Stereoelectronic Substituent Effects in Polyhydroxylated Piperidines and Hexahydropyridazines

Henrik Helligsø Jensen, Laila Lyngbye, Astrid Jensen and Mikael Bols*[a]

Abstract: From the pK_a values of the conjugate acids of a large series of hydroxylated piperidines and hexahydropyridazines, a consistent difference in basicity was found between stereoisomers having an axial or equatorial hydroxyl (OH) group either β or γ to the amine. Compounds with an equatorial OH group in the 3-position were 0.8 pH units more acidic than otherwise identical compounds with an axial OH group, whilst compounds with an equatorial OH group in the 4-position relative to the amine were 0.4 pH units more acidic than the corresponding compound with an axial OH. A similar effect was observed for the COOMe substituent. The difference in electron-withdrawing power of axial and equatorial substituents was explained by a difference in charge–dipole interactions in the two systems. Since this stereoelectronic substituent effect causes differences in basicity in different conformers, certain piperidines and hexahydropyridazines were found to change conformation upon protonation. A method for predicting the pK_a of piperidines which takes stereochemistry into account is described.

Keywords: amines · basicity · glycosidase inhibitors · piperidines · stereoelectronic effects

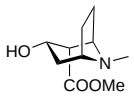
Introduction

The importance of being able to predict the effect of substitution on the reactivity of organic molecules is well recognized and various substituent constants of the Hammett or Taft type can be used to achieve this goal. The prediction of the basicity of amines using Taft substituent constants has been refined by Clark and Perrin.[1] In the Taft approach the pK_a of a protonated amine is calculated from Equation (1), where A and B are constants that depend on whether the amine is primary, secondary, or tertiary; σ^* is a substituent constant. In Clark and Perrin's approach the $B\Sigma\sigma^*$ term is merged into one base-weakening substituent constant. A modified version of this method has been used by Inouye to predict the pK_a of aminosugar derivatives.[2]

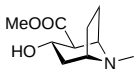
These methods take through-space effects into account, but not the configuration and conformation of the molecule. Thus the methyl esters of both ecgonine (**1**) and pseudoecgonine (**2**) are predicted to have the same pK_a (7.8) even though the

$$pK_a = A - B\Sigma\sigma^* \quad (1)$$

observed pK_a values differ by 1 unit (pK_a(**1**) = 9.2, pK_a(**2**) = 8.2).[3] Clark and Perrin noted that the OH group substituent effect was particularly unpredictable and that its base-weakening effect could vary from 0.4 to 1.2 pH units when β to the amine. They suggested intramolecular hydrogen bonding to be the cause of such anomalies.

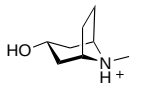


1 (pK_a 9.2)

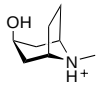


2 (pK_a 8.2)

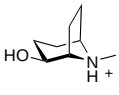
Thus in the series of β- and γ-hydroxyamines **3**–**14** a systematic differences in pK_a between stereoisomers was observed, but only in the compounds **6**, **12**, and **14** was intramolecular hydrogen bonding observed in the IR spectrum.[4, 5]



3 (pK_a 8.74)

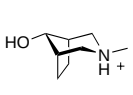


4 (pK_a 9.19)

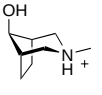


5 (pK_a 8.42)

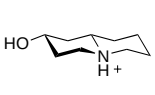
6 (pK_a 9.51)



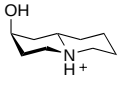
7 (pK_a 7.87)



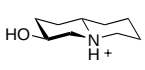
8 (pK_a 8.44)



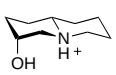
9 (pK_a 9.2)



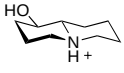
10 (pK_a 9.53)



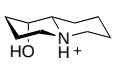
11 (pK_a 8.6)



12 (pK_a 9.87)



13 (pK_a 8.73)



14 (pK_a 10.2)

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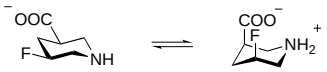
It is well known that substituents on a six-membered ring in the chair conformation prefer the equatorial position, as there would be an unfavorable 1,3-diaxial steric interaction between axial substituents. It is much less recognized that polar substituents prefer an axial orientation in piperidinium ions.[6–12] Thus 3-hydroxypiperidine, upon protonation, shifts from a predominantly equatorial to a predominantly axial orientation.[6] An even more spectacular effect is seen with 5-fluoropiperidine-3-carboxylic acid **15** (Scheme 1). Upon protonation **15** flips from the $^4C_1$ conformation to the $^1C_4$



15

Scheme 1. Conformational change of **15** upon protonation.

conformation, whilst the corresponding nonfluoro derivative piperidine-3-carboxylic acid is predominantly in the $^4C_1$ conformation regardless of pH.[11] The axial preference of polar substituents has been explained by electrostatic interactions, charge–dipole interactions, the *gauche* effect,[13] or even a fluoro-directing effect. However, no connection between the conformation and basicity of a piperidine has apparently been made.

We recently observed differences in the basicity of diastereomeric azasugars much like those in **1**–**14**.[14, 15] Since these differences in basicity appear to be systematic and since the examples of **3**–**14** suggest that hydrogen bonding alone cannot account for the difference, we have studied the basicity of a series of polyhydroxylated or otherwise substituted piperidines and hexahydropyridazines, to investigate to what extent a substituent's electronic effect is related to its stereochemistry. We found that the pK_a differences for **1**–**14** can be explained to a large extent by a difference in the electron-withdrawing power of axial and equatorial substituents. We also observed that the conformational changes in protonated piperidines are related to this dependence of electron withdrawal on geometry, and that a conformational change will occur when the difference in charge stabilization of axial and equatorial substituents is large enough to overcome the steric bias associated with axial substituents.

Results and Discussion

We have measured the pK_a of a large series of polyhydroxylated piperidines (Table 1, which includes some literature pK_a values) and hexahydropyridazines (Table 2), some of which had to be synthesized.

Syntheses: Compounds (±)-**23**,[16] **28**,[17] **31**,[18] (±)-**32**,[18] (±)-**34**,[19] (±)-**35**,[19] (±)-**36**,[19] (±)-**37**,[19] **38**,[20] **40**,[36] **41**,[18] (±)-**42**,[22] (±)-**43**,[22] **44**,[19] **45**,[19] (±)-**46**,[19] (±)-**65**,[23] **66**,[14] and (±)-**67**[23] were synthesized by previously published methods. Compounds **47**, **48**, **52**, and **54**[24] were kindly provided by Professor Asano, and **53** by Professor Stütz. The synthesis of compounds **61**–**63** and **84** will be published later.

Table 1. pK_a values of protonated piperidines at 25 °C.

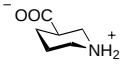
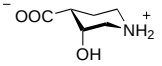
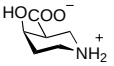
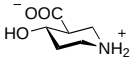
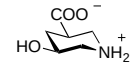
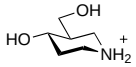
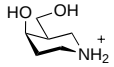
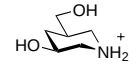
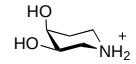
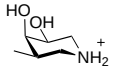
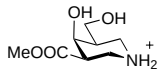
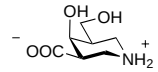
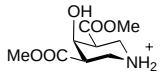
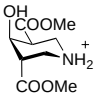
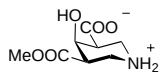
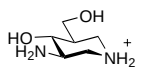
Compound	Structure	pK_a Obs.[a]	pK_a Calcd[b]	pK_a Calcd[c]
piperidine		11.2[2]	10.7	11.2
isonipecotic acid		10.5[8]	10.5	
nipecotic acid		10.3[8]	10.2	
16		10.0[8]	10.0	
17		9.3[8]	9.2	
18		10.0[8]	10.0	
19		9.4[8]	9.6	
20		8.9[8]	8.9	
21		9.7[8]	9.7	
22		8.6[8]	8.6	
23		9.6	9.7	
24		10.1	10.1	
25		9.0	9.0	
26		9.3	9.2	
27		8.8	8.8	
28		9.3	9.3	
29		8.9	8.9	
30		9.5	9.6	
31		8.2	8.1	
32		9.1	9.1	
33		9.1	8.8	
34		9.0	9.0	

Table 1. (cont.)

