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Tetrahedron 61 (2005) 115–122
Tetrahedron

Stereochemical substituent effects: investigation of the cyano, amide and carboxylate group

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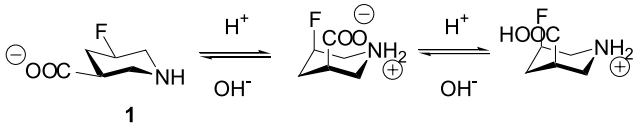
Received 18 June 2004; revised 20 September 2004; accepted 14 October 2004

Available online 28 October 2004

Abstract—Three pairs of diastereomeric piperidines, *cis*- and *trans*-2-methylpiperidine-3-carboxylate (**6a** and **6b**), *cis*- and *trans*-2-methylpiperidine-3-carboxylamide (**9a** and **9b**) and *cis*- and *trans*-2-methyl-3-cyanopiperidine (**11a** and **11b**), were synthesised for the purpose of investigating the effect of the axial versus equatorial carboxylate, carboxamide and cyano group on piperidine base strength. The pK_a values of the six compounds were determined to be 11.0 (**6a**), 10.4 (**6b**), 9.5 (**9a**), 9.3 (**9b**), 7.8 (**11a**) and 8.0 (**11b**). This shows that the strong electron-withdrawing effect of the cyano group and the effect of the amide group are relatively independent of spacial orientation. The carboxylate, on the other hand is considerably less electron-withdrawing when axial.

1. Introduction

Understanding the relationship between structure and properties is a fundamental issue in organic chemistry. Of central importance is the influence, in terms of electronic effects, of substituents on the chemistry of compounds. Substituent effects has been quantified by Hammett and Taft[1–3] and subsequently been refined so that very specific information is known about the electronic influence of functional groups.[4–6] However, relatively little attention has been given to the study of stereochemistry on substituent effects. While it was noted early that the base-strength of amines with polar groups varied widely, it was also concluded that they appeared to be unpredictable.[7,8] However, in recent work it has been observed that the basicity of piperidines and hexahydropyridazines was systematically affected by the axial or equatorial positioning of ring hydroxyl, fluorine or ester-groups.[9–11] An equatorial hydroxyl group was found to be three times more electron withdrawing than an axial hydroxyl group. This is exemplified in the difference in base strength of the epimeric glycosidase inhibitors isofagomine/galacto-isofagomine and 1-deoxynojirimycin/galactostatin (Fig. 1), in which the axial epimer is the stronger base. Similarly the piperidines with equatorial ester and fluorine groups were also found to be less basic than their axial isomers. An important and fascinating consequence of stereochemical substituent effects is, due to the principle of microscopic reversibility, that piperidines with polar substituents may change conformation on protonation.[10] Thus, as shown by Lankin and Snyder the fluoropiperidinecarboxylic acid **1** changes to the all axial conformation when the amino-group is protonated (Scheme 1).[12]



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Scheme 1. Conformational change of *cis*-3-fluoro-5-piperidinecarboxylic acid as a result of pH change.

It has been suggested that differences in charge–dipole interactions between the protonated amine and an axial or equatorial polar substituent is the prime reason for the influence of stereochemistry on piperidine base-strength. The present work is an effort to expand our knowledge about stereochemical substituent effects especially with the intent of determining the importance of charge–dipole interactions. For this purpose the nitrile-group was particularly interesting as it has a strong dipole and is a strongly electron-withdrawing group. If charge–dipole interactions are crucial for the base-strength a significant difference should be observed between piperidine isomers **A** and **B** (Fig. 1). We here report the influence of axial and equatorial positions on the base-lowering effect of carboxylic acid, carboxylic amide and nitrile groups. We have synthesised three pairs of stereoisomeric piperidines having a functional group in the 3-position and with restricted conformation and

Keywords: Electronic effect; Base strength; Piperidines; Conformation.
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0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.039

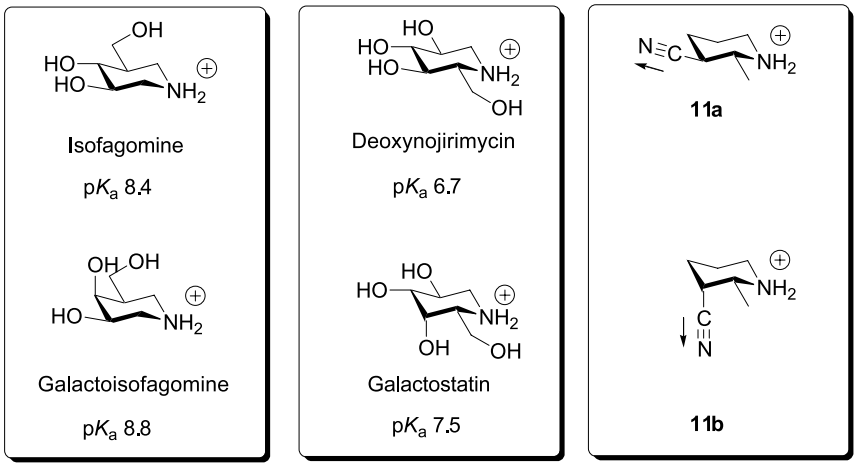


Figure 1. Base strength of epimeric glycosidase inhibitors and target molecules **11a** and **11b**.

recorded their pK_a values. We find that stereochemistry and/or conformation has a minor influence on the base-lowering effect of the cyano and carboxylic amide groups, while the base-lowering effect of the carboxylic acid is essentially eliminated in the axial position.

