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# The Synthesis of 2,7-Substituted Octahydro-2H-Pyrido[1,2-a] Pyrazines, Analogues of Quinolizidine and Piperazine Drugs

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*Abstract: The versatility of amino ketone 2 (2-benzyloctahydro-2H-pyrido[1,2-a]pyrazin-7-one) was demonstrated by the synthesis of 2,7-substituted derivatives, designed as analogues of both quinolizidine and piperazine drugs. The 7- ketone group was functionalized via Grignard reaction with o- and p-fluorophenylmagnesium bromide, followed by dehydration and hydrogenation. Final substitution of the 2-amino group afforded the 2-pyridyl and p-fluorobenzoyl target compounds 10 and 11.*

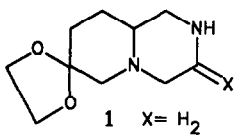
## INTRODUCTION

Recently we reported the synthesis of the complementary octahydro-2H-pyrido[1,2-a]pyrazine synthons **1** and **2** starting from the lactam precursor **3**.[1,2] The alternative protection of either the 7-ketone or 2-amino group in **1** and **2** should allow for introduction of the desired pharmacophoric substituents in the strategic order dictated by their chemical properties. The products resulting from this 2,7-functionalization[3] can be viewed either as conformationally restricted forms of piperazine drugs, e.g. **4-7**[4] or as 2-aza analogues of the neuroleptic quinolizidines derived from **8a** or **8b**, e.g. **9**.[5] This structural comparison then leads to target compounds **10**, **11**, and **12**; access to these requires introduction of *o*- and *p*-fluorophenyl groups at the 7-ketone position, and of 2-pyridyl and benzoyl substituents at the 2-amino function.

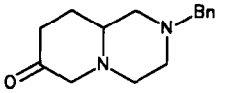
## RESULTS AND DISCUSSION

For the synthesis of the N-(2-pyridyl) target compounds **10** and **12**, we first attempted the more direct route starting from the free amine **1** (Scheme 1). Treatment of the amine with 2-fluoropyridine[1] and subsequent acidic hydrolysis of the acetal group gave the N-(2-pyridyl) ketone **13**. Grignard reaction of **13** using *p*-$FC_6H_4MgBr$ afforded two diastereomeric alcohols **14a** (39%) and **14b** (53%) which were readily separated by using column chromatography. Relative structure assignments were based on the formation of an internal H-bridge for the isomer with an axially disposed OH-group.[6] The signals detected in the $^1H$-NMR and IR-spectra for the OH-group of isomer **14a** did not shift upon dilution (3.80 ppm and 3480 $cm^{-1}$). For the isomer **14b** such a shift was indeed observed and the free OH-signal was detected at 3600 $cm^{-1}$.

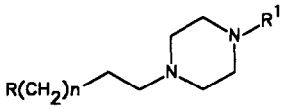
For the preparation of the *o*-fluorophenyl analogues **15a,b** special reaction conditions were required in order to suppress concurrent formation of benzyne from the reagent *o*-F-$C_6H_4MgBr$.[7] The desired addition to ketone **13** was favoured over this side reaction by generating the reagent at low temperature (40 °C) in the presence of the ketone and $MgBr_2$ (produced by reaction of Mg with 1,2-dibromoethane). However, even under these conditions, formation of benzyne was indicated by some contamination of compounds **15a,b** with defluorinated analogues.



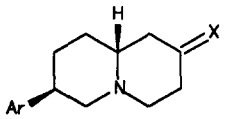
**1** X= $H_2$
**3** X= O



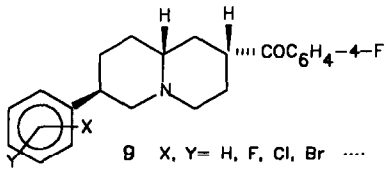
**2**



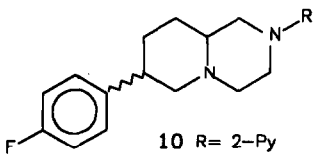
**4** $R^1$= 2–Py, R= 4–$FC_6H_4CO$, n= 1 ( Sedative; Tranquilizer)[4a]
**5** $R^1$= 4–$FC_6H_4$, R= 2–Py, n= 0 ( Antihypertensive)[4b]
**6** $R^1$= 2–Py, R= 4–$FC_6H_4$, n=2 ( Antipsychotic)[4c]
**7** $R^1$= 4–$FC_6H_4CO$, R= Ar, n= 0 ( Analgesic)[4d]



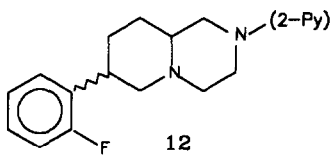
**8a** X= O
**8b** X= H, $NH_2$



**9** X, Y= H, F, Cl, Br ····



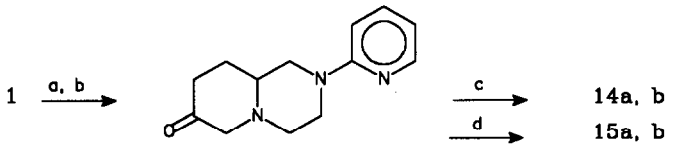
**10** R= 2–Py
**11** R= 4–$FC_6H_4CO$



**12**

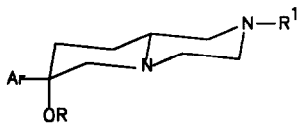
All attempts to convert tertiary alcohols **14a,b** or **15a,b** to the corresponding H-compounds were unsuccessful. Hydrogenolysis of the acetylated[8] derivatives of **15a,b** gave rise to concurrent reduction of the pyridyl group. Methods based on generating the 7-carbocation in acidic medium ($CF_3COOH$) and quenching it with various hydride donors (e.g. $NaBH_4$,[9] $NaCNBH_3$, $Et_3SiH$[10] and $Ph_3SnH$[11]) failed, probably due to protonation of the adjacent 5-N-center. Further efforts directed at replacing the alcohol group with a better leaving group (and subsequent reductive removal) mostly led to elimination or regeneration of the alcohol group. For instance, treatment of the equatorial alcohol **15b** with methanesulfonyl chloride in pyridine gave a mixture of **15b**, the 7-ene compound and a 7-chloro product of

