Synthesis of 7-Benzylideneoctahydro-2*H*-pyrido[1,2-*a*]pyrazines, Bicyclic Analogues of the Calcium Antagonist Flunarizine

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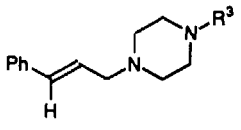
The bicyclic amino ketone **4** (2-benzyloctahydro-2*H*-pyrido[1,2-*a*]pyrazin-7-one) has been converted in four steps into the pharmacologically interesting (*Z*)- and (*E*)-7-benzylideneoctahydro-2*H*-pyrido[1,2-*a*]pyrazines **2a**, **b**, bicyclic analogues of the calcium antagonist flunarizine **1**. In the key step, olefination of the ketone group, the yield was highly improved (15–20%→82–85%) by using (a) the phosphonate anion instead of the Wittig reagent and (b) the solvent 1,3-dimethylimidazolidin-2-one instead of tetrahydrofuran. Debenzylation and final substitution of the 2-amino group with $(4\text{-}FC_6H_4)_2CHCl$ gave the geometric isomers **2a** (*Z*) and **2b** (*E*) in 53% overall yield.

The calcium antagonist flunarizine, a drug often used in the treatment of migraine, has the 1,4-substituted piperazine structure **1**.[1] In the context of our research on 2,5-substituted piperidines,[2–9] we were interested in the synthesis of the bicyclic compounds **2** which integrate structural features of the piperazine **1** and the 2,5-substituted piperidine ring system. The more rigid bicyclic framework might serve to fix the 'active conformation' of the flexible monocyclic drug compound, resulting in a more selective binding to the target receptor and improved drug activity.



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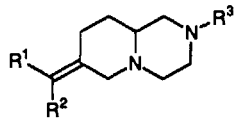


2

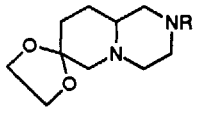
a R^1 = H, R^2 = Ph
b R^1 = Ph, R^2 = H

$R^3 = CH(4\text{-}FC_6H_4)_2$

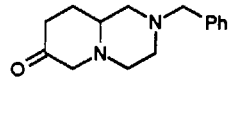
Results and Discussion

From previous work[2] two complementary synthons, *i.e.* the acetal amine **3** and the *N*-benzyl ketone 4, were available for the synthesis of the *Z*- and *E*-isomers **2a** and **2b**. In a first, more straightforward approach, the amine **3** was *N*-alkylated to afford the 2-bis(*p*-fluorophenyl)methyl derivative **5**. However, the newly introduced *N*-substituent suffered rapid hydrolysis under the vigorous acidic conditions (6 mol dm^{-3} HCl, reflux for 30 min) required for subsequent removal of the acetal protecting group. Accordingly, additional protection and deprotection of the 2-amino group had to be accommodated in our synthetic scheme, suggesting the use of the synthon 4.

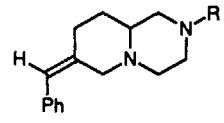
Our initial attempts for conversion of 4 into the *Z*- and *E*-benzylidene intermediates **6a** and **6b**, using the Wittig reagent $Ph_3P{=}CHPh$ in tetrahydrofuran (THF) were frustrated by low yields (15–20%). In further experiments performed on both **4** and the monocyclic model compound **9**, we varied the proportions of reagents and used different bases for generation of the Wittig reagent (*i.e.* BuLi, NaH, KOBu^t) but this resulted in equally unsatisfactory yields (Table 1). Concurrent abstraction of an acidic proton by the reagent to form an enolate anion gave rise to recovery of the starting ketone and to

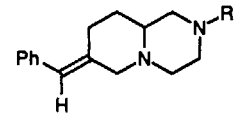


3 R = H
5 R = $CH(C_6H_4F\text{-}4)_2$

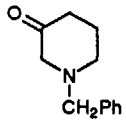


4

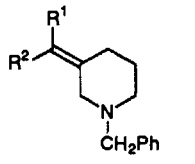




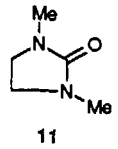
6a R = CH_2Ph **6b**
7a R = CO_2Et **7b**
8a R = H **8b**



9



10a R^1 = H, R^2 = Ph
10b R^1 = Ph, R = H



11

formation of more polar aldol dimers (*e.g.* M^+ 488 for the aldol derived from **4**).