2. Results and discussion

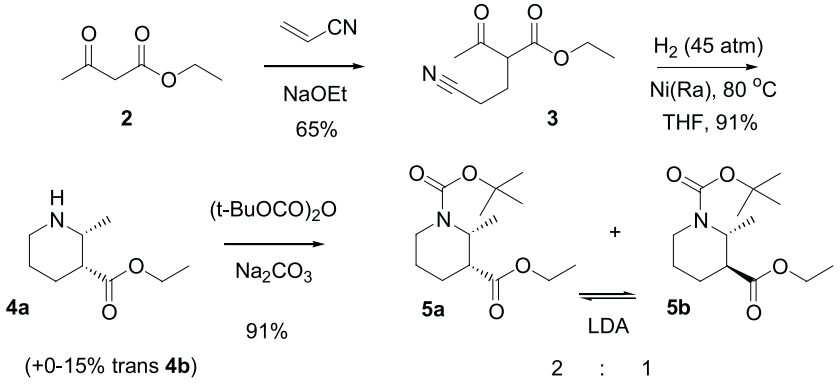
2.1. Synthesis

We decided to synthesise 3-substituted piperidines having a 2-methyl group, which should restrict the conformation of the molecule by inducing unfavourable 1,3-diaxial interaction when axial. These molecules should prefer a chair conformation with the methyl group equatorial and the 2,3-*cis* and *trans* isomers would therefore have the 3-substituent equatorial and axial, respectively. Here we rely on the work of Lapuyade et al. who studied the conformation of various methyl nipecotic acids and found that the methyl group preferred to be equatorial.[13]

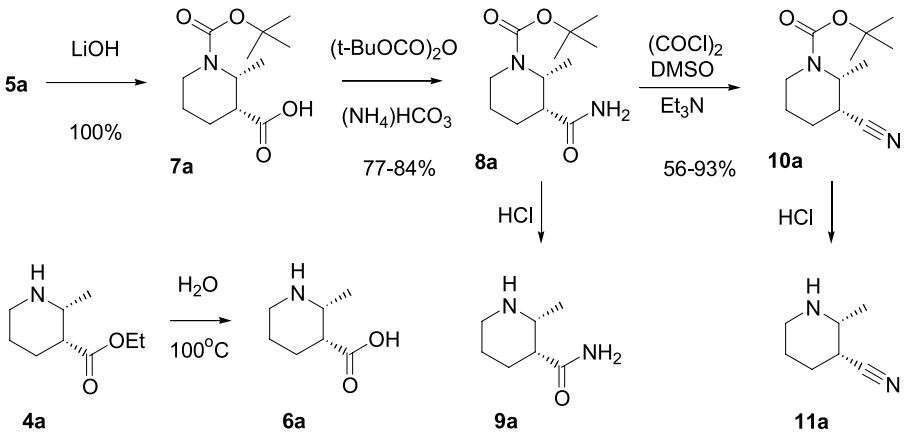
The acid, 2-methylnipecotic acid **6**, was prepared by Lapuyade et al.[13] as a mixture of *cis* and *trans* isomers. We decided to modify their synthesis to obtain all three sets of compounds with the anticipation that the stereoisomers could be separated. Thus the known Michael reaction between ethyl acetoacetate and acrylonitrile was used to obtain adduct **3** (Scheme 2).[14] Hydrogenation and reductive amination using Raney Nickel catalyst and 45 atm hydrogen pressure in EtOH gave the ester **4**, as previously reported,[14] in good yield. However, we observed that the *N*-ethyl derivative was formed as a byproduct in the reaction lowering yield and purity. This compound is presumably formed by metal catalysed dehydrogenation from ethanol to acetaldehyde and subsequent reductive amination of **4**. We therefore changed the solvent to THF which led to a yield of 91%. The reaction gives mainly the *cis*-isomer with the content of the *trans*-isomer not being entirely reproducible and varying between 0 and 15%. The catalysts Pd/C and Rh/C did not efficiently reduce the nitrile.

By careful chromatography in the polar solvent mixture EtOAc–EtOH–Et_3N 66:33:1 the *cis*- and *trans*-isomers of **4**, **4a** and **4b**, could be separated. However, it was typically more convenient to separate after protection of the amino group. The piperidine **4** was protected with Boc anhydride/Na_2CO_3 in the usual way giving **5** in 91% yield, and was separated to **5a** and **5b** by chromatography. To obtain more **5b**, the isomerization of **5a** with LDA was performed giving a product with a content of **5b** up to 37% (Scheme 2).

The *cis*-2-methylnipecotic acid **6a** was made, in 72% yield, by treatment of **4a** with boiling water as described for the mixture by Lapuyade et al. (Scheme 3).[13] The *cis* isomer **5a**, was converted, in quantitative yield, to the acid **7a** by



Scheme 2. Synthesis of esters **5a** and **5b**. The chiral compounds are racemic.



Scheme 3. Synthesis of *cis* isomers **6a**, **9a** and **11a**. All compounds are racemic.

hydrolysis with LiOH. By the use of Boc anhydride/$(NH_4)HCO_3$[15] on the acid **7a**, the primary amide **8a** was obtained in 84% yield. Dehydration of **8a** with oxalyl chloride/Et_3N[16] gave up to 93% yield of the nitrile **10a**. Deprotection of **8a** and **10a** with HCl gave the amines **9a** and **11a**, respectively.

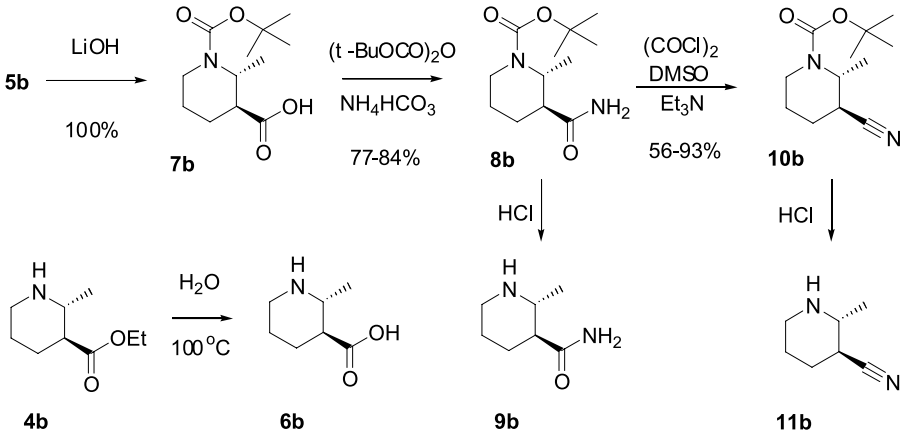
An identical sequence of reactions was carried out on the *trans*-isomeric compounds **4b** and **5b** leading to the corresponding acid, amide and nitrile **6b**, **9b** and **11b** (Scheme 4).

2.2. Configuration of the piperidines

The synthesised piperidines are all configurationally related in two families of *cis* and *trans* compounds obtained from the same two precursors **4a** and **4b**. Therefore determination of the configuration of a single member of each family is sufficient to establish the configuration of all. This determination is readily done with **6a** and **6b**. In **6b** J_{23} is 11 Hz showing that it must be diaxial coupling, which is only consistent with the 2,3-*trans* configuration of this molecule. In contrast in **6a** J_{23} is 2.3 Hz which is consistent with a axial-diequatorial coupling of the *cis*-configured molecule.