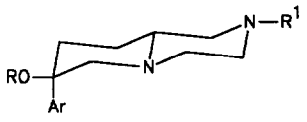
unknown configuration. Presumably, all these compounds are generated from a common aziridinum intermediate arising from expulsion of the mesylate group by the N-5 lone pair. The 7-ene compound is the main product formed on treatment of **15b** with aqueous 48% HBr-LiBr[12] or with $Me_3SiBr$ in chloroform.[13]




13

a) 2–Fluoropyridine, $Bu_4NF{\cdot}3H_2O$, 75 °C, 8h b) 6N–HCl, reflux, 3h
c) 4–Fluorophenylmagnesium bromide, ether, reflux, 15 min
d) 1,2–dibromoethane, Mg, 2–bromofluorobenzene, THF, 40 °C, 1h

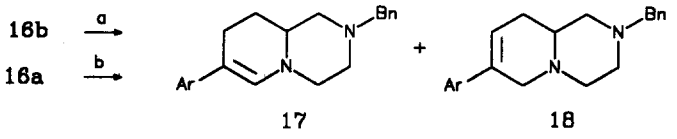



**14a** Ar= 4–F–$C_6H_4$, R= H, $R^1$= 2–Py **14b**
**15a** Ar= 2–F–$C_6H_4$, R= H, $R^1$= 2–Py **15b**
**16a** Ar= 4–F–$C_6H_4$, R=H, $R^1$= $CH_2C_6H_5$ **16b**

Scheme 1

From these results, apparently the best way for removal of the 7-hydroxy group would proceed via elimination and subsequent hydrogenation. However, in view of the concurrent reduction of the pyridyl group observed during hydrogenation, we had to change our strategy by departing from the N-benzyl protected ketone **2**. Reaction of **2** with 4-$FC_6H_4MgBr$ again furnished two diastereomeric alcohols **16a** and **16b** which were dehydrated to a mixture of the 6- and 7-ene compounds **17** and **18** by heating with 48% aqueous HBr (Scheme 2). The isomer **16b** with equatorial hydroxyl group reacted more rapidly, affording a mixture enriched in the 7-alkene **18** (yields of isolated products: 24% of **17** and 70% of **18**). Prolonged reaction of the more stable isomer **16a** resulted in isolation of 60% of **17** and 27% of **18**. Since the dehydration of the epimeric alcohols **16a,b** probably involves a common intermediate, i.e. the 7-carbocation or the related aziridinium ion, a slow acid-catalyzed conversion (**18** → **17**) was suggested by the increased concentration of **17** observed under the more vigorous conditions used for **16a**. This conversion was verified by TLC-analysis at an early stage of the dehydration of **16a** ( reaction mixture enriched in **18**), and also by subjecting the isolated compound **18** to the reaction conditions (aqueous HBr at 100°). The driving force for this transformation probably derives from formation of the 5,6-iminium ion corresponding to enamine **17**.

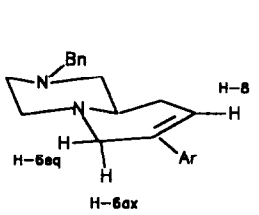



a) 48% aq· HBr, 90 °C, 20 min b) 48% aq· HBr, 100 °C, 2h

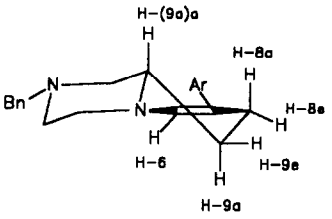
Scheme 2

Structure assignments for the isomers **17** and **18** were based on IR, $^{1}$H- and $^{13}$C-NMR, and mass spectrometry ($M^+$ 322). The IR-spectrum[14] of the enamine **17** displayed a very strong absorption at 1640 $cm^{-1}$ whereas the spectrum of the 7-isomer **18** exhibited a rather weak band at 1660 $cm^{-1}$. Characteristic signals for C-atoms 6 and 8 were detected at 55.7 and 121.1 ppm for the 7-alkene **18** and at 133.6 and 23.4 ppm for enamine **17**. The $^{1}$H-NMR spectrum of **18** was consistent with the *trans*-fused half-chair conformation **A**. The protons H-6 displayed an AB-pattern for H-6e and H-6a ( $\delta$= 3.1 and 3.59, $^{2}$J= 17 Hz). The axial proton H-6a in addition showed a characteristic[15] allylic and homoallylic coupling with the vinylic proton H-8 and both protons H-9 ($^{4}J \approx {}^{5}J$= 3 Hz). The vinylic proton H-8 was detected as a broad multiplet at $\delta$ 5.97.

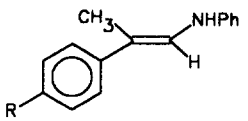
For the enamine **17**, a half-chair conformation **B** is proposed in which the angular N-atom is more or less planar. Whereas generally enamines show a varying degree of pyramidality at the N-atom,[16] extension of the conjugation to the 7-(4-F-phenyl) group could lead to further planarization as observed for the N-atom of the ß-styryl-anilines **19**.[17] In accordance with structure **B**, the 500 MHz $^{1}$H-NMR spectrum of **17** revealed the axial disposition of protons H-8a, H-9a and H-(9a)a. The axial proton H-8a, observed as *dddd*, showed couplings with H-8e ($^{2}$J= 17 Hz), H-9a ($^{3}$J= 12 Hz), H-9e ($^{3}$J= 6 Hz), and the characteristic[15] long-range coupling with the vinylic proton H-6 ($^{4}$J= 2 Hz). The angular proton H-(9a)a was detected as *tt*, showing diaxial couplings with H-1a and H-9a (12 Hz) and ax,eq couplings with H-1e and H-9e (3 Hz).