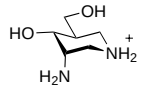
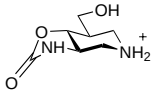
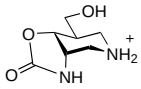
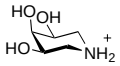
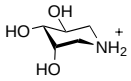
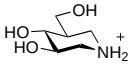
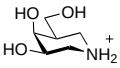
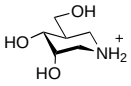
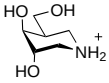
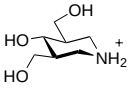
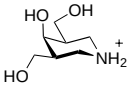
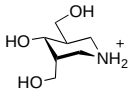
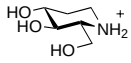
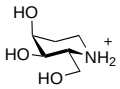
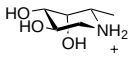
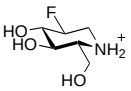
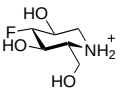
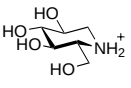
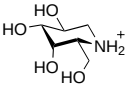
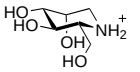
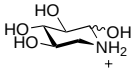
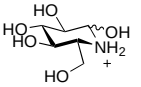
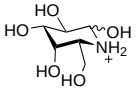
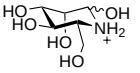
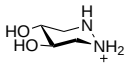
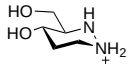
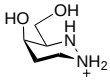
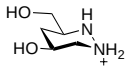
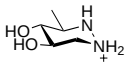
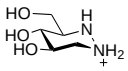
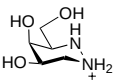
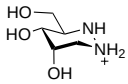
Compound	Structure	pK_a Obs.[a]	pK_a Calcd[b]	Calcd[c]
35		9.1	9.1	
36		6.9	–	
37		7.4	–	
38		7.9	7.9	
39		8.3[27]	8.3	
isofagomine (**40**)		8.4	8.4	9.3
41		8.8	8.8	9.3
42		9.2	9.2	9.3
43		9.4	9.6	9.3
44		9.3	9.3	10.0
45		9.6	9.7	10.0
46		9.2	9.2	10.0
fagomine (**47**)		8.1	8.1	8.7
48		8.5	8.5	8.7
49		8.4[28]	8.4	8.6
50		5.85[29]	5.8	
51		5.75[29]	5.7	
1-deoxynojirimycin (**52**)		6.7, 6.7[30], 6.3[31], 6.6[32]	6.8	7.7
galactostatin (**53**)		7.5, 7.1[26]	7.6	7.7

Table 1. (cont.)

Compound	Structure	pK_a Obs.[a]	pK_a Calcd[b]	Calcd[c]
1-deoxymannonojirimycin (**54**)		7.5, 7.2[28]	7.6	7.7
55		5.7[2]	5.5	5.9
nojirimycin (**56**)		5.3[2]	4.8	5.0
57		5.1[26]	5.6	5.0
58		5.6[27]	5.6	5.0

[a] See ref. or this paper. [b] pK_a values have been calculated from the formula: $pK_a = 10.7 - \Sigma\sigma_s$ (σ_s values from Table 4). [c] Calculated from the formula in ref. [2].

Table 2. pK_a values of protonated hexahydropyridazines at 25 °C determined from titration curves. The site of protonation is shown arbitrarily.

Compound	Structure	pK_a	pK_{aN1}[a]	pK_{aN2}[a]	Calcd pK_a[b]
59		7.9	7.3	7.3	7.6
60		5.5	5.4	5.4	5.7
61		6.4	6.3	5.3	6.3
62		6.8	6.7	6.1	6.8
63		6.2	5.6	6.0	6.1
64		5.5	5.5	5.5	5.8
azafagomine (**65**)		5.3	5.0	4.7	5.2
66		5.7	5.4	5.5	5.8
67		6.0	5.8	5.1	5.9

[a] Calculated from Equation (5). [b] Calculated from Equation (4).

Compound (±)-**24** was made by a simple modification of the synthesis of (±)-**23**.[16] Thus, commercially available (±)-**68** was converted into (±)-**69** by global reduction as previously described and then deprotected with aqueous HCl to provide (±)-**24** (Scheme 2). Synthesis of (±)-**25** was analogous to that of **20** by the Krogsgaard–Larsens group:[8] **70** was substituted with amine and esterified to produce **71** (overall yield 60%; Scheme 2). The ester was reduced with $LiAlH_4$ to

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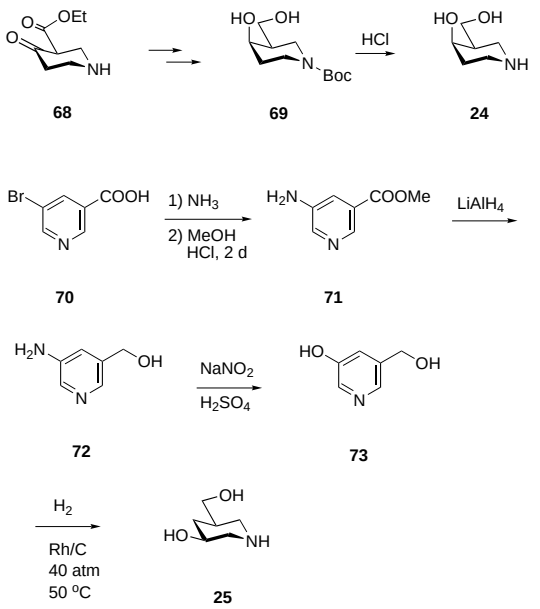
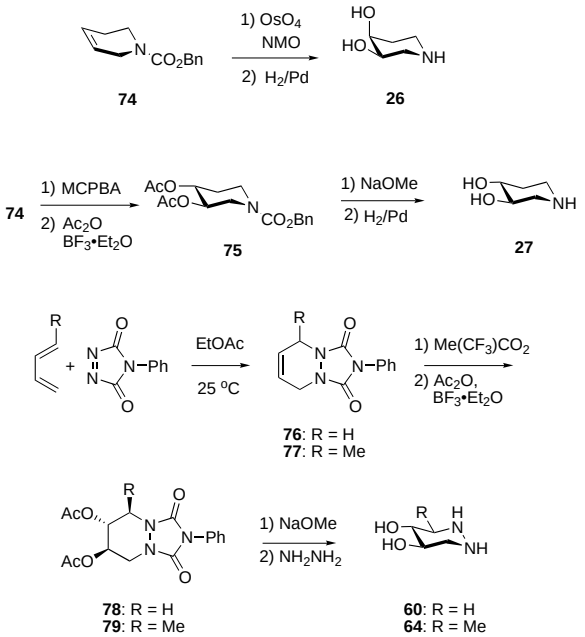


Scheme 2. Synthesis of piperidines **24** and **25**.

give **72** (yield 93%), which was diazotized with $NaNO_2$ and H_2SO_4 to give **73** (yield 83%). This pyridine was hydrogenated at 40 atm and 50 °C with a Rh catalyst, giving **25** (yield 77%) as a racemate.

Compounds (±)-**26** and (±)-**27** were both made from the known alkene **74**. *cis*-Diol (±)-**26** was obtained by dihydroxylation of **74** with OsO_4/NMO followed by conversion to (±)-**26** by hydrogenolysis (Scheme 3). *trans*-Diol (±)-**27** was



Scheme 3. Synthesis of piperidines **26** and **27** and hexahydropyridazines **60** and **64**.

obtained by epoxidation of **74** with *m*-chloroperbenzoic acid (MCPBA); the epoxide obtained was opened with Ac_2O/$BF_3 \cdot Et_2O$ in acetic acid; deacetylation of the resulting diacetate (±)-**75** with NaOMe/MeOH and hydrogenolysis gave (±)-**27**.

Compounds **29**, **30**, and **33** were made by deprotection of the known *N*-Boc-protected derivatives.[18]

Compounds (±)-**60** and (±)-**64** were synthesized by an adaptation of the synthesis of (±)-azafagomine (**65**; Scheme 3).[23] Thus the known Diels–Alder adduct **76**[25] was converted to (±)-**60** by epoxidation with trifluoromethylmethyldioxirane, which gave the epoxide **76a** in 86% yield, which was treated with acetic anhydride/acetic acid in the presence of $BF_3 \cdot Et_2O$ to yield (±)-**78** (94%). This diacetate was deprotected by deacetylation with NaOMe/MeOH, then hydrazinolyzed with neat hydrazine hydrate at 100 °C, giving (±)-**60** in 56% yield over two steps.