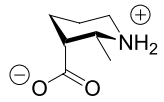
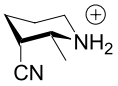
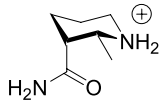
2.3. Conformation of the piperidines

As the conformation can influence the base-strength the conformational preference of the six piperidines as hydrochlorides and as free amines is important. If protonation of the piperidine is associated with a conformational change this may influence the base-strength and complicate the interpretation. In the following discussion we will, for simplicity, relate to the enantiomers shown in Schemes 3 and 4 despite the fact that the compounds are racemic. The arguments are, of course, equally valid for the antipodes. As mentioned previously, the conformation of **6a** and **6b** was determined by Lapuyade et al. to be mainly $^4C_1$ that is have the methyl group equatorial.[13] The *trans*-amide **9b** is clearly also in the diequatorial $^1C_4$ conformation both as hydrochloride and as free amine. This is readily seen by the large J_{23} proton coupling being 10 Hz in the amine and 10.8 Hz in the hydrochloride. The *cis*-amide **9a** is also in $^4C_1$ conformation in both protonated and neutral form. This is particularly evident from the H-3 proton which only has small couplings and thus must be equatorial. It is also seen that H-2 and H-3 has an essentially similar chemical shift, respectively, in both the amino and conjugate acid forms which confirm that they do not change from equatorial to axial or vice versa. Finally the 2-methyl group has a ^{13}C



Scheme 4. Synthesis of *trans* isomers **6b**, **9b** and **11b**. All compounds are racemic.

Table 1. pK_a values of the piperidines

Number	Structure	pK_a	Number	Structure	pK_a
6a		11.0	**9b**		9.3
6b		10.4	**11a**		7.8
9a		9.5	**11b**		8.0

chemical shift of 16–19 ppm in **9a** and **9b** both as amines and conjugated acids, in accordance with it being consistently equatorial. An axial methyl group is 5–7 ppm more shielded than an equatorial.[17] The *cis*- and *trans*-nitriles **11a** and **11b** were also found to be in the $^4C_1$ conformation. The ^{13}C spectra of the conjugate acids and amines quite clearly shows the 2-methyl group has essentially the same chemical shift as in **9a** and **9b**, and therefore must be predominantly equatorial. Also the H-2 proton in **11a** is found at a similar chemical shift as was the case in **9a**. In **11b** J_{23} is found to be 10.4 Hz in the amine form and 11.2 Hz in the conjugate acid form clearly consistent with $^4C_1$ conformation for both forms. So we conclude that the 2-methyl group serves its purpose as an conformational anchor and that the piperidines **6a**, **6b**, **9a**, **9b**, **11a** and **11b** are predominantly in the conformations as shown in Table 1.

2.4. Determination of base-strength

The pK_a values of amino groups of **6a**, **6b**, **9a**, **9b**, **11a** and **11b** were determined by titration and are shown in Table 1. The pK_a values of the carboxylic acid residues of **6a** and **6b** were found to 3.3 and 3.2, respectively. The data are the average of three determinations (error $\pm$0.1). The empirical formula p$K_a = 10.7 - \Sigma\sigma_s$[10] was applied to calculate the σ_s values for the new substituents, taking into account that the σ_s value of an equatorial 2-Me is -0.1. This gave the values shown in Table 2. The value for an equatorial 3-carboxylate has previously determined to 0.5 and from that value the pK_a was calculated to 10.3 and thus is underestimated by 0.1.

The results are remarkable in that only the nipecotic acids **6a** and **6b** show a significant difference in the base-strength of the amine. The difference (ΔpK_a) between the pK_a values of **6a** and **6b** is 0.5 (or 0.7 between σ_s values) which appears reasonable given the sizeable ΔpK_a found previously for the ester group in the 3-position of the piperidine.[10] However, surprisingly the ΔpK_a for the amides **9a/9b** is only 0.2, despite the fact that the very similar ester group differs largely in axial and equatorial substituent effect. Even more remarkable is the observation that the very electron-withdrawing and strongly dipolar nitrile group only has a pK_a difference of -0.2 for **11a/11b**, the *cis* isomer being slightly more basic.

Table 2. σ_s values of substituents in the β or 3-position of piperidines

Substituent	σ_s value (β, equat.)	σ_s value (β, axial)	σ_I (Ref. 5)
COO^-	0.5*	−0.2	0.58
$CONH_2$	1.5	1.3	1.78
CN	2.8	3.0	3.04
COOMe	1.2*	0.2*	1.7
OH	1.3*	0.5*	1.68
F	2.3*	1.5#	2.57

The pK_a of the piperidine is calculated using the formula p$K_a = 10.7 - \Sigma\delta_s$, *value taken from Ref. 10, #value taken from Ref. 11.

It is interesting to note that the σ_s values of the equatorial isomers are comparable in size or slightly smaller than the σ_I values determined by Grob[5] on 4-substituted quinuclidines (Table 2). Evidently an equatorial σ_s value can be estimated as 70–100% of a σ_I value. In contrast, in the axial position, the substituent effect varies widely. While the CN and $CONH_2$ groups are similar to σ_I values for the carboxylate, ester, hydroxyl and fluorine substituent a partial or complete elimination of the electron withdrawing effect takes place.