A (18)




B (17)

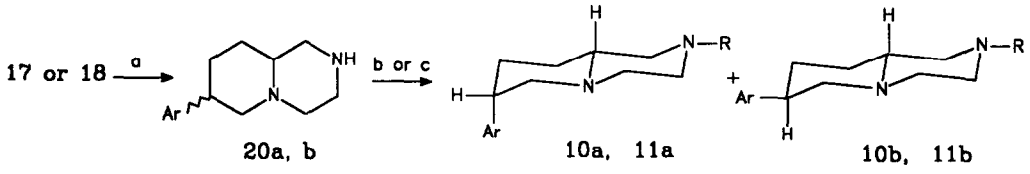



19 (R= H, MeO, $NO_2$)

Hydrogenation of the single isomers **17** and **18** was carried out with 10% Pd/C in acetic acid at 50 °C. These conditions effected both reduction of the 6,7- or 7,8- double bond and N- debenzylation, resulting in a mixture of the epimeric amines **20** (Scheme 3). Arylation of the crude amines **20** with 2-fluoropyridine was accomplished by using the amine activating reagent $Bu_4N^+F^-$.[18] When starting from the hydrogenation products of enamine **17**, the yield for *cis* compound **10a** (65%) was higher than that for *trans* compound **10b**

(9%). In the analogous sequence starting from **18**, about equal amounts of the *cis* and *trans* compounds were isolated (36 and 39%). The latter result suggests an equally favorable access of the Pd catalyst to both faces of the 7,8 double bond for the *trans*-fused structure **A**. However, for the enamine structure **B** a planar or nearly planar N-atom should favour access from the convex face corresponding to the angular proton H-(9a)a.

The analogous target compounds **11a, b** were prepared via benzoylation of the crude amines derived from the 7-alkene **18**. The yields based on **18** were 37% for the *cis* isomer **11a**, and 44% for the *trans* isomer **11b**. Both *cis* and *trans* compounds **10a, b** and **11a, b** adopt a *trans*-fused chair-chair form (Scheme 3). The *trans*-fusion was shown by the coupling pattern for the angular proton H-(9a)a in the $^1$H-NMR spectra (*tt*, $^3$J= 10, 10, 4, 4 Hz) which revealed the axial position of H-(9a)a relative to both rings. For the *cis*-isomers **10a** and **11a**, proton H-7e was detected as a broad multiplet ($\omega_{1/2}$= 10 Hz). Its equatorial orientation was confirmed by the values observed for $^3J_{6a,7e}$ (4Hz) and $^3J_{6e,7e}$ (*ca.* 3Hz). The axial position of proton H-7a for the *trans*-isomers **10b** and **11b** was indicated by diaxial couplings with protons H-6a and H-8a ($^3$J= 11 and 10 Hz).




Ar= 4–$FC_6H_4$

10 R= 2–Py
11 R= 4–$FC_6H_4CO$

a) $H_2$, 10% Pd/C, HOAc, 60 °C, 4h b) 2–fluoropyridine, $Bu_4NF{\cdot}3H_2O$, 90 °C, 3h
c) 4–$FC_6H_4COCl$, acetone, $K_2CO_3$, r·t·

Scheme 3

## CONCLUSION

The apparently trivial task of introducing the 2-pyridyl and *o*- and *p*-fluorophenyl groups in the 2- and 7-positions of synthons **1** and **2** proved to be unexpectedly difficult. This was due in part to the incompatibility of the 2-pyridyl group with reductive removal of the tertiary 7-alcohol group.

For several reasons, use of the N-benzyl ketone **2** seems more attractive than that of acetal amine **1**. Firstly, the N-benzyl group of **2** does not interfere with a number of transformations performed at the 7-position, e.g. Grignard and Wittig reactions and alcohol dehydration. Secondly, removal of the N-benzyl group can be effected by using various methods such as hydrogenation or conversion to the carbamate and hydrolysis.[19] Conversely, deprotection of the acetal group of the functionalised amine synthon **1** requires a rather drastic acid treatment, due to prior protonation of the 5-N-atom. Finally, substitution of the deprotected amine should be reserved as the last step of the synthetic sequence, since this strategy allows for introduction of a large variety of vulnerable 2-N-substituents.

## 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. $^{1}$H-NMR and $^{13}$C-NMR spectra were recorded on Bruker WM 250, AC 300P and AM 500 instruments operating at 250, 300 and 500 MHz for $^{1}$H and 63, 75 and 125 MHz for $^{13}$C measurements. The $^{1}$H 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 10000. Analytical thin layer chromatography was performed using Merk silica gel 60 PF-224. Column chromatography was carried out using 70-230 mesh silica gel 60 (E. M. Merck).

**7-(4-Fluorophenyl)-7-hydroxy-2-(2-pyridyl)octahydro-2H-pyrido[1,2-a]pyrazine (14a, 14b)**

A mixture of 7-(ethylenedioxy)-2-(2-pyridyl)octahydro-2H-pyrido[1,2-a]pyrazine[1] (3.30g, 12 mmol) and 6N-HCl (100 ml) was refluxed for 3 h. The solution was evaporated and the residue was dissolved in water (30 ml). The aqueous solution was cooled to 0 °C and made alkaline with $K_2CO_3$ after the addition of $CH_2Cl_2$ (300 ml). The aqueous phase was further extracted with $CH_2Cl_2$ (2x100 ml) and the combined dichloromethane layers were evaporated. Column chromatography of the residual oil on silica with 3% MeOH-EtOAc yielded **13** (2.55 g, 92%) as a yellow oil. Exact mass: 231.1373 (calcd. for $C_{13}H_{17}N_3O$: 231.1371).