The known adduct (±)-**77**[23] was subjected to a similar sequence of reactions to obtain (±)-**64** (Scheme 3). In this case epoxidation gave a 2:1 mixture of the *trans*- and *cis*-epoxides (±)-**77a** and (±)-**77b** in 93% yield. This mixture was unseparable, but since *cis*- and *trans*-epoxides of this type appear to be preferentially attacked at different carbon atoms (C3 and C4, respectively) the mixture was believed to yield mainly the desired isomer. Indeed, acetolysis of the mixture of (±)-**77a** and (±)-**77b** with $Ac_2O/BF_3 \cdot Et_2O$ in acetic acid gave mainly diacetate (±)-**79** containing some of the 2,3-*cis*-3,4-*trans* isomer (±)-**79a**, in a ratio of 6:1. After deprotection as above, (±)-**64** was obtained.

pK_a measurements: The p*K*a values were obtained from pH curves made by titration at 25 °C (representative examples have been included in the Supporting Information). The uncertainty in our determinations by titration at 25 °C is about ±0.1 pH units; therefore the pK_a values are given to only one decimal place. The literature pK_a values for galactostatin (**53**) and 1-deoxymannonojirimycin (**54**) (7.1 and 7.2, respectively)[26] did not fit the values we would expect (see below) so they were remeasured; a pK_a of 7.5 was obtained for both compounds. The pK_a of 1-deoxynojirimycin (**52**) was also ambiguous since three different values (6.3, 6.6, and 6.7) have been reported; our measurement confirmed it to be 6.7 (Table 1).

For epimeric pairs of 4-hydroxypiperidines where the 4-OH group is unquestionably either axial or equatorial, one finds that the axial epimer is more basic. Thus in the epimeric pairs **3**/**4**, **7**/**8**, **9**/**10**, **18**/**19**, **23**/**24**, **40**/**41**, **44**/**45**, and **47**/**48** the pK_a of the axial isomer is 0.3–0.6 pH units higher than the equatorial isomer with an average difference of about 0.4 pH units. This corresponds to a difference in protonation energies ($\Delta\Delta G$) of 2.3 kJ mol^{-1}. Thus, the basicity of the axial isomer appears to be increased consistently. Intramolecular hydrogen bonding is unlikely to cause this effect in this case, in view of the remoteness of the OH group and since it was not observed in the IR spectra of **3**–**4** and **7**–**10**.[4, 5] Similarly in the epimeric pairs of β-hydroxypiperidines **5**/**6**, **11**/**12**, **13**/**14**, **16**/**17**, **40**/**42**, **52**/**53**, and **52**/**54** the axial epimer is 0.7–1.47 pH units more basic than the equatorial one with a typical difference of 0.8 pH units. This corresponds to an average $\Delta\Delta G$ of 4.6 kJ mol^{-1}. In this case intramolecular hydrogen bonding could be affecting the basicity of the axial isomers since it has been observed in **6**, **12**, and **14**.

The basicity of amines is influenced by inductive (through-bond) effects, field (through-space) effects, resonance, solvation, steric hindrance, and internal hydrogen bonding.[1] However, the basicity differences observed here cannot be caused by through-bond or resonance effects, and steric hindrance is expected to be equal in the compounds being compared. Solvation normally affects amine basicity when the solvent shell round the amine is changed by substitution. Since the substituent changes we have studied in many cases are relatively remote from the amine, solvation does not appear to be the cause of the differences in base strength. As explained above, internal hydrogen bonding may play a role in some but not all of the basicity differences; therefore electronic effects must account for a significant fraction of them. They can be explained as a charge–dipole effect of the polar substituents (Figure 1). Each OH group (or other polar substituent) has a dipole moment along the C–O bond that will interact with the protonated amine. If the OH group is directed away from the amine the C–O dipole will destabilize the positive charge, whereas if it is perpendicular it will not affect the amine. In a piperidine axial OH groups in the 3- and 4-positions have C–O bonds that are close to perpendicular to the amine, whilst equatorial OH groups have C–O bonds directed away from it.

Alternatively the difference in electron-withdrawing effect may be explained by differences in orbital overlap between the polar substituent and the bond in the piperidine (Figure 1). In the equatorial isomer **40** the antibonding orbital of the 4-C–O may overlap with the σ orbital of the C2–C3 bond or the C5–C7 bond, thereby drawing electrons away from nitrogen. In the axial isomer **41** the antibonding orbital will overlap with the orbitals of the C3–H and C5–H bonds, thereby not reducing the electron density around nitrogen.

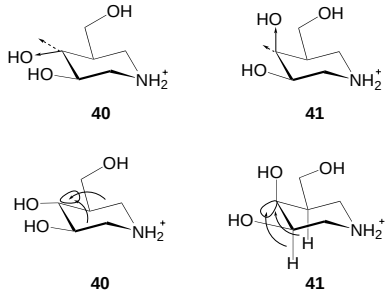


Figure 1. Explanations for the different substituents effect of axial and equatorial 4-OH groups.

Theoretical calculations: To gain support for the theory that electrostatic interactions were causing the stereoelectronic effects, we carried out semiempirical calculations on the protonated and unprotonated forms of 2-, 3-, and 4-hydroxypiperidine with the OH group in either the axial or the equatorial position (Table 3). Regardless of the position of the OH group, the difference in predicted heat of formation (ΔH_f) of the unprotonated piperidine with an axial or equatorial OH group is relatively small. However, for the 3-hydroxypiperidinium ion the axial OH is 14–17 kJ mol^{-1} more stable than the equatorial 3-OH, and for the 4-hydroxypiperidinium ion the axial OH is preferred to the equatorial one by 8–10 kJ mol^{-1}. This shows that a difference in electrostatic interactions in the two molecules is likely to be the cause of the basicity differences observed experimentally. Hydrogen bonding and solvation effects must therefore be expected to play a minor role in governing the basicity differences.

Table 3. Heat of formation of protonated and unprotonated piperidines obtained from AM1 or PM3 calculations using MOPAC in CS 6Chem3D Pro, Version 3.5.1.

Compound	ΔH_f (AM1) [kJ mol^{-1}]	ΔH_f (PM3) [kJ mol^{-1}]
2-hydroxypiperidine (axial 2-OH)	−280.7	−261.9
2-hydroxypiperidine (equat. 2-OH)	−277.8	−260.2
2-hydroxypiperidine, H$^+$ (axial 2-OH)	349.9	392.1
2-hydroxypiperidine, H$^+$ (equat. 2-OH)	346.5	387.6
3-hydroxypiperidine (axial 3-OH)	−280.7	−251.8
3-hydroxypiperidine (equat. 3-OH)	−280.7	−253.1
3-hydroxypiperidine, H$^+$ (axial 3-OH)	347.8	399.7
3-hydroxypiperidine, H$^+$ (equat. 3-OH)	364.9	413.6
4-hydroxypiperidine (axial 4-OH)	−279.4	−253.5
4-hydroxypiperidine (equat. 4-OH)	−281.1	−253.9
4-hydroxypiperidine, H$^+$ (axial 4-OH)	354.9	406.0
4-hydroxypiperidine, H$^+$ (equat. 4-OH)	365.4	414.4

Prediction of pK_a: From the pK_a of a series of compounds with and without OH groups in various positions (Table 1) it was possible to determine the average regio- and stereochemical effect on piperidine basicity by introducing an OH group in a given position. Thus introduction of an equatorial OH group in the β position decreases the pK_a of the piperidinium ion by 1.3 units, whereas introducing an axial β-OH decreases the pK_a by 0.5 units. Similarly the average pK_a values of other substituents were determined (Table 4). From them it is possible to predict the pK_a of a substituted piperidine from $pK_a = 10.7 - \Sigma\sigma_s$, where σ_s is the substituent constant. The pK_a was predicted for piperidine, isonipocetic acid, nipocetic acid, and **16**–**58** to check the consistency of the σ_s values assigned (Table 1).