2.5. PM3 calculations

To get more insight into these differences semi-empirical calculations (MOPAC, PM3) were made on 3-substituted piperidine, in ammonium and amine form, with the substituent placed axial and equatorial. The results are shown in Table 3. These calculations are valid in the gas phase and their significance in solution must be interpreted with caution. Nevertheless some general trends are evident and consistent with the experimental facts. It is seen that while the axial and equatorially substituted amines essentially have similar heat of formation, the ammonium ions generally differ with the equatorial isomer being less stable. The smallest difference, 6 kJ/mol, is found for the cyano substituted piperidine, which explains why a large pK_a

Table 3. Heat of formation, in kJ/mol of monosubstituted piperidines calculated using PM3, MOPAC in Chem3D 6.0 Ultra

Substituent	Amine	Ammonium
3-CN (axial)	80.0	762.8
3-CN (equatorial)	79.6	768.9
3-$CONH_2$ (axial)	−222.1	400.6
3-$CONH_2$ (equatorial)	−224.2	437.4
3-COO^- (axial)	−539.7	−289.9
3-COO^- (equatorial)	−538.8	−189.0
3-COOMe (axial)	−404.3	245.5
3-COOMe (equatorial)	−404.3	273.2
3-OH (axial)	−251.8	399.7
3-OH (equatorial)	−253.1	413.6
3-F (axial)	−258.9	411.0
3-F (equatorial)	−256.4	423.6

difference not is found between **11a** and **11b**. Also the difference observed in the pK_a of **6a** and **6b** is qualitatively supported by the large difference observed in heat of formation for the ammonium ions. On the other hand the size of the pK_a difference (0.5–0.7) is relatively small compared to the huge energy difference calculated. Also the clear difference in heat of formation between the protonated amides is not very consistent with the insignificant difference found in pK_a (0.2) between **9a** and **9b**. This is contrasted by the ester were a similar energy difference is calculated between axial and equatorial isomer but a significant pK_a difference (1.0) is observed. It is proposed that these inconsistencies may be caused by effects of solvation of the carboxylate and amide groups reducing the electrostatic interaction with the ammonium ion compared to the gas phase.

3. Conclusion

It was found that the strong electron withdrawing power of the cyano group is not significantly influenced by its axial or equatorial orientation. The through space or solvent component of the electron withdrawing effect must be minor, and a charge dipole effect cannot be important. The substituent effect from the amide group was also found relatively independent on stereochemistry. In contrast the substituent effect from a carboxylate group was significantly different in the axial and equatorial positions.

4. Experimental

4.1. General

^{13}C-, ^{1}H- and H,H-COSY NMR were recorded on a Varian Gemini 200 (200 MHz) NMR instrument and when specifically noted on a Mercury 400 (400 MHz) NMR instruments. The spectra were referenced to solvent residues. MS was recorded on a Micromass LC-TOF instrument. Chromatography was performed in Merck 60 silica. TLC was performed on Merck silica 60 E_{254} coated glass plates and developed using either vanillin (3 g in 100 mL EtOH with 1 mL H_2SO_4 added), potassium permanganate (aq), Ce-mol (10 g Ce(IV)SO_4 and 15 g $(NH_4)_2MoO_4$ in 1 L 10% H_2SO_4) or ninhydrin (2% in *n*-BuOH) and subsequent heating.

4.1.1. Ethyl (2-cyanoethyl)-acetoacetate (3).[14] This product, a clear oil, was prepared as described in Ref. 14. ^{1}H NMR ($CDCl_3$): δ 4.23 (q, J=7.8 Hz, 2H, –OCH_2CH$_3$), 3.65 (t, J=6.8 Hz, 1H, H_2), 2.45 (t, J=6.8 Hz, 2H, H_6), 2.30 (s, 3H, H_4), 2.2 (m, 2H, H_5), 1.3 (t, J=7.8 Hz, 3H, OCH$_2$CH_3).

4.1.2. *cis* and *trans* Ethyl 2-methyl nipecotate (4a and 4b). *Compound* **3**. (2.52 g, 13.8 mmol) was dissolved in freshly distilled dry THF, and Raney nickel (0.5 g, prewashed in THF) was added. The mixture was transferred to an autoclave with magnet, and the atmosphere replaced by flushing with a stream of nitrogen. The container was closed and a pressure of 45 atm. H_2 was applied for 15 h at 80 °C. The mixture was filtered through Celite® and concentrated. The yield of **4** was 2.14 g (91%) and further purification was not necessary unless the pure stereoisomers were required. The *cis*/*trans* ratio (**4a**/**4b**) was normally 10/1 (as determined from ^{1}H NMR) but varied between 1:0 and 6:1 depending on the scale. Separation of the **4a** and **4b** was carried out by chromatography in EtOAc–EtOH 2:1 containing 1% Et_3N added. Separation of 1.0 g of the mixture gave 634 mg **4a** and 74 mg **4b**.

Compound **4a**. Clear oil, ^{1}H NMR ($CDCl_3$, assigned with COSY): δ 4.1 (q, J=7.3 Hz, 2H, –OCH_2CH$_3$), 3.02 (dt, J=13.6, 4.4 Hz, 1H, H_{6e}), 2.9 (dq, J=6.4, 3.5 Hz, 1H, H_{2a}), 2.62 (dt, J=10.2, 3.5 Hz, 1H, H_{6a}), 2.48 (q, J=3.5 Hz, 1H, H_{3e}), 2.05 (bs, 1H, N–H), 1.95 (dt, J=5.8, 1.5 Hz 1H, H_{4e}), 1.5–1.8 (m, 2H, H_{5e}, H_{4a}), 1.35 (m, 1H, H_{5a}), 1.22 (t, J=7.3 Hz, 3H, –OCH$_2$CH_3), 1.08 (d, J=7 Hz, 3H, –CH_3). ^{13}C NMR ($CDCl_3$): **4a**: δ=174.3 (C=O), 60.1 (–OCH_2CH$_3$), 52.5 (C_3), 45.4 (C_2), 44.3 (C_6), 26.5 (C_4), 22.9 (–OCH$_2$CH_3), 19.2 (C_5), 14.5 (–CH_3).

Compound **4b**. Clear oil, ^{1}H NMR ($CDCl_3$) (assigned with COSY): δ 4.1 (q, J=7.3 Hz, 2H, –OCH$_2$CH_3), 3.05 (m, 1H, H_{6a}), 2.8 (dq, J=10, 5.8 Hz, 1H, H_{2a}), 2.68 (dt, J=12, 2.6 Hz, 1H, H_{6a}), 1.9–2.1 (m, 2H, H_{3a}, N–H), 1.4–1.7 (m, 5H, H_{4e}, H_{5e}, H_{4a}, H_{5a}), 1.25 (t, J=7.7 Hz, 3H, –OCH$_2$CH_3), 1.06 (d, J=5.8 Hz, 3H, –CH_3). MS: Calcd for $C_9H_{17}NO_2$ (M+H)=172.1338. Found: 172.1328.