To a stirred suspension of magnesium turnings (520 mg, 0.022 atom) in 50 ml of dry ether, was added a solution of 4-bromofluorobenzene (3.79 g, 21.7 mmole) in 5 ml of dry ether under nitrogen. The mixture was refluxed for 3.5 h, the reagent solution cooled to r.t., and a solution of compound **13** (2.55 g, 11.0 mmole) in dry ether (15 ml) was added dropwise. After being stirred for 20 min., the reaction mixture was poured into ice containing 20 ml of 2N-HCl. The solution then was made alkaline with $K_2CO_3$ and extracted with $CH_2Cl_2$ (2x200 ml). The combined extracts were evaporated and the residue was chromatographed on a silica column using EtOAc as eluent to afford two diastereoisomers: the less polar isomer **14b** (1.92 g, 53%) and the more polar isomer **14a** (1.4 g, 39%), both as pale yellow crystalline products, m.p. (EtOAc) 62-64 °C and 129-130 °C, respectively. The total yield thus was 92%.

**14b**: $\nu_{max}$ (KBr)/cm$^{-1}$: 3470; 2700-2800 (Bohlmann bands); in $CCl_4$: 3500 ( intramolecular OH···N bonding). $^{1}$H NMR (250 MHz, $CDCl_3$): δ 1.65-1.95 ( 4H, H-8,9, m); 2.17 (1H, H-(9a)a, txt, J= 10, 10, 3, 3 Hz); 2.38 (1H, H-6a, d, J= 11 Hz); 2.43 (1H, H-4a, txd, J= 12, 11, 3 Hz); 2.66 (1H, H-1a, dxd, J= 12, 10 Hz); 2.70 (1H, H-6e, br d, J= 11 Hz); 2.80 (1H, H-4e, dxt, J= 11, 3, 3 Hz); 3.03 (1H, H-3a, txd, J= 12, 12, 3 Hz); 4.16 (1H, H-3e, dxq, J= 12, 3, 3, 2 Hz); 4.24 (1H, H-1e, dxt, J= 12, 3, 2 Hz); 3.8 (1H, OH, s: position unchanged in concentrated and diluted soln.); 4-$FC_6H_4$: [7.05 (2H, H-*m*, t, J= 8.5 Hz); 7.51 (2H, H-*o*, dxd, J= 8.5, 6 Hz)]; 2'-Py: [6.65 (1H, H-4', dxd, J= 7, 5 Hz); 6.7 (1H, H-6', d, 8.5 Hz); 7.5 (1H, H-5', txd, J= 8.5, 7, 2 Hz); 8.22 (1H, H-3', dxd, J= 5, 2.2 Hz)]. Exact mass: 327.1743 (calcd. for $C_{19}H_{22}FN_3O$: 327.1746). Anal. Calcd. for $C_{19}H_{22}FN_3O$: C, 69.70; H, 6.75; N, 12.83; F, 5.73. Found: C, 69.34; H, 6.75; N, 12.73; F, 5.73.

**14a**: $\nu_{max}$ (KBr)/cm$^{-1}$: 3200-3400 (OH). In $CCl_4$: 3300-3400 ($\nu_{OH}$: intermolecular hydrogen bonding), 3600 (free OH). $^{1}$H NMR (250 MHz, $CDCl_3$): δ 1.12 (1H, H-9a, txdxd, J= 12, 12, 10, 3 Hz); 1.61 (1H, H-9e, dxq, J= 12, 4, 4, 4 Hz); 1.75 (1H, H-8a, txd, J= 13, 13, 4 Hz); 2.1-2.25 (2H, H-(9a)a,8e, m); 2.35 (1H, H-6a, d, J= 11 Hz); 2.4 (1H, H-4a, txd, J= 12, 12, 3 Hz); 2.56 (1H, H-1a, dxd, J= 12, 10 Hz); 2.9 (1H, H-4e, dxt, J= 12, 3, 3 Hz); 3.01 (1H, H-3a, txd, J= 12, 12, 3 Hz); 3.25 (1H, H-6e, dxd, J= 11, 2 Hz); 4.07 (1H, H-1e, dxt, J= 12, 3, 2 Hz); 4.12 (1H, H-3e, dxq, J=12, 3, 3, 2 Hz); 4'-$FC_6H_4$: [7.2 (2H, H-*m*, t, J= 8.5 Hz); 7.7 (2H, H-*o*, dxd, J= 8.5, 6 Hz)]; 2'-Py: [6.6 (1H, H-4', dxd, J= 7, 5 Hz); 6.65 (1H, H-6', d, J= 8.5 Hz); 7.45 (1H, H-5', txd, J= 8.5, 7, 2 Hz); 8.15 (1H, H-3', dxd, J= 5, 2.2 Hz)]; 2.15 (1H, OH, br s: shifts to 1.95 in dilute soln.). Exact mass: 327.1742 (calcd. for

$C_{19}H_{22}FN_3O$: 327.1746). Anal. Calcd. for $C_{19}H_{22}FN_3O.C_2H_5OH$: C, 67.54; H, 7.56; N, 11.25; F, 5.09. Found: C, 67.71; H, 7.24; N, 11.57; F, 5.29.

**2-(2-Pyridyl)-7-(2-fluorophenyl)-7-hydroxyoctahydro-2H-pyrido[1,2-a]pyrazine (15a, 15b)**

A stirred suspension of magnesium turnings (1.40 g, 0.058 atom) in a mixture of 1,2-dibromoethane (1.88 g, 1 mmol) and dry THF (40 ml) was heated under nitrogen at 50 °C for about 20 min. The mixture was cooled to 40 °C, and a solution of **13** (920 mg, 3.98 mmol) and 1,2-dibromoethane (2.60 g, 7.7 mmol) in THF (25 ml) was added dropwise over a period of 1 h. The brown-red clear solution was stirred at 50 °C for 30 min, then at r.t. for another 30 min. The solution then was poured into a stirred mixture of ice-cold water and 50 ml of 2N-HCl. The aq. solution was made alkaline with $K_2CO_3$ and extracted with $CH_2Cl_2$ (2x200 ml). The combined organic layers were filtered and evaporated. The residue was chromatographed over a column of silica (gradient elution with 10 to 30 % EtOAc-hexane) to give the two diastereomers: the less polar isomer **15b** (652 mg, 50%) and the more polar isomer **15a** (377 mg, 29%) both as pale yellow cristals, m.p. 72-75 and 101-102 °C respectively. The total yield thus was 79%.