The σ_s values can also be used to predict the pK_a values of hexahydropyridazines. However, to predict the overall pK_a it is necessary to take into account the two ways in which these compounds can become protonated. In this case Equations (2)–(4) apply, where HA_1 and HA_2 are the products of protonation at either nitrogen; K_{a1} and K_{a2} are the acidity constants of the two nitrogen atoms; and pK_{a1} and pK_{a2} were predicted from Equation (5) using substituent values from Table 4.

$$K_{a\,overall} = [H^+][A]/[HA] = [H^+][A]/([HA_1] + [HA_2]) \quad (2)$$

$$1/K_a = 1/K_{a1} + 1/K_{a2} \quad (3)$$

$$pK_a = \log(1/K_{a1} + 1/K_{a2}) \quad (4)$$

$$pK_a = 7.3 - \Sigma\sigma_s \quad (5)$$

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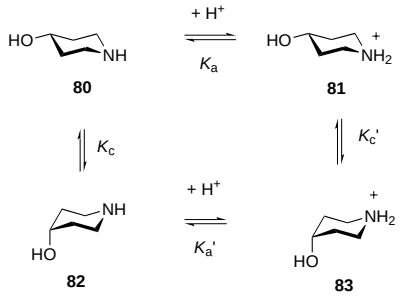
Table 4. Average effect (σ_s [pH units]) of various substituents on the pK_a[a] of a piperidine.

Substituent	α-position	β-position	γ-position
H	0	0	0
OH (eq)	≈2	1.3	0.6
OH (ax)	≈2	0.5	0.2
CH_2OH (eq)	0.7	0.4	–
CH_2OH (ax)	–	0.5[b]	–
Me (eq)	−0.1[b]	−0.1[b]	–
F (eq)	–	2.3[b]	1.7[b]
NH_2 (eq)	–	0.7[b]	–
NH_2 (ax)	–	0.6[b]	–
COO^-(eq)	–	0.5	0.2
COOMe (eq)	–	1.2	–
COOMe (ax)	–	0.2[b]	–
NHAc (eq)	–	1.6[b]	–
NHAc (ax)	–	–	0.5[b]

[a] Determined from the formula p$K_a = 10.7 - \Sigma\sigma_s$. [b] Based on the p$K_a$ of a single compound.

It is clear from Tables 1 and 2 that the predicted pK_a values of all the substituted piperidines and most of the hexahydropyridazines fit remarkably well with experimental values. The difference between prediction and measured value is normally within 0.1 pH units, which is also the experimental uncertainty on the pK_a measurements with the titration method used. The success of these predictions supports the hypothesis that electronic effects and not hydrogen bonding or solvation are the cause of the observed changes in basicity. Only the unsubstituted compounds piperidine and hexahydropyridazine are poorly estimated by this method of calculation.

Effect on conformation: If a polar substituent destabilizes a piperidinium ion more when it is equatorial than when it is axial, this must influence the conformational equilibrium of the molecule. This can be seen in the conformational equilibria and acid–base reactions of 4-hydroxypiperidine (Scheme 4). 4-Hydroxypiperidine in the $^4C_1$ conformation



Scheme 4. Protonation and conformational change of 4-hydroxypiperidine. $K_c = [\mathbf{82}]/[\mathbf{80}]$, $K'_c = [\mathbf{83}]/[\mathbf{81}]$, $K_a = [\mathbf{80}][H^+]/[\mathbf{81}]$, $K'_a = [\mathbf{82}][H^+]/[\mathbf{83}]$.

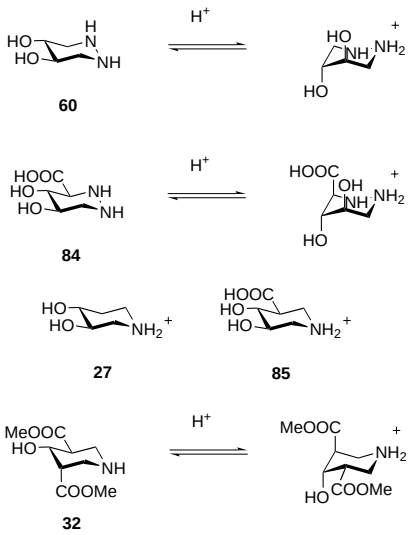
(**80**) can be converted into the $^1C_4$ piperidinium ion **83** in two ways, through either **81** or **82** depending on the sequence of conformational change and protonation. Since both routes result in the same equilibrium, $K_c/K_a = K_c/K_{a'}$ and therefore $K_{a'}/K_a = K_c/K_{c'}$, which shows that a difference in the acidity constant between **80** and **82** will be reflected in similar differences in conformational equilibria between **80** and **82** and between **81** and **83**. This suggests that a change in the conformation may occur when a piperidine is protonated, provided that the stereoelectronic substituent effects are powerful enough to overcome the unfavorable steric interactions associated with 1,3-diaxial substituents, which would explain the conformational change of 3-fluoropiperidine-5-carboxylic acid **15** upon protonation.[11] Fluorine is strongly electronegative and a strong charge–dipole interaction will occur in the protonated piperidine, which will tend to be eliminated by moving the fluorine to the axial position. At the same time fluorine is small and has almost no steric preference for the equatorial position (Table 5).[33]

Table 5. Energy difference between equatorial and axial substituents in a cyclohexane (ΔG_{steric}) and a protonated piperidine ($\Delta G_{electrostatic}$).

Group	ΔG_{steric} [kJ mol^{-1}][a]	$\Delta G_{electrostatic}$ [kJ mol^{-1}]
3-OH	≈4	4.6
4-OH	≈4	2.3
Me	7.3	≈0
3-COOMe	5.4	5.6
F	1	–

[a] From ref. [33].

One may predict that certain hydroxylated piperidines change chair conformation upon protonation. The free energy difference between an equatorial and an axial OH in a cyclohexane is about 4 kJ mol^{-1}.[33] This is less than the electrostatic free energy difference (4.6 kJ mol^{-1}) between an axial and an equatorial β-OH group in a piperidinium ion, but more than the electrostatic energy difference (2.3 kJ mol^{-1}) for a γ-OH (Table 5). Thus 4-hydroxypiperidine should be predominantly in the $^4C_1$ conformation regardless of protonation, whereas 3-hydroxypiperidine should have a small preference (0.6 kJ mol^{-1}) for $^1C_4$ conformation when protonated, and this has indeed been observed.[6] Also, some of the compounds in Tables 1 and 2 might be expected to change conformation. Thus **60** changes from predominantly $^4C_1$ conformation to predominantly $^1C_4$ upon protonation of the amine (Scheme 5). The coupling constant $J_{3ax,4}$,in water, changed from 9.6 Hz to 4.5 Hz upon protonation, from which it can be estimated[37] that the conformer ratio goes from 9:1 to 1:4. Piperidine **27**, on the other hand, does not change its predominant conformation in water, although the equilibrium is shifted toward more $^1C_4$ conformer. The similar coupling constant, $J_{2ax,3}$, changed from 8.4 Hz (pH 11) to 6.2 Hz (pH 1), from which it can be estimated[37] that the conformer ratio goes from 4:1 to 1:1. In these cases the predicted values of ΔG_{steric} for two equatorial OH, and $\Delta G_{electrostatic}$ for a 3-OH and a 4-OH interaction, would be 8 kJ mol^{-1} and 6.9 kJ mol^{-1}, respectively. Therefore the predicted preference for the $^4C_1$ conformation after protonation would still be 1.1 kJ mol^{-1}. The more profound change in conformation of **60** than of **27** is probably due to ΔG_{steric} being smaller in the case of hexahydropyridazines than the values in Table 5, as one 1,3-diaxial interaction is absent because of the presence of the extra nitrogen atom. Thus one of the nitrogen atoms in **60** will not have an axial H atom, whereas protonated **27** will have a CH_2 in that position.



Scheme 5. Conformational change of **32**, **60** and **84** upon protonation.

The same phenomenon was seen with the carboxylic acids **84** and **85**. Compound **84** was observed to flip to predominantly $^1C_4$ conformation when the nitrogen was protonated, regardless of whether the carboxylate was protonated or not. It had an estimated conformer ratio in water of 9:1 at pH 11 and 1:4 at pH 1. However, the known compound **85** is predominantly in the $^4C_1$ conformation as the hydrochloride.[20]

Clear evidence for the change of piperidine **32** from predominantly $^4C_1$ to predominantly $^1C_4$ upon protonation in water was seen from the coupling constant $J_{4,5}$, which was 7.6 Hz at pH 11 but 4.8 Hz at pH 2. Based on these values the conformer ratios $^4C_1/^1C_4$ for **32** were estimated[37] to be 2:1 at pH 11 and 1:2 at pH 2.

Another way of explaining the observed conformational changes is that the two conformers of a hydroxylated piperidine or hexahydropyridazine have different basicity, and protonation will cause the amine to prefer the less acidic conformation.