4.1.3. *cis* and *trans* Ethyl *N*-*tert*-butoxycarbonyl-2-methylnipecotate (5a and 5b). A mixture of **4a** and **4b** (2.30 g, 13.4 mmol) was dissolved in 40 mL 50% aq THF. Na_2CO_3 (1.46 g, 13.7 mmol) was added under stirring at 0 °C. A mixture of 3.32 g (15.3 mmol) di-*tert*-butyl dicarbonate (boc-anhydride) and 1.43 g (16.1 mmol) Na_2CO_3 in 30 mL 50% aq THF was added, and the mixture stirred for 30 min at 0 °C. The reaction mixture was allowed to reach room temperature and stirred for 2 h and acidified with 1.0 M HCl. The mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$. After concentration a white crystalline product of **5a** and **5b** was obtained. Yield: 3.32 g (91%, mixture of *cis* and *trans*). Compounds **5a** and **5b** could be separated using chromatography in CH_2Cl_2/EtOAc 20:1 (see also below).

Compound **5a**. White crystals, mp=72 °C, ^{1}H NMR ($CDCl_3$): δ 4.84* (bs, 0.5H, H_2), 4.63* (bs, 0.5H, H_2), 4.12 (q, J=6.6 Hz, 2H, –CH_2CH$_3$), 3.99* (d, J=11.6 Hz, 0.5H, H_{6e}), 3.86* (d, J=13.2 Hz, 0.5H, H_{6e}), 2.77 (dt, J=11.6, 13.2 Hz, 1H, H_{6a})*, 2.60 (dt, J=3.6, 12.8 Hz, 1H, H_{3e}), 1.65–1.9 (m, 3H, H_{4e}, H_{5e}, H_{4a}), 1.46 (s, 9H, Boc), 1.40 (m, 1H, H_{5a}), 1.25 (t, J=6.6 Hz, 3H, –CH$_2$CH_3), 1.03 (d, J=7.2 Hz, 3H, –CH_3) (*Rotamers present).

Compound **5b**. White crystals, mp=74 °C, ^{1}H NMR ($CDCl_3$): δ 4.86 (q, J=6.4 Hz, 1H, H_{2e}), 4.12 (dq, J=2.4, 7.4 Hz, 2H, –CH_2CH$_3$), 3.92 (bd, J=13.2 Hz, 1H, H_{6e}), 2.79 (dt, J=3.2, 13.2 Hz, 1H, H_{6a}), 2.37 (bs, 1H, H_{3e}), 2.02 (dd, J=3.2, 14 Hz, 1H, H_{4e}), 1.74 (tt, J=4.0, 13.4 Hz, 1H, H_{4a}), 1.75 (m, 1H, H_{5e}) 1.62 (tk, J=4.0, 13.2 Hz, 1H, H_{5a}), 1.43 (s, 9H, Boc), 1.24 (t, J=6.8 Hz, 3H, –CH$_2$CH_3), 1.19 (d, J=7.2 Hz, 3H, –CH_3). MS: Calcd for $C_{14}H_{25}NO_4$ (M+Na)=294.1681. Found 294.1680.

4.1.4. Epimerisation of 5a. A 50 mL oven dried round-bottomed flask was purged with nitrogen and closed with septum. Then 20 mL freshly distilled THF and dry diisopropylamine (0.50 mL, 3.5 mmol) was injected. The mixture was cooled, and *n*-BuLi (2.20 mL, 3.5 mmol, 1.6 M in hexane) was added. The mixture was stirred on ice for 10 min. The LDA solution was cooled on dry ice/acetone and **5a** (800 mg, 3.0 mmol) in THF was added. The reaction mixture was stirred for 1 h and quenched with water. The mixture was acidified with 1.0 M HCl and extracted with CH_2Cl_2. The yellowish product was separated by chromatography in CH_2Cl_2/EtOAc 20:1 giving **5b** (160 mg, 27%) and **5a** (428 mg, 47%).

4.1.5. *cis*- and *trans*-2-Methylnipecotic acid (6a and 6b). These acids were prepared as described for the mixture in Ref. 13. Compund **4a** (133 mg) or **4b** (74 mg) was boiled in water for 5 h, concentrated and dried. This gave **6a** (115 mg) or **6b** (65 mg), respectively. Yield: 95–100%.

Compound **6a**. White solid, ^{1}H NMR (D_2O): δ 3.4 (dt, J= 1.9, 3.8 Hz, 1H, H_{6e}), 3.3 (dq, J=2.3, 6.8 Hz, 1H, H_{2a}), 3.0 (m, 1H, H_{6a}), 2.62 (bq, J=2.3 Hz, 1H, H_{3e}), 1.6–2.1 (m, 4H, H_{4a}, H_{4e}, H_{5a}, H_{5e}), 1.32 (d, J=6.8 Hz, 3H, H_7). ^{13}C NMR (D_2O): δ 180.1 (C=O), 53.1 (C_2), 44.0 (C_3), 43.5 (C_6), 24.7 (C_4), 18.3 (C_5), 15.6 (C_7).

Compound **6b**. White solid, ^{1}H NMR (D_2O): δ 3.4 (m, 1H, H_{6e}), 3.2 (dq, J=6.5, 11 Hz, 1H, H_{2a}), 2.95 (dt, J=3.2, 12.5 Hz, 1H, H_{6a}), 2.28 (dt, J=3.2, 11 Hz, 1H, H_{3a}), 1.5–2.1 (m, 4H, H_{4a}, H_{4e}, H_{5a}, H_{5e}), 1.27 (d, J=6.5 Hz, 3H, H_7). ^{13}C NMR (D_2O): δ 179.9 (C=O), 53.5 (C_2), 50.2 (C_6), 43.8 (C_3), 26.3 (C_4), 21.1 (C_5), 16.8 (C_7).

4.1.6. *cis*- and *trans*-*N*-*tert*-Butoxycarbonyl-2-methylnipecotic acid (7a and 7b). *Compound* **5a** or **5b** (1.69 g) was dissolved in THF and treated with excess 2 M LiOH solution. After 18 h at room temperature, the solution was acidified with 1.0 M HCl. The mixture was extracted with EtOAc, dried over $MgSO_4$ and concentrated giving a white solid of **7a** or **7b**. Yield: 1.50 g (100%).

