with petroleum ether, and the solution was refrigerated. The solid that formed was collected and recrystallized from MeOH/petroleum ether to give a 46:54 mixture of two tetracyclic compounds (0.5 g, 14%). Column chromatography using 95:5 CH_2Cl_2/petroleum ether as eluant gave the minor compound (R_f 0.6), **diethyl 10b,10c-*trans*-4,9-dihydroxy-5,10-dioxoperhydro-3a,5a,8a,10a-tetraazapyrene-4,9-dicarboxylate (13)** as small plates: mp 248–250 °C; IR (Nujol) 3387, 1759, 1665, 1463, 1381, 1238, 1110, 1060, 724, 711 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96, 1.02 (2 × s, (2-$(CH_3)_{ax}$ and 7-$(CH_3)_{ax}$) and (2-$(CH_3)_{eq}$ and 7-$(CH_3)_{eq}$), 1.28 (t, J = 7.1 Hz, $CO_2CH_2CH_3$), 2.11 (dd, J = 11.4, 2.4 Hz, $H_{eq}1$ and $H_{eq}6$), 2.44 (d, J = 13.1 Hz, $H_{ax}3$ and $H_{ax}8$), 2.73 (d, J = 11.4 Hz, $H_{ax}1$ and $H_{ax}6$), 4.16 (dd, J = 13.1, 2.4 Hz, $H_{eq}3$ and $H_{eq}8$), 4.24 (dq, J = 10.7, 7.1 Hz, $CO_2CH_aH_bCH_3$), 4.39 (dq, J = 10.7, 7.1 Hz, $CO_2CH_aH_bCH_3$), 4.44 (brs, OH), 4.59 (s, H10b and H10c); ^{13}C NMR ($CDCl_3$) δ 14.07 ($CO_2CH_2CH_3$), 22.36, 25.68 (CH_3); 29.15 (C2 and C7), 50.11, 54.18 (C1, C8 and C3, C6), 63.50 ($CO_2CH_2CH_3$), 68.18 (C10b and C10c), 86.56 (C4 and C9), 164.75 ($CO_2CH_2CH_3$), 169.65 (C5 and C10); MS m/z 482 (M, absent), 481 (<1%), 409 (100), 335 (74), 277 (17), 237 (67), 208 (10), 108 (16), 126 (34), 67 (44), 56 (45), 41 (65). Anal. Calcd for $C_{22}H_{34}N_4O_8$: C, 54.8, H, 7.1, N, 11.6. Found: C, 54.8, H, 7.3, N, 11.5. The second isomer was not purified but was identified as **diethyl 10b,10c-*trans*-4,10-dihydroxy-5,9-dioxoperhydro-3a,5a,8a,10a-tetraazapyrene-4,10-dicarboxylate (14)** from NMR spectal data on the crude mixture: ^1H NMR (300 MHz, $CDCl_3$) δ 0.88, 0.98, 1.04, 1.08 (4 × s, 2-$(CH_3)_{ax}$, 2-$(CH_3)_{eq}$, 7-$(CH_3)_{ax}$ and 7-$(CH_3)_{ax}$), 1.28 (t, J = 7.1 Hz, $CO_2CH_2CH_3$), 2.00 (d, J = 10.9 Hz), 2.56 (d, J = 13.1 Hz), 2.58 (d, J = 10.9 Hz), 3.85 (s), 4.20 (d (partially obscured), J = 14.1 Hz), 4.23 (dq, J = 10.8, 7.1 Hz, $CO_2CH_aH_bCH_3$), 4.37 (d, J = 7.2 Hz, H10b or H10c), 4.40 (dq, J = 10.9, 7.1 Hz, $CO_2CH_aH_bCH_3$), 4.85 (d, J = 7.2 Hz, H10b or H10c); ^{13}C NMR ($CDCl_3$) δ 14.05 ($CO_2CH_2CH_3$), 21.89, 23.06, 25.01, 26.29 ((2-$(CH_3)_{ax}$, 7-$(CH3)_{ax}$, 2-$(CH_3)_{eq}$ and 7-$(CH_3)_{eq}$), 28.97, 29.29, (C2 and C7), 50.55, 53.60 (C1, C3 and C6, C8), 63.39 ($CO_2CH_2CH_3$), 65.25, 70.33 (C10b and C10c), 87.00 (C4 and C10), 164.97 ($CO_2CH_2CH_3$), 169.71 (C5 and C9).

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