Recently it was reported by Pinto's group that a trihydroxylated six-membered sulfonium salt adopted a conformation with all three OH groups axial, contrary to expectations.[38] This observation can also be explained using the stereoelectrostatic substituent effects postulated in this paper.

The *gauche* effect has been used to explain why 3-hydroxypiperidinium salts prefer a conformation with the *O*-substituent axial.[13] It is possible that the *gauche* effect can account for some of the conformational changes observed here, but it cannot explain that of **32**, which does not have two heteroatoms *gauche*.

Conclusion

We have shown that an equatorial OH group is more strongly electron-withdrawing than an axial OH group in the 3- and 4-positions of piperidines and hexahydropyridazines. This stereoelectronic effect affects the basicity of these compounds and also causes some piperidine or hexahydropyridazine conformers to have different basicity, which can cause them to change conformation upon protonation. The effect must also be expected to play a role in many other systems. Thus it can explain the difference in basicity of cocaine derivatives **1** and **2**. It should also affect the reactivity of compounds in reactions where positive charge is developed in the transition state. Thus as we demonstrated previously,[15] the rate of acidic glycoside hydrolysis is correlated with piperidine basicity; that is, glycosides with axial OH groups are hydrolyzed faster than glycosides with equatorial OH groups because the equatorial OH makes it more difficult to build positive charge on C1. Other reactions may be found to be affected similarly.

Experimental Section

General: All reactions were carried out under an inert atmosphere in preheated glass equipment. Solvents were distilled under anhydrous conditions. Thus THF was distilled from sodium/benzophenone and used directly. All reagents were used as purchased, without further purification. Columns were packed with silica gel 60 (230—400 mesh) as the stationary phase. TLC glass plates (Merck 60, F_{254}) were visualized by spraying with cerium ammonium sulfate (1%) and phosphomolybdic acid (1.5%) in H_2SO_4 (10%) and heating until colored spots appeared.

(±)-(3,4-*cis*)-3-Hydroxymethyl-4-hydroxypiperidine (24): Piperidone (±)-**68** was converted to *N-tert*-butoxycarbonyl-3-ethoxycarbonyl-4-piperidone (**68a**) as previously described.[21] Then (±)-**68a** (300 mg, 1.1 mmol) was dissolved in absolute ethanol (30 mL), and DIEA (140 mg, 1.1 mmol) was added. A flow of nitrogen was bubbled through the solution for 5 min, then 10% Pd on carbon (200 mg) was added. The mixture was hydrogenated for 24 h (40 atm, 50 °C) before filtering through Celite and evaporating to dryness. To get rid of the DIEA the remaining oil was dissolved in ether (20 mL) and a saturated solution of $KHSO_4$ (20 mL) was added. The aqueous phase was extracted with diethyl ether (3×20 mL), then the combined organic phases were dried ($MgSO_4$) and evaporated to crude 3,4-*cis*-*N*-*tert*-butoxycarbonyl-3-ethoxycarbonyl-4-hydroxypiperidine (**68b**).

Without further purification the resulting alcohol (±)-**68b** (300 mg, 1.1 mmol) was dissolved in dry THF (50 mL) and treated with $LiBH_4$ (24 mg, 1.1 mmol). The solution was refluxed for 10 min and cooled to 0 °C before a solution of saturated $KHSO_4$ (40 mL) was added slowly. The two layers were separated, and the aqueous phase was extracted with AcOEt (2×30 mL). The combined organic phases were washed with brine (40 mL), dried over $MgSO_4$ and evaporated to dryness, leaving crude (±)-**69**.

The diol **69** was deprotected by stirring it in hydrochloric acid (4 M, 10 mL) overnight. Removal of the solvent at reduced pressure gave (±)-**24**.[39] ^{1}H NMR (D_2O): $\delta = 4.17$ (q, $J = 3.0$ Hz, 1H, H4), 3.67 (dd, $J_{(5,5'a)} = 6.6$, $J_{(5'a,5'b)} = 11.0$ Hz, 1H, H5′a), 3.54 (dd, $J_{(5,5'b)} = 7.4$ Hz, 1H, H5′b), 3.06–3.20 (m, H2eq, H2ax, H6eq), 2.93 (t, $J_{(6ax,6eq;6ax,5)} = 11.8$ Hz, 3H, H6ax), 1.80–2.14 (m, 3H, H3eq, H3ax, H5); ^{13}C NMR (D_2O): $\delta = 62.8$ (C4), 60.4 (C5′), 40.9, 40.0 (C2, C6), 38.8 (C5), 29.4 (C3). These NMR data were essentially identical to those in DMSO published previously.[39]

Methyl 5-aminonicotinate (71): 5-Bromonicotinic acid (**70**, 4.04 g, 20 mmol) and $CuSO_4 \cdot 5H_2O$ (1 g, 4 mmol) were dissolved in concentrated aqueous ammonia (18 mL) and heated in a sealed container to 180 °C for 24 h. The solvent was then carefully removed, and the residue was dissolved in methanol (175 mL). Acetyl chloride (10 mL) and trimethyl orthoacetate (30 mL) were added to this solution, and the mixture was refluxed for 48 h. Evaporation under reduced pressure and addition of aqueous sodium carbonate solution (10%, 50 mL) followed by extraction with CH_2Cl_2 (10×50 mL) yielded **71** as a brown powder (1.82 g, 60%). The product was sufficiently pure for further reaction.[40] ^{1}H NMR ($CD_3C(O)CD_3$): $\delta =$ 8.39 (s, 1H, ArH), 8.25 (s, 1H, ArH), 7.54–7.56 (m, 1H, ArH), 5.2 (br s, 2H, NH_2), 3.87 (s, 3H, OCH_3); ^{13}C NMR ($CD_3C(O)CD_3$): $\delta = 166.8$ (CO_2CH_3), 145.3, 141.3, 139.2, 126.8, 120.8 (Ar), 52.3 (CO_2CH_3).

3-Hydroxy-5-hydroxymethylpyridine (73): Methyl ester **71** (584 mg, 3.84 mmol) was dissolved in dry THF (12 mL) and the solution was cooled

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to 0 °C. After addition of lithium aluminum hydride (584 mg, 15.4 mmol) the cooling bath was removed, and the mixture stirred for 21 h at room temperature. The solution was then carefully acidified (aqueous HCl) to pH 3 and thereafter alkalized (solid Na_2CO_3) to pH 8. The solvents were removed under reduced pressure and the residue was filtered through a column of silica gel (CH_2Cl_2/CH_3OH 9:1). This gave the aminopyridine **72** as a yellow oil (428 mg, 93 %). ^{1}H NMR ($CD_3C(O)CD_3$): $\delta = 7.92$ (s, 1H, ArH), 7.80 (s, 1H, ArH), 7.04 (m, 1H, ArH), 4.53 (s, 2H, CH_2), 4.36 (br s, 3H, OH, NH_2); ^{13}C NMR ($CD_3C(O)CD_3$): $\delta = 144.5$, 137.9, 136.4, 135.2, 119.1 (Ar), 61.4 (CH_2).

The aminopyridine **72** (424 mg, 3.53 mmol) was dissolved in sulfuric acid (2.5 M, 5 mL) and put on an ice bath. Small portions of $NaNO_2$ (268 mg, 3.89 mmol) were added over a 10 min period. The solution was then stirred for a further 30 min, whereafter sulfuric acid (1 M, 15 mL) was added and the mixture heated to 70 °C for 1 h. After ion exchange (Amberlite IR-120, H^+) the product mixture was released from the resin with 5 % NH_4OH, which gave **73** (357 mg, 83 %).[41] ^{1}H NMR (D_2O): $\delta = 7.86 - 7.82$ (m, 2H, ArH), 7.30 (t, $J = 2.0$ Hz, 1H, ArH), 4.58 (s, 2H, CH_2); ^{13}C NMR (D_2O): $\delta = 157.3$, 138.3, 133.4, 132.9, 126.1 (Ar), 60.3 (CH_2).