Since the α-amino ketones 4 and **9** are inherently unstable as the free bases, we sought to suppress their self-condensation by enhancing the nucleophilic properties of the olefination reagent. When using the phosphonate anion reagent PhCH(Na)-$PO(OEt)_2$ in THF, with and without addition of 15-crown-5 ether,[10] the yields of olefins **6a**, **b** and **10a**, **b** were increased to 40–45%. Following the same line of reasoning, the solvent THF was replaced with 1,3-dimethylimidazolidin-2-one **11**, a known substitute for the alkali-metal complexing agent hexamethylphosphoramide (HMPA).[11] In our application, the enhanced reactivity of the phosphonate anion led to rapid conversion of the ketones 4 and **9**, at low temperature (5→20 °C), into the

Table 1 Yields for olefination of ketones **4** and **9**

Reagents	Solvent	Base	Yields[a] of **10a, b** or **6a, b** (%)
Ph_3PCH_2PhCl	THF	BuLi	15–20
Ph_3PCH_2PhCl	THF	NaH	15–20
Ph_3PCH_2PhCl	THF	Bu^{t}OK	15–20
Ph_3PCH_2PhCl	**11**	NaH[b]	40
$(EtO)_2P(O)CH_2Ph$	THF	NaH[b]	40–45
$(EtO)_2P(O)CH_2Ph$	THF + **11**	NaH[b]	40–45
$(EtO)_2P(O)CH_2Ph$	**11**	NaH[b]	82–85

[a] The yields are based on the acetal precursor of **4** (2-benzyl-7,7-ethylenedioxyoctahydro-2*H*-pyrido[1,2-*a*]pyrazine),[2] and **9**·HCl. [b] With and without the addition of 15-crown-5.

Table 2 δ Values[a] in ppm in the ^{13}C NMR spectra for the allylic C-atoms of *Z*- and *E*-isomers

Z-isomers	C-6	C-8	*E*-isomers	C-6	C-8
2a	55.7	34.1	**2b**	63.2	26.8
6a	55.7	34.1	**6b**	63.3	26.8
7a	55.8	33.9			
8a	56.2	34.3			
Z-isomer	C-2	C-4	*E*-isomer	C-2	C-4
10a[b]	54.5	35.0	**10b**[b]	62.2	27.3

[a] δ Values were assigned by selective ^1H–^{13}C decoupling. [b] Measurement carried out on the mixture of *E,Z*-**10a, b**.

alkenes **6a, b** and **10a, b** in 82–85% yield. When **11** was used as a solvent in the reaction of 4 and **9** with Ph_3P=CHPh, the yield was improved from 15–20 to 40% (Table 1).

The geometric isomers **6a** and **6b** were readily separated by using column chromatography. Several methods were tried to effect deprotection of the *N*-benzyl group. Catalytic hydrogenation or reduction with sodium in liquid ammonia[12] led to preferential saturation of the double bond (M^+ 320). Treatment with $AlCl_3$ in benzene[13] gave rise to electrophilic substitution of the solvent, presumably with formation of the 7-diphenylmethyl derivative (M^+ 396, *m/z* 165). Finally, debenzylation of **6a** and **6b** was effected in 95% yield by reaction with ethyl chloroformate[14] in dichloromethane. The resulting carbamates **7a** and **7b** were converted into the corresponding amines **8a** and **8b** by refluxing with KOH in isopropyl alcohol[15] (acidic hydrolysis of **7** was very slow and did not go to completion). The conditions required for the final *N*-alkylation of **8a** and **8b** to form the target compounds **2a** and **2b** proved to be quite critical. No reaction was observed with the reagent $(4\text{-}FC_6H_4)_2CHCl$ under the usual conditions (acetone, K_2CO_3, KI, reflux).[16] However, the desired transformation was effected in high yield by subjecting the purified amines to treatment with the alkylating reagent and an excess of $Bu_4N^+Br^-$ in refluxing *o*-dichlorobenzene. No reaction occurred for the unpurified amines **8a** and **8b** obtained upon alkaline treatment of the carbamates **7a** and **7b**.