Compound **7a**. White solid, mp=178 °C. ^{1}H NMR ($CDCl_3$): δ 9.2 (bs, 1H, –COO*H*), 4.8 (bs, 1H, H_2), 3.9 (bs, 1H, H_{6e}), 2.8 (bs, 1H, H_3), 2.65 (dt, J=4.8, 11.9 Hz, 1H, H_{6a}), 1.6–1.9 (m, 3H, H_{4e}, H_{5e}, H_{4a}), 1.46 (s, 9H, Boc), 1.24 (dt, J=1.6, 7.2 Hz, 1H, H_{5a}), 1.08 (d, J=6.7 Hz, 1H, –C*H*$_3$). IR (KBr): 1660 (–*CO*O^{t}Bu), 1734 (–*CO*NH$_2$), 2979 (C–H sp^3), 3000–2900 (small bands –COO*H*). MS: Calcd for $C_{12}H_{21}NO_4$ (M+Na)=266.1368. Found: 266.1367.

Compound **7b**. White crystals, mp=115 °C. ^{1}H NMR ($CDCl_3$): δ 4.82 (q, J=6.8 Hz, 1H, H_{2e}), 3.90 (d, J= 12 Hz, 1H, H_{6e}), 2.75 (dt, J=3.2, 13.2 Hz, 1H, H_{6a}), 2.38 (bs, 1H, H_{3e}), 2.00 (bd, J=13.2 Hz, 1H, H_{4e}), 1.73 (tt, J= 4.8, 13.6 Hz, 1H, H_{4a}), 1.58 (tq, J=4.0, 13.2 Hz, 1H, H_{5a}), 1.45 (bd, J=13.2 Hz, 1H, H_{5e}), 1.38 (s, 9H, Boc), 1.16 (d, J=7.2 Hz, 3H, –C*H*$_3$). IR (KBr): 1653 (–*CO*OH), 1730 (*CO*O^{t}Bu), 3000–2850 (small bands –CO*OH*). MS: Calcd for $C_{12}H_{21}NO_4$ (M+Na)=266.1368, Found: 266.1367.

4.1.7. *cis*- and *trans*-*N*-*tert*-Butoxycarbonyl-2-methylpiperidine-3-carboxylic amide (8a and 8b). *Compound* **7a** or **7b** (0.890 g, 3.27 mmol) was dissolved in 1,4-dioxane (6 mL) and (0.125 mL, 1.5 mmol) pyridine was added dropwise. Boc anhydride (0.75 g, 3.4 mmol) was added and the reaction was stirred for 15 min. Now ammonium hydrogencarbonate (0.27 g) was added and stirring continued for 18 h. EtOAc was added, the mixture separated and the organic layer washed with 5% H_2SO_4 and water. The organic phase was dried with $MgSO_4$ and concentrated. The products were thick yellowish syrups. After trituration with ether **8a** becomes crystalline and white. Yield: 0.745 g (84%).

Compound **8a**. White crystals, mp=163–165 °C. ^{1}H NMR ($CDCl_3$): δ 5.65 (bs, 1H, –N*H*$_2$), 5.5 (bs, 1H, –N*H*$_2$), 4.64 (dq, J=4.8, 6.4 Hz, 1H, H_{2e}), 3.92 (bd, J=13 Hz, 1H, H_{6e}), 2.8 (dt, J=3.2, 12 Hz, 1H, H_{6a}), 2.5 (dt, J=4.8, 11.2 Hz, 1H, H_{3e}), 1.8 (dq, J=13, 4.1 Hz, 1H, H_{4a}), 1.6–1.9 (m, 2H, H_{4e}, H_{5e}), 1.43 (s, 9H, Boc), 1.2–1.4 (m, 1H, H_{5a}), 1.1 (d, J=6.6 Hz, 3H, –C*H*$_3$). ^{13}C NMR ($CDCl_3$): δ 175.7 (*CO*NH$_2$), 154.9 (Boc), 80.7 (–O–*C*(CH$_3$)$_3$), 48.3 (C_2), 46.0 (C_6), 38.3 (C_3), 28.6 (O–C(*C*H$_3$)$_3$), 24.8 (C_4), 20.6 (C_5), 11.9 (–*C*H$_3$). IR (KBr): 1685 (–*CO*O^{t}Bu), 1625 (–*CO*NH$_2$), 2975/2944 (C–H sp^3), 3393 (–CO*N*H$_2$). MS: Calcd for $C_{12}H_{22}N_2O_3$ (M+Na)=265.1528, Found: 265.1516.

Compound **8b**. White solid, mp=165 °C. ^{1}H NMR ($CDCl_3$): δ 5.41 (bs, 1H, –N*H*$_2$), 4.71 (q, J=6.4 Hz, 1H, H_{2e}), 3.93 (bd, $J\approx$13.5 Hz, 1H, H_{6e}), 2.91 (dt, J=4.0, 13.2 Hz, 1H, H_{6a}), 2.35 (ddd, J=2.0 Hz, 1H, H_{3e}), 2.19 (bd, $J\approx$12.4 Hz, 1H, H_{4e}), 1.85 (tt, J=4.8, 12.8 Hz, 1H, H_{4a}), 1.46–1.53 (m, 2H, H_{5e}, H_{5a}), 1.46 (s, 9H, Boc), 1.26 (d, J= 6.8 Hz, 3H, –C*H*$_3$). ^{13}C NMR ($CDCl_3$): δ 177 (amide C=O), 156 (Boc C=O), 80.5 (–O–*C*(CH$_3$)$_3$), 46.5 (C_2), 45 (C_6), 39 (C_3), 29.5 (O–C(*C*H$_3$)$_3$), 22.4 (C_4), 22 (C_5), 16.5 (–*C*H$_3$). IR (KBr): 1684 (–*CO*O^{t}Bu), 1659 (–*CO*NH$_2$), 2975/2930 (C–H sp^3), 3389 (–CO*N*H$_2$). MS: Calcd for $C_{12}H_{22}N_2O_3$ (M+Na)=265.1528. Found: 265.1526.

4.1.8. *cis*- and *trans*-2-Methylpiperidine-3-carboxylic amide (9a and 9b). *Compound* **8a** or **8b** was treated with 0.2 M HCl in excess and concentrated to dryness to give the hydrochloride of **9a** or **9b**. To obtain the amine, the hydrochloride was dissolved in water and subjected to ion-exchange chromatography on Amberlite IR-120, H^+. The amine was eluted with 5% aq ammonia.