***cis*-3-Hydroxy-5-hydroxymethylpiperidine (25)**: Pyridine **73** (107 mg, 0.86 mmol) was dissolved in ethanol (10 mL) and Rh/C was added (5 %, 100 mg). A hydrogen pressure of 40 atm was applied and the reaction vessel was heated to 50 °C for 48 h. The reaction mixture was filtered through Celite and flash chromatography of the residue with ethanol/CH_2Cl_2/conc. NH_4OH 10:9:1 ($R_f = 0.19$) gave **25** (86 mg, 77 %). ^{1}H NMR (D_2O): $\delta = 3.68$ (tt, $J_{ax,ax} = 10.6$, $J_{ax,eq} = 4.6$ Hz, 1H, H3), 3.45 (d, $J_{5,5'} = 6.2$ Hz, 2H, H5′a, H5′b), 3.11 (dd, $J_{2eq,3} = 3.8$, $J_{2eq,2ax} = 11.8$ Hz, 1H, H2eq), 2.98 (dd, $J_{5,6eq} = 3.6$, $J_{6eq,6ax} = 12.4$ Hz, 1H, H6eq), 2.26 (t, 1H, H2ax), 2.16 (t, 1H, H6ax), 1.94–2.10 (m, 1H, H4eq), 1.64–1.88 (m, 1H, H5), 1.02 (q, 1H, H4ax); ^{13}C NMR (D_2O): $\delta = 66.3$ (C3), 63.8 (C5′), 50.5, 46.5 (C2, C6), 37.3, 35.0 (C4, C5). Acetylation of a sample with pyridine and acetic anhydride followed by evaporation gave the triacetate which was characterized by MS: MS (ES): m/z: 280.1161 [M+Na$^+$]; calcd for $C_{12}H_{19}NO_5$+Na: 280.1161.

(±)-3,4-*cis*-3,4-Dihydroxypiperidine (26): *N*-Benzyloxycarbonyl-1,2,5,6-tetrahydropyridine[34] (**74**; 0.10 g, 0.45 mmol) was dissolved in acetone/H_2O (1:1, 0.4 mL) and *N*-methylmorpholine *N*-oxide (80 mg) was added, followed by a solution (0.2 mL) of OsO_4 in *tert*-butanol (10 g L^{-1}), then the mixture stirred for five days at 25 °C. A saturated solution of $Na_2S_2O_5$ (6 mL) was added and the mixture was extracted with EtOAc (5 × 5 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated to give the diol product ($R_f = 0.29$, pentane/EtOAc 5:1). This compound was dissolved in EtOH (3 mL), adding one drop of HCl (conc.), and hydrogenated (1 atm, 2 h) using Pd/C (25 mg, 10 %) as a catalyst. The resulting solution was filtered and concentrated to give (±)-**26** (38 mg, 56 %) as a hydrochloride. The free amine could be obtained by ion exchange chromatography in Amberlite IR-120. The NMR spectrum of the free amine was identical to the previously published spectra of the optically pure compound.[35]

3,4-*trans*-3,4-Dihydroxypiperidine (27): *N*-Benzyloxycarbonyl-1,2,5,6-tetrahydropyridine[34] (**74**, 0.28 g, 1.27 mmol) was dissolved in dichloromethane (4 mL) at 0 °C, and a solution of *m*-chloroperbenzoic acid (0.34 g, 1.78 mmol) was added in CH_2Cl_2 (8 mL). Cooling was stopped and the mixture was stirred for 4 h at 25 °C, then washed with 5 % aqueous K_2CO_3 solution (10 mL) followed by a saturated aqueous NaCl solution (10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated. The product was purified by flash chromatography (pentane/EtOAc 5:1, R_f = 0.21) giving *N*-benzyloxycarbonyl-3,4-epoxypiperidine (92 %, 0.27 g).

This epoxide was dissolved in acetic acid (7 mL) and acetic anhydride (0.47 mL) was added. Boron trifluoride etherate (0.15 mL, 1.15 mmol) was slowly added, and the mixture was stirred at room temperature for 3 h. An aqueous saturated solution of $NaHCO_3$ (3 mL) was added, and the mixture extracted with EtOAc (10 mL). The organic layer was washed with saturated aqueous Na_2CO_3 solution (10 mL) followed by saturated aqueous NaCl solution (10 mL), and was dried over $MgSO_4$. After filtration crude **75** was obtained in quantitative yield.

This product was dissolved in MeOH (2 mL), and a solution of a catalytic amount of NaOMe in MeOH (1 mL) was added. The mixture was stirred for 1.5 h, then dry ice was added and the solution was concentrated. The product diol was purified by flash chromatography (pentane/EtOAc 4:1, $R_f = 0.35$), then dissolved in EtOH (3 mL, adding one drop of HCl (conc.), and hydrogenated (1 atm, 2 h) using Pd/C (25 mg, 10 %) as catalyst. The resulting solution was filtered and concentrated to give **27** (50 mg, 65 %) as the hydrochloride. The NMR spectrum was identical to previously published spectra of the optically pure hydrochloride.[20]

(3*R*,4*S*,5*R*)-4-Hydroxy-5-hydroxymethyl-3-piperidinecarboxylic methyl ester hydrochloride (29): Prepared by treating *N*-*tert*-butoxycarbonyl-(3*R*,4*S*,5*R*)-4-hydroxy-5-hydroxymethyl-3-piperidinecarboxylic methyl ester[18] with hydrochloric acid, and subsequent evaporation. ^{1}H NMR (D_2O): $\delta = 4.5$ (br s, 1H, H4), 3.7 (s, 3H, OMe), 3.4–3.6 (m, 3H, H5′a, H5′b, H2eq), 3.2 (m, 2H, H2ax, H6eq), 3.0 (ddd, $J_{3,4} = 2.5$, $J_{2eq,3} = 4$, $J_{2ax,3} = 13$ Hz, 1H, H3), 2.9 (t, $J = 13$ Hz, 1H, H6ax), 2.1 (m, 1H, H5).

(3*R*,4*S*,5*R*)-4-Hydroxy-5-hydroxymethyl-3-piperidinecarboxylic acid hydrochloride (30): Prepared by treating *N*-*tert*-butoxycarbonyl-(3*R*,4*S*,5*R*)-4-hydroxy-5-hydroxymethyl-3-piperidinecarboxylic acid[18] with hydrochloric acid, and subsequent evaporation. The NMR spectrum was identical to that previously published for the racemic compound.[19]

(3*R*,4*S*,5*S*)-3-Carboxymethyl-4-hydroxy-5-piperidinecarboxylic acid hydrochloride (33): Prepared by treating *N*-*tert*-butoxycarbonyl-(3*R*,4*S*,5*S*)-3-carboxymethyl-4-hydroxy-5-piperidinecarboxylic acid[18] with hydrochloric acid, and subsequent evaporation. ^{1}H NMR (D_2O): $\delta = 4.8$ (m, 1H, H4), 3.7 (s, 3H, OMe), 3.5 (dt, $J_{gem} = 14$ Hz, 2H, H2eq, H6eq), 3.0–3.3 (m, 4H, H2ax, H3, H5, H6ax).

(±)-8-Phenyl-1,6,8-triazabicyclo[4.3.0]non-3-ene-7,9-dione (76): Prepared as previously described.[25] Yield: 57 % (Lit.:[25] 62 %); ^{1}H NMR ($CDCl_3$): $\delta = 7.5$ (m, 5H, Ar), 5.97 (s, 2H, H3, H4), 4.19 (s, 4H, H2a, H2b, H5a, H5b); ^{13}C NMR ($CDCl_3$): $\delta = 152.6$ (*C*=O), 131.4, 128.3, 129.3, 125.6 (Ar), 121.0 (C3, C4), 43.6 (C2, C5); MS (ES): m/z: 230.0925 [M+H$^+$]; calcd for $C_{12}H_{11}O_2N_3H$: 230.0930.

(±)-(3,4-*trans*)-3,4-Epoxy-8-phenyl-1,6,8-triazabicyclo[4.3.0]nonane-7,9-dione (76a): Alkene **76** (20 mg, 0.87 mmol) was dissolved in CH_3CN (6.8 mL) and water (4.5 mL) in a two-necked flask equipped with a dropping funnel with a dry ice/acetone condenser, and the solution was cooled to 0 °C. 1,1,1-Trifluoroacetone (0.9 mL) and $NaHCO_3$ (0.59 g) were added, followed by Oxone (2.8 g) in small portions over a 5 min period. The reaction mixture stirred at room temperature for 20 h. An extra amount of $NaHCO_3$ (0.29 g) and Oxone (1.39 g) were added and after reaction for another 2.5 h the mixture was worked up. Water (45 mL) was added and the mixture was extracted with $CHCl_3$ (8 × 25 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated to give **76a** (0.185 g, 86 %). ^{1}H NMR ($CDCl_3$): $\delta = 7.4$ (m, 5H, Ar), 4.18 (d, $J_{2,2} = 13.6$ Hz, 2H, H2a, H5a), 3.90 (d, 2H, H2b, H5b), 3.57 (s, 2H, H3, H4); ^{13}C NMR ($CDCl_3$): $\delta = 151.6$ (*C*=O), 129.9, 128.1, 127.3, 124.4 (Ar), 47.4 (C3, C4), 41.7 (C2, C4); MS (ES): m/z: 268.0703 [M+Na$^+$]; calcd for $C_{12}H_{11}O_2N_3Na$: 268.0698.