The overall yield for compounds **2** was 53% (14% for **2a** and 39% for **2b**) when calculated from the acetal precursor[2] of the synthon 4 and 63 and 60% from the intermediates **6a** and **6b**. Relative structure assignments of the *Z*- and *E*-isomers were based on the γ-effect[17] exerted by the phenyl group on the proximate allylic C-6 or C-8 atoms in the ^{13}C NMR spectrum (Table 2). For the *E*-isomers, shielding of C-8 and deshielding of C-6 was observed, whereas the reverse situation occurred for the *Z*-isomers.

No significant pharmacological activity was observed for compounds **2a** and **2b** from the *in vitro* and *in vivo* tests responding to flunarizine **1**. Although a molecular model of the *E*-isomer **2b** is superimposable with some of the more stable conformations of piperazine compound **1**, apparently the rather rigid bicyclic structure of **2b** does not fit well onto the binding site of the receptor molecule involved.

Conclusions

The synthesis of the bicyclic analogues **2a** and **2b** of flunarizine involved 13 steps starting from 1-benzylpiperidin-3-one, and was accomplished with an overall yield of 27% (7% for **2a** and 20% for **2b**). By a suitable choice of reagent and solvent, the crucial step in this sequence, *i.e.* olefination of the bicyclic α-amino ketone **4**, was optimized to give an 85% yield of intermediates **6a** and **6b**. The lack of bioactivity observed for the *E*-isomer **2b** may give an important clue with respect to the 'active conformation' of the piperazine drug **1**, *i.e.* the distance and orientation of active centres such as the N-atoms and the phenyl group.

Experimental

All m.p.s are uncorrected. IR spectra were recorded as thin films between NaCl plates or as solids in KBr pellets on a Perkin-Elmer 297 grating IR spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker WM 250 instrument operating at 250 MHz for ^1H and 63 MHz for ^{13}C measurements. The ^1H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane as an internal reference. *J* Values are recorded in Hz. Mass spectra were run on a Kratos MS50 instrument; the ion source temperature was 150–250 °C as required. Exact mass measurements were performed at a resolution of 10 000. Analytical thin layer chromatography was performed using Merck silica gel 60 PF-224. Column chromatography was carried out using 70–230 mesh silica gel 60 (E. M. Merck).

2-[*Bis*(p-*fluorobenzylidene*)]-7,7-*ethylenedioxyoctahydro*-2H-*pyrido*[1,2-a]*pyrazine* **5**.—A stirred mixture of the crude product **3** (350 mg) [prepared from 7,7-ethylenedioxyoctahydro-2*H*-pyrido[1,2-*a*]pyrazin-3-one (400 mg, 1.89 mmol) and $LiAlH_4$][2] in *o*-dichlorobenzene (10 cm^3), Bu_4NBr (600 mg, 1.86 mmol) and chlorobis(4-fluorophenyl)methane (630 mg, 2.73 mmol) was heated at reflux for 10 min under an atmosphere of nitrogen. The cooled mixture was chromatographed on a silica column with EtOAc as the eluent to afford **5** (600 mg, 80%) as a solid, m.p. 190–191 °C (from EtOAc) (Found: C, 68.6; H, 6.6; N, 6.9. $C_{23}H_{26}F_2N_2O_2$ requires C, 68.98; H, 6.54; N, 7.00%); $\delta_H(CDCl_3)$ 1.4–1.6 (4 H, m, 8,9-H), 1.78 (1 H, td, *J* 10, 3, 3_{ax}-H), 1.82 (1 H, t, *J* 10, 1_{ax}-H), 2.02 (1 H, m, $9a_{ax}$-H), 2.17 (1 H, d, *J* 11, 6_{ax}-H), 2.20–2.35 (2 H, m, 4_{ax}-H, 1_{eq}-H), 2.60–2.74 (2 H, m, 4_{eq}-H, 3_{eq}-H), 2.75 (1 H, dd, *J* 11, 2, 6_{eq}-H), 4.0 (4 H, m, OCH_2CH_2O), 4.25 (1 H, s, C*H*Ar$_2$), Ar, 7.0 (4 H, t, *J* 8.5, 3-H) and 7.35 (4 H, m, 2-H).