**15b**: $\nu_{max}$ (KBr)/$cm^{-1}$: 3140-3500; 2700-2800 (Bohlmann bands), in $CCl_4$: 3400 ($\nu_{OH}$: intermol. hydrogen bonding), 3620 (free OH), on high dilution: only 3620 (free OH). $^1H$ NMR (250 MHz, $CDCl_3$): δ 1.16 (1H, H-9a, m); 1.75 (2H, H-9e,8a, m); 2.37 (1H, H-(9a)a, txt, J= 11, 11, 3, 3 Hz); 2.5 (1H, H-1a, m); 2.48 (1H, H-6a, d, J= 12 Hz); 2.46-2.6 (1H, H-8e, m); 2.63 (1H, H-4a, dxd, J= 12, 10 Hz); 2.96 (1H, H-4e, dxt, J= 12, 4, 2 Hz); 3.05 (1H, H-3a, txd, J= 12, 11, 4 Hz); 3.46 (1H, H-6e, dxd, J= 12, 3 Hz); 4.1 (2H, H-3e,1e, m); 2'-Py: [6.6 (1H, H-4' dxd, J= 7, 5 Hz); 6.65 (1H, H-6', d, J= 8.5 Hz); 7.16 (1H, H-5', txd, J= 8.5, 7, 2 Hz); 8.18 (1H, H-3', dxd, J= 5, 2 Hz)]; 2"-$FC_6H_4$: [7.12 (1H, H-4", dxdxd, J= 12, 8.5, 2 Hz); 7.3 (1H, H-6", m); 7.5 (1H, H-5", m); 7.45 (1H, H-3", txd, J= 8.5, 8.5, 2 Hz)]. $^{13}C$ NMR ($CDCl_3$): δ 26.4 (C-9); 35.9 (C-8); 44.0 (C-3); 48.9 (C-1); 53.8 (C-4); 59.0 (C-9a); 62.3 (C-6); 71.1 (C-7); 2'-Py.: 107.1, 113.3 (C-4', C-6'); 137.5 (C-5'); 147.0 (C-3'); 159.1 (C-1'); 2"$FC_6H_4$: 116.0 (C-3"); 123.75 (C-5"); 129.0 (C-4"); 130.0 (C-6"); 131.4 (C-1"); 161.2 (C-2"). Exact mass: 327.1744 (calcd. for $C_{19}H_{22}FN_3O$: 327.1746).

**15a**: $\nu_{max}$ (KBr)/$cm^{-1}$: 3140-3500, in $CCl_4$: 3400-3500 ($\nu_{OH}$: intramol. hydrogen bonding). $^1H$ NMR (250 MHz, $CDCl_3$): δ 1.8 (3H, H-9,8a, m); 2.2 (2H, H-(9a)a,8e, m); 2.42 (1H, H-6a, d, J= 11 Hz); 2.47 (1H, H-4a, txd, J= 11, 10, 3 Hz); 2.85 (1H, H-6e, dxd, J= 11, 2 Hz); 2.6-2.8 (2H, H-4e,1a, m); 3.05 (1H, H-3a, txd, J= 12, 12, 4 Hz); 4.18 (2H, H-3e,1e, m); Ar: similar to compound **15b**. $^{13}C$ NMR ($CDCl_3$): δ 25.3 (C-9); 34.0 (C-8); 45.0 (C-3); 50.5 (C-1); 53.9 (C-4); 59.7 (C-9a); 63.3 (C-6); 70.45 (C-7); Py: 107.2, 113.5 (C-4', C-6'); 137.6 (C-5'); 147.9 (C-3'); 159.0 (C-1'); 2"-$FC_6H_4$: 115.9 (C-3"); 124.2 (C--5"); 127.75 (C-4"); 128.9 (C-6"); 131.4 (C-1"); 159.75 (C-2"). Exact mass: 327.1747 (calcd. for $C_{19}H_{22}FN_3O$: 327.1746).

$^{13}C$ NMR ($CDCl_3$): for defluorinated compound (impurity), δ 25.6 (C-9); 35.7 (C-8); 45.1 (C-3); 50.6 (C-1); 54.0 (C-4); 59.7 (C-9a); 66.3 (C-6); 70.95 (C-7); $C_6H_5$: 124.7 (C-*o*); 127.05 (C-*p*); 128.2 (C-*m*); 145.0 (C-*ipso*).

**2-Benzyl-7-(4-fluorophenyl)-7-hydroxyoctahydro-2H-pyrido[1,2-a]pyrazine (16a, 16b)**

A solution of compound **2**[1] (5.00 g, 20.5 mmol) in dry ether (20 ml) was added to the Grignard reagent p-fluorophenylmagnesium bromide, prepared from magnesium turnings (1.00 g, 0.042 atom) and 4-bromofluorobenzene (7.50 g, 42.9 mmol) in dry ether in the manner described for **14**. After being stirred for 15 min., the reaction mixture was worked-up in the usual way. Column chromatography of the resulting poduct over silica with EtOAc as eluent furnished two diastereoisomers: the less polar isomer **16a** (2.58 g, 36%) as a yellow oil and the more polar isomer **16b** (3.33 g, 47%) as yellow crystals, m.p. (EtOAc) 78-80 °C ( total yield 83%).