(±)-(3,4-*trans*)-3,4-Diacetoxy-8-phenyl-1,6,8-triazabicyclo[4.3.0]nonane-7,9-dione (78): Epoxide **76a** (0.64 g, 2.6 mmol) was dissolved in acetic anhydride (2.49 mL) and dry acetic acid (35 mL) was added. Boron trifluoride etherate (0.77 mL) was added carefully at 25 °C, and the reaction mixture was kept at 25 °C for 2.5 h. After neutralization with a saturated $NaHCO_3$, the solution was extracted with EtOAc (4 × 200 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution and with saturated NaCl solution. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated to give **78** (0.86 g, 94 %). ^{1}H NMR ($CDCl_3$): $\delta = 7.4$ (m, 5H, Ar), 5.11 (d, $J_{3,2a} = 1.2$ Hz, 2H, H3, H4), 4.07 (dd, $J_{2a,2b} = 13.2$, $J_{2a,3} = 1.2$ Hz, 2H, H2a, H5a), 3.69 (d, 2H, H2b, H5b), 2.14 (s, 6H, 2 CH_3); ^{13}C NMR ($CDCl_3$): $\delta = 168.3$ (O−*C*=O), 151.4 (N-*C*=O), 129.9, 128.2, 124.5, 127.3 (Ar), 64.0 (C3, C4), 42.9 (C2, C5), 19.9 (CH_3); MS (ES): m/z: 370.1019 [M+Na$^+$]; calcd for $C_{16}H_{17}O_6N_3Na$: 370.1015.

(±)-(4,5-*trans*)-4,5-Dihydroxyhexahydropyridazine (60): Diacetate **78** (0.198 g, 0.57 mmol) was dissolved in methanol (10 mL) containing a catalytic amount of Na and was kept at room temperature for 1 h 15 min. The solution was concentrated to give the crude diol. ^{1}H NMR (CD_3OD): $\delta = 7.35$ (m, 5H, Ar), 3.88 (m, 2H, H3, H4), 3.77 (dd, $J_{2a,2b} = 12.4$, $J_{2a,3} = 2.3$ Hz, 2H, H2a, H5a), 3.68 (m, 2H, H2b, H5b). This diol (0.57 mmol) was dissolved in hydrazine hydrate (10 mL) and kept at 100 °C for 18 h. The hydrazine was removed by evaporation and the crude product was dissolved in water and poured onto an ion exchange resin column (Amberlyst 15, H^+). The column was washed with water and eluted with NH_4OH (2.5 %). The eluent was removed at reduced pressure and the product was further purified by EtOH/25 % NH_4OH 99:1 to give **60**[42]

(38 mg, 56%); ^{1}H NMR (D_2O): $\delta = 3.44$ (m, 2H, H4, H5), 3.10 (dd, $J_{3eq,4} = 4.4$, $J_{3eq,3ax} = 12.8$ Hz, 2H, H3eq, H6eq), 3.07 (dd, $J_{3ax,4} = 9.6$ Hz, 2H, H3ax, H6ax); ^{13}C NMR (D_2O): $\delta = 51.2$ (C3, C6), 70.8 (C4, C5).

(±)-(2,3-*trans*-3,4-*cis*)- and (2,3-*cis*-3,4-*cis*)-3,4-Epoxy-2-methyl-8-phenyl-1,6,8-triazabicyclo[4.3.0]nonane-7,9-dione (77a and 77b): Alkene **77**[23] (1.04 g, 4.3 mmol) was dissolved in CH_3CN (33.3 mL) and water (22.2 mL) in a two-necked flask equipped with a dropping funnel and a dry ice/acetone condenser, and the solution was cooled to 0 °C. 1,1,1-Trifluoroacetone (4.5 mL) and $NaHCO_3$ (2.89 g) was added, followed by Oxone (13.7 g) in small portions over a 5 min period. The reaction mixture was stirred at room temperature for 1 h, and the mixture was worked up. Water (200 mL) was added and the mixture was extracted with $CHCl_3$ (8 × 100 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated to give a 2:1 mixture of **77a** and **77b** as a yellow solid (1.03 g, 93%). **77a**: ^{1}H NMR ($CDCl_3$): $\delta = 7.4$ (m, 5H, Ar), 4.58 (dq, $J_{2,2'} = 6.8$, $J_{2,3} = 1.6$ Hz, 1H, H2), 4.00 (d, $J_{5a/5b,4} = 2.4$ Hz, 2H, H5a, H5b), 3.53 (dt, $J_{4,3} = 4.0$ Hz, 1H, H4), 3.28 (dd, 1H, H3), 1.39 (d, 3H, H2′); ^{13}C NMR ($CDCl_3$): $\delta = 129.9$, 128.1, 127.2, 124.3 (Ar), 52.0, 48.0 (C3, C4), 46.8 (C2), 41.2 (C5), 13.3 (C2′); **77b**: ^{1}H NMR ($CDCl_3$): $\delta = 7.4$ (m, 5H, Ar), 4.40 (dq, 1H, $J_{2,2'} = 6.0$, $J_{2,3} = 4.4$ Hz, H2), 4.27 (dd, $J_{5b/5a} = 13.6$, $J_{5b,4} = 1.2$ Hz, 1H, H5b), 3.58 (dd, $J_{5a,4} = 2.0$ Hz, 1H, H5a), 3.53 (m, 1H, H4), 3.47 (t, $J_{3,2/4} = 4.2$ Hz, H3, 1H), 1.42 (d, 3H, H2′); ^{13}C NMR ($CDCl_3$): $\delta = 129.9$, 128.1, 127.2, 124.3 (Ar), 51.6, 49.1 (C3, C4), 47.7 (C2), 42.7 (C5), 11.9 (C2′); MS (ES): m/z: 282.0854 [M+Na$^+$]; calcd for $C_{13}H_{13}N_3O_3Na$: 282.0855.

(±)-(2,3-*trans*-3,4-*trans*)- and (2,3-*cis*-3,4-*trans*)-3,4-Diacetoxy-2-methyl-8-phenyl-1,6,8-triazabicyclo[4.3.0]nonane-7,9-dione (79 and 79a): Epoxides **77a** and **77b** (1.04 g, 4.0 mmol) were dissolved in acetic anhydride (3.79 mL) and dry acetic acid (50 mL) was added. Boron trifluoride etherate (1.14 mL) was added carefully at 0 °C, and the reaction mixture was kept at 25 °C temperature for 2 h. After addition of water (100 mL) and neutralization with a saturated $NaHCO_3$ solution, the solution was extracted with $CHCl_3$ (3 × 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (200 mL) and with saturated NaCl solution (200 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated to give a 6:1 ratio of **79** and **79a** (1.26 g, 87%). **79**: ^{1}H NMR ($CDCl_3$): $\delta = 7.4$ (m, 5H, Ar), 5.06 (m, $J_{4,3} = 2.6$ Hz, H4, 1H), 4.96 (t, $J_{3,4/2} = 1.8$ Hz, H3, 1H), 4.34 (dq, $J_{2,2'} = 7$ Hz, H2, 1H), 4.12 (dd, $J_{5b,5a} = 13.4$, $J_{5b,4} = 2.2$ Hz, H5b, 1H), 3.61 (dd, $J_{5a,4} = 2.6$ Hz, H5a, 1H), 2.13 (2s, 6H, CH_3CO), 1.43 (d, $J_{2',2} = 6.8$ Hz, H2′, 3H); ^{13}C NMR ($CDCl_3$): $\delta =$ 169.4 (CH_3CO), 131.2, 129.4, 128.5, 125.6 (Ar), 68.8, 66.2 (C3, C4), 53.1 (C2), 44.6 (C5), 21.1 (CH_3CO), 13.7 (C2′); MS (ES): m/z: 384.1175 [M+Na$^+$]; calcd for $C_{17}H_{19}N_3O_6Na$: 384.1172.