(E, Z)-1-*Benzyl*-3-*benzylidenepiperidine* **10a, b**.—A solution of 1-benzylpiperidin-3-one·HCl (2.00 g, 8.86 mmol) in water (20 cm^3) was made alkaline with K_2CO_3 and extracted with CH_2Cl_2 (2 × 100 cm^3). The combined extracts were evaporated to dryness to give the free base 1-benzylpiperidin-3-one **9** (1.55 g) as an oil. To a stirred slurry of NaH (80% dispersion in mineral oil; 333 mg) in 1,3-dimethylimidazolidin-2-one (3 cm^3), a mixture of **9** and $PhCH_2PO(OEt)_2$ (2.20 g, 9.6 mmol) in 1,3-dimethylimidazolidin-2-one (3 cm^3) was added dropwise over 5 min. The reaction mixture was stirred for 30 min, and then was quenched with water and extracted with CH_2Cl_2 (200 cm^3). The extract was washed with water (2 × 50 cm^3) and evaporated. The residue was chromatographed over a silica column, using 50% EtOAc–hexane as eluent to give **10** (1.88 g, 81% from **9**·HCl) as a semisolid. ^1H and ^{13}C NMR analysis showed that the product **10** consisted of two isomers: the *Z*-isomer **10a** (45%) and *E*-isomer **10b** (55%).

10a: $\delta_H(CDCl_3)$ 1.74 (2 H, quintet, *J* 5.6, 5-H), 2.42 (2 H, t, *J* 6, 4-H), 2.58 (2 H, t, *J* 6, 6-H), 3.17 (2 H, s, 2-H), 3.50 (2 H, NCH_2Ph, s), 6.3 (1 H, s, vinyl-H) and 7.25 (10 H, m, 2 Ph); $\delta_C(CDCl_3)$ 26.6 (C-5), 34.95 (C-4), 54.15 (C-6), 54.45 (C-2), 63.0 (NCH_2Ph) and 123.7 (*C*H=C).

10b: (Found: M^+, 263.1672. $C_{19}H_{21}N$ requires *M*, 263.1672); $\delta_H(CDCl_3)$ 1.65 (2 H, quintet, *J* 5.5, 5-H), 2.28 (2 H, t, *J* 6, 4-H), 2.55 (2 H, t, *J* 6, 6-H), 3.07 (2 H, s, 2-H), 3.61 (2 H, s, NCH_2Ph), 6.30 (1 H, s, vinyl-H) and 7–7.5 (10 H, m, 2 Ph); $\delta_C(CDCl_3)$ 25.7 (C-5), 27.3 (C-4), 53.9 (C-6), 62.2 (C-2), 63.1 (NCH_2Ph) and 124.2 (*C*H=C).