Compound **9a**. Clear syrup, ^{1}H NMR (D_2O): δ 3.19 (dq, J= 3.4, 6.6 Hz, 1H, H_{2a}), 2.96 (dt, J=4.2, 12.6 Hz, 1H, H_{6e}), 2.74 (ddd, J=3, 9.8, 12.6 Hz, 1H, H_{6a}), 2.62 (q, J=4.2 Hz, 1H, H_{3e}), 1.85 (m, 1H, H_{4e}), 1.48–1.8 (m, 3H, H_{4a}, H_{5e}, H_{5a}), 1.14 (d, J=6.8 Hz, 3H, –C*H*$_3$). (hydrochloride): δ= 3.42 (dq, J=6.4, 3.1 Hz, 1H, H_{2a}), 3.36 (m, 1H, H_{6e}), 3.02 (dt, J=4.6, 12 Hz, 1H, H_{6a}), 2.84 (q, J=3.1 Hz, 1H, H_{3e}), 1.7–2.05 (m, 4H, H_{4e}, H_{5e}, H_{4a}, H_{5a},), 1.32 (d, J=6.4 Hz, 3H, –C*H*$_3$). ^{13}C NMR (CD_3OD): δ 179.0 (*C*=O), 53.7 (C_2), 45.1 (C_6), 43.5 (C_3), 27.0 (C_4), 21.1 (C_5), 17.4 (–*C*H$_3$). (hydrochloride): δ 178 (*C*=O), 54.4 (C_2), 45.2 (C_6), 42.0 (C_3), 27.0 (C_4), 19.5 (C_5), 16.9 (–*C*H$_3$). IR (KBr, hydrochloride): 1608 (–CONH$_2$), 1660 (–*C*=*O*), 2753/ 2857 ($R_2N^+H_2$), 2960 (C–H sp^3), 3318/3151 (–CONH$_2$). MS: Calcd for $C_7H_{14}N_2O$ (M+H)=143.1184, Found: 143.1080.

Compound **9b**. Clear syrup, ^{1}H NMR (D_2O): δ 3.0 (bd, J= 12.8 Hz, 1H, H_{6e}), 2.74 (dq, J=6.4, 10 Hz, 1H, H_{2a}), 2.6 (dt, J=2.8, 12.4 Hz, 1H, H_{6a}), 2.08 (ddd, J=3.6, 10.0, 10.4 Hz, 1H, H_{3a}), 1.9 (bdd, J=2.8, 13.6 Hz, 1H, H_{4e}), 1.72 (dt, J= 2.8, 13.2 Hz, 1H, H_{5e}), 1.55 (dq, J=2.8, 13 Hz, 1H, H_{4a}), 1.42 (tq, J=2.8, 13 Hz, 1H, H_{5a}), 1.02 (d, J=6.4 Hz, 3H, CH_3). (hydrochloride): δ 3.06 (bd, J=12.8 Hz, 1H, H_{6e}), 2.94 (dq, J=6.4, 10.8 Hz, 1H, H_{2a}), 2.65 (dt, J=2.5, 12.4 Hz, 1H, H_{6a}), 2.19 (dt, J=3.6, 10.8 Hz, 1H, H_{3a}), 1.69 (bd, J=11.6 Hz, 1H, H_{4e}), 1.62 (bd, J=13.6 Hz, 1H, H_{5e}), 1.39 (ddd, J=3.2, 13.2 Hz, 1H, H_{5a}), 1.32 (dq, J=3.2, 11.4 Hz, 1H, H_{4a}), 0.95 (d, J=6.4 Hz, 3H, –CH_3). ^{13}C NMR (CD_3OD): δ 180 (C=O), 53 (C_2), 50 (C_6), 45 (C_3), 27 (C_4), 23 (C_5), 19 (–CH$_3$). (hydrochloride): δ 175.5 (C=O), 52.9 (C_2), 43.9 (C_6), 42.8 (C_3), 24.7 (C_4), 20.1 (C_5), 15.6 (–CH$_3$). IR (KBr, hydrochloride): 1613 (–$CONH_2$), 1667 (–C=O), 2807 ($R_2N^+H_2$), 2950 (C–H sp^3), 3368/3180 (–$CONH_2$). MS: Calcd for $C_7H_{14}N_2O$ (M+H): 143.1184. Found: 143.1086.

4.1.9. *cis*- and *trans*-*N*-*tert*-Butoxycarbonyl-3-cyano-2-methylpiperidine (10a and 10b). *Compound* **8a** or **8b** (0.58 g, 2.4 mmol) was dissolved in DCM (7 mL) and DMSO (0.27 mL, 0.30 g; 3.8 mmol) was added. The mixture was cooled to −78 °C and oxalylchloride (0.25 mL, 0.37 g; 2.88 mmol) was added. After 15 min triethylamine (1.0 mL, 0.73 g; 7.19 mmol) was added dropwise. After further 15 min of stirring, the reaction was quenched with 15 mL water and extracted with three times 15 mL EtOAc. The organic layer was washed with concd NaCl solution, dried over $MgSO_4$ and concentrated. Purification by chromatography—eluent DCM/EtOAc 50:1—gave 480 mg **10a** or **10b** (93%).

Compound **10a**. White crystals. mp=61 °C. ^{1}H NMR ($CDCl_3$): (assigned using Cosy) δ 4.64 (dq, J=3.5, 6.6, 6.6, 6.6 Hz, 1H, H_{2e}), 3.95 (bd, J=13.2 Hz, 1H, H_{6e}), 2.80 (dt, J=3.3, 13.2, 13.2 Hz, 1H, H_{6a}), 2.76 (dt, J=3.5, 3.5, 11.5 Hz, 1H, H_{3a}), 1.9–2.1 (m, 1H, H_{4e}), 1.90 (ddd, J=3.5, 13.2, 13.2 Hz, 1H, H_{4a}), 1.70 (ddd, J=2.0, 3.3, 13.2 Hz, 1H, H_{5e}), 1.46 (s, 9H, Boc), 1.38 (m, 1H, H_{5a}), 1.31 (d, J= 6.6 Hz, 3H, –CH_3) ^{13}C NMR ($CDCl_3$): δ 155 (Boc C=O), 120.5 (–C≡N), 80.5 (–O–C(CH_3)$_3$), 47 (C_6), 37.5 (C_2), 31.7 (C_3), 28.6 (O–C(CH_3)$_3$), 24.5 (C_5), 23.0 (C_4), 12.4 (–CH_3). IR (KBr): 1690 (C=O), 2240 (–C≡N), 2977 (C–H sp^2). MS: Calcd for $C_{12}H_{22}N_2O_3$ (M+Na)=247.1422. Found: 247.1415.