(±)-(3,4-*trans*-4,5-*trans*)-4,5-Dihydroxy-3-methylhexahydropyridazine (64): Diacetates **79** and **79a** (1.24 g, 3.4 mmol) were dissolved in methanol (50 mL) containing a catalytic amount of Na, and kept at room temperature for 20 min. The solution was concentrated to give the crude diol. The diol (3.4 mmol) was dissolved in hydrazine hydrate (45 mL) and kept at 100 °C for 18 h. The hydrazine was removed by evaporation and the crude product was purified by flash chromatography in EtOH/25% NH_4OH 99:1 to give **64** as a white solid (0.158 g, 35%). The product contained approximately 6% *cis* isomer. ^{1}H NMR (D_2O): $\delta = 3.51$ (ddd, $J_{5,4} = 9.2$, $J_{5,6eq} = 5.0$, $J_{5,6ax} = 10.6$ Hz, H5, 1H), 3.15 (dd, $J_{6eq,6ax} = 12.8$, $J_{6eq,5} = 5.2$, H6eq, 1H), 3.06 (t, $J_{4,5/3} = 9.2$ Hz, H4, 1H), 2.61 (dq, $J_{3,3'} = 6.6$, $J_{3,4} = 9.2$ Hz, H3, 1H), 2.55 (dd, $J_{6ax,5} = 11$ Hz, H6ax, 1H), 1.09 (d, H3′, $J_{3',3} = 6.2$ Hz, 3H); ^{13}C NMR (D_2O): $\delta = 76.8$, 70.7 (C4, C5), 57.2 (C3), 51.4 (C6), 14.2 (C3′).

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[1] J. Clark, D. D. Perrin, *Q. Rev.* **1964**, *18*, 295 – 320.
[2] S. Inouye, *Chem. Pharm. Bull.* **1968**, *16*, 1134 – 1137.
[3] J. Chilton, J. B. Stenlake, *J. Pharm. Pharmacol.* **1955**, *7*, 1004 – 1007.
[4] H. S. Aaron, G. E. Wicks Jr., C. P. Rader, *J. Org. Chem.* **1964**, *29*, 2248 – 2252.
[5] H. O. House, H. C. Müller, C. G. Pitt, P. P. Wickham, *J. Org. Chem.* **1963**, *28*, 2407 – 2416.
[6] C. Y. Chen, R. J. Lefevre, *Tetrahedron Lett.* **1965**, *45*, 4057 – 4063.
[7] Y. Terui, K. Tori, *J. Chem. Soc. Perkin Trans. 2* **1975**, 127 – 133.
[8] P. Jacobsen, I. M. Labouta, K. Schaumburg, E. Falch, P. Krogsgaard-Larsen, *J. Med. Chem.* **1982**, *25*, 1157 – 1162.
[9] H. Booth, J. M. Bailey, H. A. R. Y. Shirayda, M. L. Trimble, *J. Chem. Soc. Perkin Trans. 2* **1984**, 737 – 743.
[10] R. J. Abraham, C. J. Medforth, P. E. Smith, *J. Comput.-Aided Mol. Des.* **1991**, *5*, 205 – 212.
[11] D. C. Lankin, N. S. Chandrakumar, S. N. Rao, D. P. Spangler, J. P. Snyder, *J. Am. Chem. Soc.* **1993**, *115*, 3356 – 3357.
[12] J. P. Snyder, N. S. Chandrakumar, H. Sato, D. C. Lankin, *J. Am. Chem. Soc.* **2000**, *122*, 544 – 545.
[13] B. Bernet, U. Piantini, A. Vasella, *Carbohydr. Res.* **1990**, *204*, 11 – 25.
[14] H. H. Jensen, M. Bols, *J. Chem. Soc. Perkin Trans. 1* **2001**, 905 – 909.
[15] H. H. Jensen, L. Lyngbye, M. Bols, *Angew. Chem.* **2001**, *113*, 3555 – 3557; *Angew. Chem. Int. Ed.* **2001**, *40*, 3447 – 3449.
[16] H. H. Jensen, A. Lohse, B. O. Petersen, J. Ø. Duus, M. Bols, *J. Chem. Soc. Perkin Trans. 1* **2000**, 667 – 670.
[17] A. Hansen, T. M. Tagmose, M. Bols, *Tetrahedron* **1997**, *53*, 697 – 706.
[18] X. Liang, A. Lohse, M. Bols, *J. Org. Chem.* **2000**, *65*, 7432 – 7437.
[19] A. Lohse, H. H. Jensen, P. Bach, M. Bols, *J. Chem. Soc. Perkin Trans. 1* **2000**, 659 – 665.
[20] Y. Ichikawa, Y. Igarashi, M. Ichikawa, Y. Suhura, *J. Am. Chem. Soc.* **1998**, *120*, 3007 – 3018.
[21] M. Willert, M. Bols, *Acta Chem. Scand.* **1998**, *52*, 461 – 468.
[22] S. U. Hansen, M. Bols, *J. Chem. Soc. Perkin Trans. 1* **2000**, 911 – 915.
[23] M. Bols, R. G. Hazell, I. B. Thomsen, *Chem. Eur. J.* **1997**, *3*, 940 – 947.
[24] N. Asano, K. Oseki, H. Kizu, K. Matsui *J. Med. Chem.* **1994**, *37*, 3701 – 3706.
[25] R. C. Cookson, S. S. H. Gilani, I. D. R. Stevens, *J. Chem. Soc.* (*C*) **1967**, 1905 – 1909.
[26] G. Legler, S. Pohl, *Carbohydr. Res.* **1986**, *155*, 119 – 129.
[27] G. Legler, E. Jülich, *Carbohydr. Res.* **1984**, *128*, 61 – 72.
[28] B. Winchester, C. Barker, S. Baines, G. Jacob, S. K. Nagoong, G. W. J. Fleet, *Biochem. J.* **1990**, *256*, 277 – 285.
[29] S. M. Andersen, M. Ebner, C. W. Ekhart, G. Gradnig, G. Legler, I. Lundt, A. E. Stutz, S. G. Withers, T. Wrodnigg, *Carbohydr. Res.* **1997**, *301*, 155 – 166.
[30] M. P. Dale, H. E. Ensley, K. Kern, K. A. R. Sastry, L. D. Byers, *Biochemistry* **1985**, *24*, 3530 – 3539.
[31] D. D. Schmidt, W. Frommer, L. Müller, E. Truscheit, *Naturwissenschaften* **1979**, *66*, 584 – 585.
[32] S. Inouye, T. Tsurouka, T. Ito, T. Niida, *Tetrahedron* **1968**, *23*, 2125 – 2144.
[33] a) J. March, *Advanced Organic Chemistry*, 3rd ed., Wiley, New York, **1985**; b) F. R. Jensen, C. H. Bushweller, *Adv. Alicyclic Chem.* **1971**, *3*, 139 – 194.
[34] S. V. D'Andrea, E. T. Michalson, J. P. Freeman, C. G. Chidester, J. Szmuszkovicz, *J. Org. Chem.* **1991**, *56*, 3133 – 3137.
[35] L. Chen, D. P. Dumas, C. -H. Wong, *J. Am. Chem. Soc.* **1992**, *114*, 741 – 748.
[36] T. M. Jespersen, M. Bols, M. R. Sierks, T. Skrydstrup, *Tetrahedron* **1994**, *50*, 13449 – 13460.
[37] The conformer ratios were calculated in the usual way[13] from the following Equation: equatorial conformer = $(J_{ax,ax} - J)/(J_{ax,ax} - J_{ax,eq})$, with $J_{ax,ax} = 10$ Hz and $J_{eq,ax} = 2.5$ Hz, which are typical values for similar compounds.
[38] L. Svansson, B. D. Johnston, J. -H. Gu, B. Patrick, B. M. Pinto, *J. Am. Chem. Soc.* **2000**, *112*, 10769 – 10775.
[39] M. D. Sørensen, N. M. Khalifa, E. B. Pedersen, *Synthesis* **1999**, 1937 – 1943.
[40] C. Gandolfo, G. Buemi, G. Favini, *Gazz. Chim. Ital.* **1971**, *101*, 946 – 955.
[41] Y. V. Morozov, V. P. Almazov, F. A. Savin, N. P. Bazhulina, *Bioorg. Khim.* **1982**, *8*, 1119 – 1132.
[42] R. Gabler, H. R. Meyer, *Angew. Chem.* **1962**, *74*, 942; *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 660.

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