(Z)- *and* (E)-2-*Benzyl*-7-*benzylideneoctahydro*-2H-*pyrido*-[1,2-a]*pyrazine* **6a**, **6b**.—To a stirred and cooled (5 °C) slurry of NaH (80% dispersion in mineral oil; 790 mg) in 1,3-dimethylimidazolidin-2-one (7 cm^3) was added dropwise over a period of 15 min a mixture of $PhCH_2PO(OEt)_2$ (5.30 g, 23.2 mmol) and the crude product 4 (5.0 g) [prepared from the acetal precursor of **4** (6.25 g, 21.7 mmol) and 6 mol dm^{-3} HCl (180 cm^3)].[2] The suspension was stirred at room temp. for 25 min after which work-up in the manner described for **10a**, **b** and column chromatography on silica gel with EtOAc as the eluent afforded two isomers: the less polar *Z*-isomer **6a** (1.50 g, 22%), and the more polar *E*-isomer **6b** (4.40 g, 64%). Both were isolated as crystalline products, m.p. (from EtOAc) 91–92 and 121–122 °C, respectively. The total yield thus was 86% from the acetal precursor of 4.

6a: (Found: C, 82.7; H, 8.35; N, 8.7%; M^+, 318.2097. $C_{22}H_{26}N_2$ requires C, 82.98; H, 8.23; N, 8.80%; *M*, 318.2095); ν_{max}(KBr)/cm^{-1} 1660w (C=C exocyclic); $\delta_H(CDCl_3)$ 1.38 (1 H, qd, *J* 12, 5, 9_{ax}-H), 1.6 (1 H, m, 9_{eq}-H), 1.9 (1 H, t, *J* 12, 1_{ax}-H), 2.23 (1 H, tt, *J* 11, 3, $9a_{ax}$-H), 2.31 (1 H, td, *J* 11, 3, 4_{ax}-H), 2.1–2.5 (3 H, m, 8_{ax}-H, 4_{eq}-H, 1_{eq}-H), 2.61 (1 H, d, *J* 12, 6_{ax}-H), 2.65–2.8 (3 H, m, 3_{eq}-H, 4_{eq}-H, 1_{eq}-H), 3.47 (2 H, s, NCH_2Ph), 3.85 (1 H, d, *J* 12, 6_{eq}-H), 6.3 (1 H, s, vinyl-H) and 7.2 (10 H, m, 2 Ph); $\delta_C(CDCl_3)$ 30.5 (C-9), 34.1 (C-8), 52.8 (C-3), 54.9 (C-4), 58.9 (C-1), 60.5 (C-9a), 55.7 (C-6), 62.9 (CH_2Ph), 124.1 (*C*H=C), 137.1 (C-7), C=CH*Ph*, 126.1 (C-*p*), 127.8 (C-*o*), 129 (C-*m*), 137.2 (C-*ipso*), CH_2*Ph*, 126.9 (C-*p*), 128.1 (C-*o*), 128.9 (C-*m*) and 138 (C-*ipso*).

6b: (Found: C, 82.8; H, 8.2; N, 8.7%; M^+, 318.2098. $C_{22}H_{26}N_2$ requires C, 82.98; H, 8.23; N, 8.80%; *M*, 318.2095); ν_{max}(KBr)/cm^{-1} 1660w (C=C exocyclic); $\delta_H(CDCl_3)$ 1.25 (1 H, q, *J* 11, 4, 9a-H), 1.56 (1 H, m, 9_{eq}-H), 1.88 (1 H, t, *J* 11, 1_{ax}-H), 1.98 (1 H, td, *J* 11.5, 4, 8_{ax}-H), 2.2 (1 H, tt, *J* 11, 4, $9a_{ax}$-H), 2.33 (1 H, td, *J* 11, 3, 4_{ax}-H), 2.4 (1 H, td, *J* 11, 3, 3_{ax}-H), 2.73 (1 H, dt, *J* 11, 3, 2, 1_{eq}-H), 2.88 (1 H, d, *J* 12, 6_{ax}-H), 2.73–3.0 (3 H, m, 3_{eq}-H, 4_{eq}-H, 8_{eq}-H), 3.31 (1 H, d, *J* 12, 6_{eq}-H), 3.45–3.52 (2 H, dd, *J* 12, 12, NCH_2Ph), 6.4 (1 H, s, vinyl-H) and 7.1–7.4 (10 H, m, 2 Ph); $\delta_C(CDCl_3)$ 26.8 (C-8), 30.2 (C-9), 52.9 (C-3), 54.8 (C-4), 58.9 (C-1), 60.9 (C-9a), 63.3 (C-6), 63 (CH_2Ph), 124.5 (*C*H=C) and 137.1 (C-7), C=CH*Ph*, 126.2 (C-*p*), 128 (C-*o*), 129.1 (C-*m*), 137.3 (C-*ipso*), CH_2*Ph*, 126.9 (C-*p*), 128.1 (C-*o*), 128.9 (C-*m*) and 138 (C-*ipso*).