**16a**: $\nu_{max}$ (KBr)/$cm^{-1}$: 3480; 2700-2800 (Bohlmann bands), in $CCl_4$: 3480 (intramolecular OH···N bonding). $^1H$ NMR (250 MHz, $CDCl_3$): δ 1.45-1.65 (2H, H-9a,8a, m); 1.72-1.83 (2H, H-9e,8e, m); 1.88 (1H, H-1a, t, J= 10, 10 Hz); 2.13 (1H, H-(9a)a, txt, J= 11, 11, 3, 3 Hz); 2.2 (1H, H-3a, txd, J=

11.5, 11.5, 3 Hz); 2.33 (1H, H-6a, d, J= 11.5 Hz); 2.41 (1H, H-4a, txd, J= 11, 11, 3 Hz); 2.6 (2H, H-4e,6e, m); 2.77 (2H, H-3e,1e, m); 3.5 (2H, N$CH_2$Ph, s); 3.83 (1H, OH, br s: position unchanged in dilute and conc. soln.); 7.3 (5H, Ph) ; 7.0 (2H,t); 7.45 (2H, dxd). $^{13}$C NMR ($CDCl_3$): δ 25.7 (C-9); 35.65 (C-8); 52.85 (C-3); 54.1 (C-4); 58.9 (C-1); 59.6 (C-9a); 62.8 ($\underline{C}H_2$Ph); 66.3 (C-6); 70.5 (C-7); $CH_2\underline{Ph}$: 126.9 (C-*p*); 128.05 (C-*o*); 128.95 (C-*m*); 137.8 (C-*ipso*); 4'F-$C_6H_4$: 114.6 (C-*m*); 126.3 (C-*o*); 141.15 (C-*ipso*); 161.5 (C-F). Exact mass: 340.1950 (calcd. for $C_{21}H_{25}N_2O$: 340.1951).

**16b**: $\nu_{max}$ (KBr)/cm$^{-1}$: 3250, in $CCl_4$: 3400 (intermolecular hydrogen bonding), 3600 (free OH), on high dilution: 3600 (free OH). $^1$H NMR (300 MHz, $CDCl_3$): δ 0.94 (1H, H-9a, m); 1.39 (1H, H-9e, dxm); 1.66 (1H, H-8a, txd, J= 12.5, 12.5, 4 Hz); 1.8 (1H, H-1a, t, J= 10.5, 10.5 Hz); 2.05 (1H, H-8e, dxdxd, J= 12.5, 6, 3.5 Hz); 2.15 (1H, H-(9a)a, txt, J= 10.5, 10.5, 3.5, 3.5 Hz); 2.23 (1H, H-3a, txd, J= 12, 11, 3 Hz); 2.31 (1H, H-6a, d, J= 11 Hz); 2.39 (1H, H-4a, txd, J= 11, 11, 2.5 Hz); 2.66 (1H, H-1e, dxm); 2.73 (1H, H-4e, dxdxd, J= 11, 5, 2.5 Hz); 2.78 (1H, H-3e, dxm); 3.14 (1H, H-6e, dxd, J= 11, 2.5 Hz); 3.52, 3.45 (2H, N$CH_2$Ph, d,d, J= 12 Hz); 3.1 (1H, OH: shifts to 2.55 on dilution); 7.3 (5H, Ph, m); $C_6H_4$F: [6.95 (2H, H-*m*, t, J= 10.4 Hz); 7.75 (2H, H-*o*, dxd, J= 9 Hz, 5.8 Hz)]. $^{13}$C NMR ($CDCl_3$): δ 26.6 (C-9); 38.65 (C-8); 52.6 (C-3); 54.3 (C-4); 58.1 (C-1); 59.7 (C-9a); 62.9 ($\underline{C}H_2$Ph); 64.9 (C-6); 71.1 (C-7); $CH_2\underline{Ph}$: 127.0 (C-*p*); 128.1 (C-*o*); 129.1 (C-*m*); 137.8 (C-*ipso*); 4'F-$C_6H_4$: 114.4 (C-*m*); 128.7 (C-*o*); 141.8 (C-*ipso*); 161.7 (C-F). Exact mass: 340.1951 (calcd. for $C_{21}H_{25}N_2O$: 340.1949). Anal. Calcd for $C_{21}H_{25}N_2O$: C, 74.09; H, 7.40; N, 8.23 Found: C, 73.70; H, 7.59; N, 7.37.

**2-Benzyl-7-(4-fluorophenyl)-1,3,4,8,9,9a-hexahydro-2H-pyrido[1,2-a]pyrazine (17)**
**2-Benzyl-7-(4-fluorophenyl)-1,3,4,6,9,9a-hexahydro-2H-pyrido[1,2-a]yrazine (18)**

A) From **16b**: A mixture of **16b** (1.20 g, .3.5 mmol) and 10 ml of HBr (48% in water) was heated at 90 °C for 20 min. The solution was made alkaline with aq. $K_2CO_3$ after addition of dichloromethane (200 ml). The aqueous phase was further extracted with $CH_2Cl_2$ (200 ml), and the combined dichloromethane layers were evaporated. Column chromatography of the residue over silica with EtOAc as eluent afforded the less polar product **17** (277 mg, 24%) and the more polar product **18** (796 mg, 70%). Both were isolated as crystals, m.p. (EtOAc) 89-90 °C, and 92-93 °C respectively. The total yield thus was 94%.

B) From **16a**: A mixture of **16a** (1.60 g, 4.7 mmole) and 10 ml of HBr (48% in $H_2O$) was heated at 100 °C for 2 h. Subsquent work-up and chromatography as described above, yielded **17** (1.00 g, 66%) and **18** (407 mg, 27%) (total yield 93%).