Compound **10b**. White crystals. mp=69 °C. ^{1}H NMR ($CDCl_3$): (assigned using Cosy) δ 4.63 (q, J=6.8 Hz, 1H, H_{2e}), 3.99 (bd, J=14 Hz, 1H, H_{6e}), 2.75 (dt, J=3.5, 13, 13 Hz, 1H, H_{6a}), 2.63 (bs, 1H, H_{3e}), 1.81 (m, 1H, H_{4e}), 1.75 (tt, J=3.6, 13 Hz, 1H, H_{4a}), 1.58 (m, 1H, H_{5e}), 1.41 (s, 9H, Boc), 1.22 (m, 1H, H_{5a}), 1.15 (d, J=6.8 Hz, 3H, –CH_3). ^{13}C NMR ($CDCl_3$): δ 155 (Boc C=O), 120.5 (–C≡N), 80.5 (–O–C(CH_3)$_3$), 48 (C_6), 38 (C_2), 31.6 (C_3), 28.5 (O–C(CH_3)$_3$), 21.8 (C_5), 21.6 (C_4), 15.6 (–CH_3). IR (KBr): 1693 (C=O), 2239 (–C≡N), 2977 (C–H sp^3). MS: Calcd for $C_{12}H_{22}N_2O_3$ (M+Na) 247.1422, Found: 247.1430.

4.1.10. *cis*- and *trans*-3-Cyano-2-methylpiperidine (11a and 11b). *Compound* **11a** or **11b** were prepared from **10a** or **10b** as described for **9** above.

Compound **11a**. Syrup, ^{1}H NMR (D_2O/CD_3OD): δ 3.2 (bd, J=12.2 Hz, 1H, H_{6e}), 2.97 (m, 1H, H_{3e}), 2.85 (dq, J=6.4, 3 Hz, 1H, H_{2a}), 2.65 (ddd, J=4, 10.4, 12.2 Hz, 1H, H_{6a}), 2.05 (bd, J=13 Hz, 1H, H_{4e}), 1.55–1.85 (m, 3H, H_{4a}, H_{5e}, H_{5a}), 1.24 (d, J=6.4 Hz, 3H, –CH_3). (hydrochloride) δ 3.55 (dq, J=3.7, 6.0 Hz, 1H, H_{2a}), 3.45 (bd, J=3.7 Hz, 1H, H_{3e}), 3.42 (dd, J=3, 13 Hz, 1H, H_{6e}), 3.05 (dt, J=3.6, 12 Hz, 1H, H_{6a}), 2.18 (m, 1H, H_{4e}), 1.7–2.1 (m, 3H, H_{4a}, H_{5e}, H_{5a}), 1.45 (d, J=6.4 Hz, 3H, –CH_3). ^{13}C NMR (CD_3OD): δ 121.8 (–C≡N), 52.9 (C_2), 46.5 (C_6), 35.0 (C_3), 28.3 (C_4), 22.9 (C_5), 20.7 (–CH_3). (hydrochloride): δ=118.7 (–C≡N), 52.5 (C_2), 45.1 (C_6), 33 (C_3), 26.2 (C_4), 20.1 (C_5), 17.7 (–CH_3). IR (KBr, hydrochloride): 2242 (–C≡N), 2700–2800 ($R2N^+H_2$), 2940 (C–H sp^3). For MS the *N*-acetate was prepared by treatment of 8–10 mg sample with 2 mL acetic anhydride/CH_2Cl_2 (1:1) for 18 h and evaporating. MS (*N*-acetate): Calcd for $C_9H_{14}NO$ (M+Na)=189.1004, Found: 189.1006.

Compound **11b**. Syrup, ^{1}H NMR (D_2O): δ 3.92 (dt, J=2.4, 12.8 Hz, 1H, H_{6e}), 2.75 (dq, J=6.4, 10.4 Hz, 1H, H_{2a}), 2.53 (dt, J=2.8, 12.4 Hz, 1H, H_{6a}), 2.35 (ddd, J=3.6, 10.4, 10.4 Hz, 1H, H_{3a}), 2.16 (m, 1H, H_{5e}), 1.58–1.75 (m, 2H, H_{4a}, H_{4e}), 1.33 (m, 1H, H_{5a}), 1.20 (d, J=6.4 Hz, 3H, –CH_3). (hydrochloride) δ 3.56 (dq, J=6.56, 11.2 Hz, 1H, H_{2a}), 3.47 (bd, J=12.9 Hz, 1H, H_{6e}), 3.08 (dd, J=3.6, 13.2 Hz, 1H, H_{6a}), 3.04 (dd, J=3.6, 11.2 Hz, 1H, H_{3a}), 2.34 (ddq, J=1.6, 3.6, 13.6 Hz, 1H, H_{4e}), 2.05 (dk, J=3.6, 14.4 Hz, 1H, H_{5e}), 1.95 (ddd, J=3.6, 12, 12 Hz, 1H, H_{4a}, 1.76 (m, 1H, H_{5a}). ^{13}C NMR (CD_3OD): δ 121.8 (–C≡N), 52.6 (C_2), 44.1 (C_6), 35.0 (C_3), 26.7 (C_4), 24.6 (C_5), 17.8 (–CH_3). (hydrochloride): δ=118.7 (–C≡N), 53.1 (C_2), 42.7 (C_6), 32.7 (C_3), 25.0 (C_4), 20.1 (C_5), 15.9 (–CH_3). IR (KBr): 2254 (–C≡N), 2650–2750 ($R_2N^+H_2$), 2939 (C–H sp^3). For MS the *N*-acetate was prepared by treatment of 8–10 mg sample with 2 mL acetic anhydride/CH_2Cl_2 (1:1) for 18 h and evaporating. MS (*N*-acetate): Calcd for $C_9H_{14}NO$ (M+Na)=189.1004, Found: 189.1005.

4.1.11. Determination of pK_a of piperidine hydrochlorides. The piperidine hydrochloride (30 mg) was dissolved in 15–20 mL distilled water and subjected to titration with 0.1 M NaOH following the pH with a pH electrode. The pK_a was determined from the resulting titration curve, and was the average of three determinations (error ±0.1).

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