(Z)-7-*Benzylidene*-2-*ethoxycarbonyloctahydro*-2H-*pyrido*-[1,2-a]*pyrazine* **7a**.—To a stirred solution of **6a** (2.00 g, 6.3 mmol) in CH_2Cl_2 (50 cm^3) was added dropwise at 0 °C ethyl chloroformate (0.61 cm^3, 6.4 mmol). The reaction mixture was kept under nitrogen at 0 °C for 2 h and then at room temp. for 1 h. The solution was made alkaline with aq. K_2CO_3 and extracted with CH_2Cl_2 (2 × 200 cm^3). The combined extracts were evaporated and the residual product was chromatographed on silica with EtOAc–$CHCl_3$ (3 : 7) to afford **7a** (1.78 g, 95%) as an oil (Found: M^+, 300.1838. $C_{18}H_{24}N_2O_2$ requires *M*, 300.1836); ν_{max}(NaCl)/cm^{-1} 1700 (CO_2Et); $\delta_H(CDCl_3)$ 1.25 (3 H, t, *J* 7, CH_2CH_3), 1.38 (1 H, qd, *J* 13, 12, 11, 5, 9a-H), 1.74 (1 H, m, 9_{eq}-H), 2.07 (1 H, tt, *J* 11, 3, $9a_{ax}$-H), 2.18 (1 H, td, *J* 12, 3.5, 4_{ax}-H), 2.30 (1 H, td, *J* 12, 5, 8_{ax}-H), 2.60 (1 H, d, *J* 12, 6_{ax}-H), 2.6–2.7 (2 H, m, 3_{ax}-H, 4_{eq}-H), 3.0 (1 H, t, *J* 11, 1_{ax}-H), 3.85 (1 H, d, *J* 12, 6_{eq}-H), 3.9–4.1 (2 H, m, 1_{eq}-H, 3_{eq}-H), 4.15 (2 H, q, *J* 7, CH_2CH_3), 6.38 (1 H, s, vinyl-H) and 7.15–7.4 (5 H, m, Ph); $\delta_C(CDCl_3)$ 14.7 (CH_3), 30.1 (C-9), 33.9 (C-8), 43.4 (C-3), 48.8 (C-1), 54.6 (C-4), 55.8 (C-6), 60.5 (C-9a), 61.3 (CH_2O), 124.5 (*C*H=C), 137.1 (C-7), 155.2 (C=O), C=CH*Ph*, 126.3 (C-*p*), 128 (C-*o*), 129 (C-*m*) and 137 (C-*ipso*).

(E)-7-*Benzylidene*-2-*ethoxycarbonyloctahydro*-2H-*pyrido*-[1,2-a]*pyrazine* **7b**.—A stirred solution of **6b** (2.00 g, 6.4 mmol) was treated with ethyl chloroformate (0.61 cm^3, 6.4 mmol) in the manner described above to afford **7b** (1.75 g, 93%) as an oil after column chromatography.