**17**: $\nu_{max}$ (KBr)/cm$^{-1}$: 1640, very strong ($\nu_{C=C}$: olefine); 2810, 2770. $^1$H NMR (500 MHz, $CDCl_3$): δ 1.72 (1H, H-9a, txdxd, J= 14, 12, 12, 6 Hz); 1.89 (1H, H-9e, dxdxt, J= 14, 6, 3, 3 Hz); 1.91 (1H, H-1a, t, J= 13, 12 Hz); 2.22 (1H, H-4a, txd, J= 12, 12, 4 Hz); 2.29 (1H, H-8e, dxdxd, J= 17, 6, 3 Hz); 2.51 (1H, H-8a, dxdxdxd, J= 17, 12, 6, 2 Hz); 2.83 (2H, H-4e,1e, m); 2.9 (1H, H-(9a)a, txt, J= 12, 12, 3, 3 Hz); 3.0 (1H, H-3a, txd, J= 13, 12, 2 Hz); 3.03 (1H, H-3e, dxdxd, J= 13, 4, 2 Hz); 3.52 (2H, N$CH_2$Ph, s); 6.3 (1H, H-6, d, J= 2 Hz); 4'F$C_6H_4$: [6.92 (2H, H-*m*, t, J= 8.5 Hz); 7.18 (2H, H-*o*, dxd, J= 8.5, 6 Hz)]; 7.23 (5H, Ph, m). $^{13}$C NMR ($CDCl_3$): δ 23.4 (C-8); 26.6 (C-9); 51.7 (C-3); 53.15 (C-4); 54.25 (C-9a); 58.35 (C-1); 63.0 (N$\underline{C}H_2$Ph) ; 108.2 (C-7); 133.6 (C-6); $CH_2\underline{Ph}$ : 127.0 (C-*p*); 128.2 (C-*o*); 129.0 (C-*m*); 138.0 (C-*ipso*); 4-$FC_6H_4$: 114.9 (C-*m*); 124.9 (C-*o*); 137.3 (C-*ipso*); 160.5 ($\underline{C}$-F). Exact mass: 322.1847 (calcd. for $C_{21}H_{23}FN_2$: 322.1843). Anal. Calcd for $C_{21}H_{23}FN_2$: C, 78.23, H; 7.19; N, 8.69. Found: C, 77.86; H, 7.31; N, 8.60.

**18**: $\nu_{max}$ (KBr)/cm$^{-1}$: 1660, weak ($\nu_{C=C}$: olefine); 2810, 2760, 2780 (Bohlmann bands). $^1$H NMR (250 MHz, $CDCl_3$): δ 1.9 (1H, H-1a, t, J= 11, 11 Hz); 2.12 (2H, H-9, m) ; 2.33 (1H, H-4a, txd, J= 11, 11, 3 Hz); 2.25-2.4 (1H, H-(9a)a, m); 2.48 (1H, H-3a, txd, J= 11, 11, 3 Hz); 2.92 (3H, H-3e,4e,1e, m); 3.1 (1H, H-6a, dxq, J= 16, 3, 3, 3 Hz), [decoupling at δ 5.97 gives (dxt), $^2$J= 16, $^5J_{6a,9e}$= 3, $^5J_{6a,9a}$= 3 Hz]; 3.52 (2H, N$CH_2$Ph, s); 3.59 (1H, H-6e, d, J= 16 Hz); 5.97 (1H, H-8, br s); 4'-$FC_6H_5$: [6.92 (2H, H-*m*, t, J= 8.5 Hz); 7.23 (2H, H-*o*, dxd, J= 8.5, 6 Hz)]; 7.2-7.4 (5H, Ph, m). $^{13}$C NMR ($CDCl_3$): δ 30.5 (C-9); 53.1 (C-3); 54.4 (C-4); 55.3 (C-9a); 55.7 (C-6); 59.5 (C-1); 63.0 (N$\underline{C}H_2$Ph); 133.7 (C-7);

121.1 (C-8); $CH_2$Ph : 127.0 (C-*p*); 128.2 (C-*o*); 129.0 (C-*m*); 138.0 (C-*ipso*); 4'-$FC_6H_4$: 115.0 (C-*m*); 126.6 (C-*o*); 135.9 (C-*ipso*); 162.0 (C-F). Exact mass: 322.1845 (calcd. for $C_{21}H_{23}FN_2$: 322.1843).

**2-(2-Pyridyl)-7-(4-fluorophenyl)octahydro-2H-pyrido[1,2-a]pyrazine (10a, 10b)**

A) from **17**: To a solution of **17** (1.20 g, 3.7 mmol) in 20 ml af acetic acid was added 10% palladized carbon (1.5 g). The reaction vessel was evacuated and the mixture was brought under an atmosphere of hydrogen (balloon). After being stirred at 60 °C for 4h, the cooled mixture was filtered and the catalyst washed with MeOH (300 ml). The combined filtrates were evaporated. The residue was dissolved in 20 ml of water, the solution was made alkaline with $K_2CO_3$ and extracted with $CH_2Cl_2$ (2x250 ml). The organic phase was filtered and evaporated to dryness to give crude product **20** (730 mg) as an oil ( MS: $M^+$ 234).

A stirred mixture of the crude product **20** (730 mg), 2-fluoropyridine (2.0 g, 20.6 mmol) and $Bu_4NF.3H_2O$ (2.0 g, 6.3 mmole) was heated at 90 °C under nitrogen for 3 h. The mixture was cooled and applied to a column of silica gel. Elution with EtOAc afforded the two diastereoisomers: the less polar *cis*-isomer **10a** (753 mg, 65%), and the more polar *trans*-isomer **10b** (92 mg, 9%), both as pale yellow crystalline products, m.p. 96-96.5 °C, 88-90 °C respectively. The overall yield thus was 73% from **17**.

B) from **18**: An analogous procedure starting from **18** (1.00 g, 3.11 mmole) yielded **10a** (350 mg, 36%) and **10b** (380 mg, 39%). The overall yield thus was 75%.