(Z)-7-*Benzylideneoctahydro*-2H-*pyrido*[1,2-a]*pyrazine* **8a**.—A stirred solution of **7a** (7.59 g, 25.3 mmol) in isopropyl alcohol (6 cm^3) was refluxed with KOH (20 g, 0.36 mol) for 1 h under nitrogen. The mixture was concentrated by rotary evaporation and the residue was washed with CH_2Cl_2 (4 × 300 cm^3) and filtered. The filtrate was evaporated and the residue was chromatographed on a short column of silica gel eluting with Et_2NH–MeOH–EtOAc (1 : 5 : 94) to give pure **8a** (4.62 g, 80%) as an oil; ν_{max}(NaCl)/cm^{-1} 3300 (NH); $\delta_H(CDCl_3)$ 1.39 (1 H, tdd, *J* 12, 10, 5, 9a-H), 1.67 (1 H, d × quint, *J* 12, 3, 2, 3, 2, 9_{eq}-H), 1.92 (1 H, s, NH), 2.05 (1 H, tt, *J* 10, 3, $9a_{ax}$-H), 2.2 (1 H, ddd, *J* 12, 9, 6, 4_{ax}-H), 2.32 (1 H, tm, *J* 14, 13, 8_{ax}-H), 2.43 (1 H, d × quint, *J* 14, 3, 2, 2, 2, 8_{eq}-H), 2.52 (1 H, dd, *J* 12, 10, 1_{ax}-H), 2.63 (1 H, d, *J* 13, 6_{ax}-H), 2.70 (1 H, dt, *J* 12, 3, 2, 4_{eq}-H), 2.9 (2 H, m, 3_{eq}-H, 3_{ax}-H), 2.91 (1 H, dd, *J* 11, 2.5, 1_{eq}-H), 3.84 (1 H, dd, *J* 13, 2, 6_{eq}-H), 6.35 (1 H, s, vinyl-H) and 7.1–7.4 (5 H, m, Ph); $\delta_C(CDCl_3)$ 30.5 (C-9), 34.3 (C-8), 45.8 (C-3), 51.9 (C-1), 56.2 (C-6), 56.3 (C-4), 62.3 (C-9a), 124.1 (*C*H=C), 137.2 (C-7), 126.2 (C-*p*), 127.9 (C-*o*), 129 (C-*m*) and 137 (C-*ipso*); *m*/*z* 228 (M^+), 199, 198, 186 (100%) and 91.

(E)-7-*Benzylideneoctahydro*-2H-*pyrido*[1,2-a]*pyrazine* **8b**.—A stirred solution of **7b** (3.40 g, 11.3 mmol) in isopropyl alcohol (5 cm^3) was refluxed with KOH (17 g, 0.30 mol) under nitrogen for 1 h. Work-up as described for **8a** and column chromatography on silica afforded **8b** (2.08 g, 81%) as an oil; mass and IR spectra were similar to those of **8a**.

(Z)-7-*Benzylidene*-2-[*bis*(p-*fluorophenyl*)*methyl*]*octahydro*-2H-*pyrido*[1,2-a]*pyrazine* **2a**.—A stirred mixture of **8a** (4.46 g, 19.6 mmol) in *o*-dichlorobenzene (70 cm^3), Bu_4NBr (11.4 g, 35.4 mmol) and chlorobis(4-fluorophenyl)methane (7.00 g, 29.3 mmol) was heated at reflux under nitrogen for 40 min. The solvent was removed by rotary evaporation and the residue was dissolved in CH_2Cl_2 (300 cm^3). The solution was treated with aqueous K_2CO_3 and the aqueous phase was further extracted with CH_2Cl_2 (200 cm^3). The combined extracts were evaporated and the residue was chromatographed over silica gel (gradient elution 5 to 10% EtOAc–$CHCl_3$) to afford **2a** (6.9, 82%) as pale brown crystals. Recrystallization from methanol or hexane gave an analytical sample, m.p. 124 °C (Mettler) (Found: C, 77.9; H, 6.6; F, 8.76; N, 6.4%; M^+, 430.2221. $C_{28}H_{28}F_2N_2$ requires C, 78.11; H, 6.55; F, 8.83; N, 6.51%; *M*, 430.2219); $\delta_H(CDCl_3)$ 1.32 (1 H, tdd, *J* 14, 10.5, 5, 9a-H), 1.52 (1 H, m, 9_{eq}-H), 1.77 (1 H, dd, *J* 11, 10, 1_{ax}-H), 2.08 (1 H, td, *J* 11, 2.5, 3_{ax}-H), 2.22 (1 H, tt, *J* 10, 2.5, $9a_{ax}$-H), 2.34 (1 H, td, *J* 11, 3, 4_{ax}-H), 2.2–2.45 (2 H, m, 8-H), 2.62 (1 H, dd, *J* 11, 2.5, 1_{eq}-H), 2.63 (1 H, d, *J* 12, 6_{ax}-H), 2.6–2.67 (2 H, m, 3_{eq}-H, 4_{eq}-H), 3.85 (1 H, d, *J* 12, 6_{eq}-H), 4.2 (1 H, s, $CHAr_2$), 6.31 (1 H, s, vinyl-H) and 7.7 (13 H, m, Ar); $\delta_C(CDCl_3)$ 30.6 (C-9), 34.1 (C-8), 51.4 (C-3), 55.7 (C-6), 57.6 (C-1), 60.8 (C-9a), 74.3 ($CHAr_2$), 124.2 (*C*H=C), 137.3 (C-7), Ph, 126.2 (C-*p*), 127.9 (C-*o*), 129 (C-*m*), 137.1 (C-*ipso*), CH-Ar_2, 115.3 (C-*m*), 129.2 (C-*o*), 138.1 (C-*ipso*) and 161.7 (C-F).

(E)-7-*Benzylidene*-2-[*bis*(p-*fluorophenyl*)*methyl*]*octahydro*-2H-*pyrido*[1,2-a]*pyrazine* **2b**.—A mixture of **8b** (2.10 g, 9.2 mmol) in *o*-dichlorobenzene (50 cm^3), Bu_4NBr (4.00 g, 12.4 mmol) and chlorobis(4-fluorophenyl)methane (2.50 g, 10.5 mmol) was heated at reflux for 40 min under nitrogen. Work-up in the manner described above and column chromatography of the resulting product on silica gel using 10% EtOAc–$CHCl_3$ afforded **2b** (3.2 g, 80%) as pale brown crystals, m.p. 122.8 °C (from MeOH) (Found: C, 77.9; H, 6.6; F, 9.00; N, 6.4%; M^+, 430.2210. $C_{28}H_{28}F_2N_2$ requires C, 78.11; H, 6.55; F, 8.83; N, 6.51%; *M*, 430.2219); $\delta_H(CDCl_3)$ 1.20 (1 H, tdd, *J* 14, 10.5, 5, 9a-H), 1.46 (1 H, m, 9_{eq}-H), 1.76 (1 H, t, *J* 10, 1_{ax}-H), 1.98 (1 H, td, *J* 14, 5, 8_{ax}-H), 2.18 (1 H, td, *J* 11, 3, 3_{ax}-H), 2.22 (1 H, m, $9a_{ax}$-H), 2.40 (1 H, td, *J* 11, 3, 4_{ax}-H), 2.71 (1 H, dd, *J* 10, 2, 1_{eq}-H), 2.7–2.8 (2 H, m, 3_{eq}-H, 4_{eq}-H), 2.90 (2 H, br d, 6_{ax}-H, 8_{eq}-H), 3.32 (1 H, dd, *J* 12, 2, 6_{eq}-H), 4.20 (1 H, s, NC*H*Ar_2), 6.41 (1 H, s, vinyl-H), 7.00 (4 H, t, *J* 8, Ar) and 7–7.1 (9 H, m, Ar); δ_C(250 MHz, $CDCl_3$) 30.1 (C-9), 26.8 (C-8), 51.4 (C-3), 54.9 (C-4), 63.2 (C-6), 57.4 (C-1), 61.1 (C-9a), 74.3 (*C*HAr_2), 124.6 (*C*H=C), 137.3 (C-7), Ph, 126.3 (C-*p*), 128 (C-*o*), 129 (C-*m*), 137.1 (C-*ipso*), CH*Ar*$_2$, 115.3 (C-*m*), 129.2 (C-*o*), 139.1 (C-*ipso*) and 161.8 (C-F).

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