**10a**, *cis:* $^1$H NMR (250 MHz, $CDCl_3$): δ 1.3-1.4 (2H, H9, m); 1.8-1.9 (2H, H-8, m); 2.1 (1H, H-(9a)a, txt, J= 10, 10, 4 , 4 Hz); 2.28 (1H, H-4a, txd, J=12, 12, 3 Hz); 2.47 (1H, H-6a, dxd, J= 12, 4 Hz); 2.62 (1H, H-1a, dxd, J= 12, 10 Hz); 2.80 (1H, H-4e, dxt, J= 12, 3, 2 Hz); 3.0 (1H, H-7e, br s), [in $C_6D_6$: δ 2.65, m, $\omega_{1/2}$= 10 Hz]; 3.05 (1H, H-3a, txd, J= 12, 12, 3 Hz); 3.12 (1H, H-6e, br d, J= 12 Hz); 4.05 (1H, H-1e, dxt, J= 12, 3, 2 Hz); 4.12 (1H, H-3e, dxm, J= 12 Hz); 2'-Py: [6.53 (1H, H-4', dxd, J= 7, 5 Hz); 6.55 (1H, H-6', d, J= 8.5 Hz); 7.50 (1H, H-5', txd, J= 8.5, 2 Hz); 8.30 (1H, H-3', dxd, J= 5, 2.2 Hz)]; 4'-$FC_6H_4$: [6.9 (2H, H-*m*, t, J= 8.5, 8.5 Hz); 7.57 (2H: H-*o*, dxd, J= 8.5, 6 Hz)]. $^{13}$C NMR ($CDCl_3$): δ 24.5 (C-9); 30.5 (C-8); 45.0 (C-3); 50.4 (C-1); 54.5 (C-4); 60.3 (C-9a); 57.9 (C-6); 37.6 (C-7); Py: 106.8, 112.9 (C-4', C-6'); 137.2 (C-5'); 147.8 (C-3'); 159 (C-1'); 4'-$FC_6H_4$: 114.2 (C-*m*); 130.1 (C-*o*); 140.9 (C-*ipso*); 161.0 (C-F). Exact mass: 311.1801 (calcd. for $C_{19}H_{22}FN_3$: 311.1797). Anal. Calcd for $C_{19}H_{22}FN_3$: C, 73.29; H, 7.12; N, 13.49; F, 6.10. Found: C, 72.91; H, 7.15; N, 13.44; F, 5.91.

**10b**, *trans:* $^1$H NMR (250 MHz, $CDCl_3$): δ 1.4-1.65 (2H, H-9a,8a m); 1.75-2.05 (2H, H-9e,8e, dxm); 2.08 (1H, H-(9a)a, m); 2.12 (1H, H-6a, t, J= 11, 11 Hz); 2.36 (1H, H-4a, txd, J= 12, 12, 3 Hz); 2.65 (1H, H-1a, dxd, J= 12, 10 Hz); 2.91 (2H, H-4e,6e, m); 2.98 (1H, H-7a, txd, J= 11, 10, 3, 3 Hz); 3.05 (1H, H-3a, txd, J= 12, 12, 3 Hz); 4.14 (1H, H-3e, m); 4.20 (1H, H-1e, dxt, J= 13, 3, 2 Hz); Ar: similar to **10a**. $^{13}$C NMR ($CDCl_3$): δ 29.7 (C-9); 31 (C-8); 45.1 (C-3); 50.7 (C-1); 54.5 (C-4); 60.3 (C-9a); 62.6 (C-6); 42 (C-7); Py: 106.8, 113 (C-4', C-6'); 137.3 (C-5'); 147.9 (C-3'); 159.2 (C-1'); 4'-$FC_6H_4$: 115.0 (C-*m*); 128.4 (C-*o*); 139.7 (C-*ipso*); 161.3 (C-F). Exact mass: 311.1805 (calcd. for $C_{19}H_{22}FN_3$: 311.1797). Anal. Calcd. for $C_{19}H_{22}FN_3$: C, 73.29; H, 7.12; N, 13.49; F, 6.10. Found: C, 72.85; H, 7.16; N, 13.42; F, 5.93.

**7-(4-Fluorophenyl)-2-(p-flurobenzoyl)octahydro-2H-pyrido[1,2-a]pyrazine (11a, 11b)**

A mixture of the crude product **20** (660 mg, 2.8 mmol: prepared from 1.00 g, of **18**, 3.11 mmol), *p*-fluorobenzoylchloride (536 mg, 3.4 mmol), and $K_2CO_3$ (600 mg, 4.4 mmol) was stirred in acetone overnight. The solvent was evaporated and the residue was partitioned between $CH_2Cl_2$ (2x100) and water (100 ml). The combined organic phases were concentrated and the residue was chromatographed on a column of silica, using EtOAc as eluent to give the two diasteroisomers: the less polar *cis*-isomer **11a** (410 mg, 37 %) and the more polar *trans*-isomer **11b** (487 mg, 44 % ) both as white crystaline products, m.p. 117 °C, 154 °C respectively. The overall yield thus was 81 % from **18**.

***11a***: $^1$H NMR (250 MHz, $C_6D_6$):.δ 0.95 (2H, H-9a,8a, m); 1.45 (2H, H-8e,9e, m); 1.69 (1H, H-(9a)a, txt, J= 10, 10, 4, 4Hz); 1.85 (1H, H-4a, txd, J= 12, 12, 3 Hz); 2.13 (1H, H-6a, dxd, J= 12, 4 Hz); 2.25

(1H, H-4e, dxt, J= 12, 3, 3Hz); 2.44 (1H, H-1a, dxd, J= 12, 10 Hz); 2.63 (1H, H-7e, m); 2.77 (1H, H-6e, br d, J= 12 Hz); 2.82 (1H, H-3a, txd, J= 12, 12, 3 Hz); 3.90 (2H, H-1e,3e, m); Ar: [6.75, 6.88 (4H, H-*m*, 2t, J= 8.5 Hz); 7.23, 7.4 (4H, H-*o*, 2(dxd), J= 8.5 Hz, 6 Hz)]. Anal. Calcd. for $C_{21}H_{22}F_2N_2O$: C, 70.77; H, 6.22; N, 7.86. Found: C, 70.71; H, 6.22; N, 7.75.

***11b***: $^1$H NMR ( 250 MHz, $C_6D_6$): δ 1.2 (4H, H-8,9, m); 1.65 (1H, H-(9a)a, txt, J= 10, 10, 4, 4 Hz); 1.83 (1H, H-6a, t, J= 11, 11 Hz); 1.94 (1H, H-4a, txd, J= 12, 12, 3 Hz); 2.32 (1H, H-4e, dxt, J= 12, 3, 3 Hz); 2.52 (1H, H-1a, dxd, J= 13, 10 Hz); 2.64 (2H, H-6e,7a , m); 2.7 (1H, H-3a, txd, J= 12, 12, 3 Hz); 4.0 (2H, H-1e,3e , m); Ar: similar to **11a**. Anal. Calcd. for $C_{21}H_{22}F_2N_2O$: C, 70.77; H, 6.22; N, 7.86. Found: C, 69.83; H, 6.10; N, 7.65.

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