Pergamon

Tetrahedron 58 (2002) 7869–7873

TETRAHEDRON

1,4-Dihydropyridine equivalents: a novel approach to 2,6-dicyanopiperidine derivatives

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Received 27 May 2002; revised 2 July 2002; accepted 25 July 2002

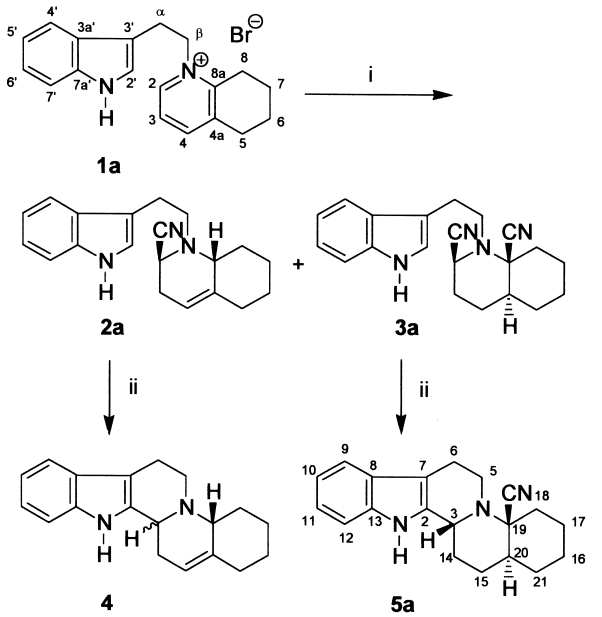
Abstract—For the first time, it has been shown that 2,6-dicyanopiperidines are formed in the Fry reaction via 1,4-dihydropyridine intermediates. A new synthetic approach for building 2,6-dicyanopiperidine derivatives by an extension of the sodium dithionite reduction of pyridinium salts is described. The stereochemistry of 2,6-dicyanopiperidine derivatives formed is discussed.

1. Introduction

N-substituted 2,6-dicyanopiperidines are versatile synthetic intermediates in the preparation of various pharmacologically important piperidine alkaloids.[1] These 1,4-dihydropyridine equivalents can also be converted to substituted α,β-unsaturated cyclohexenones and δ-diketones by alkylation and subsequent hydrolysis.[2] 2,6-Dicyanopiperidines are commonly prepared by the reaction of glutaraldehyde with amines in the presence of cyanide ion.[3] The general tendency of glutaraldehydes to polymerize and the limited availability of substituted glutaraldehydes are the main disadvantages of this method. In this paper, we report a new approach to synthesize analogous substituted *N*-alkyl 2,6-dicyanopiperidines using 1,4-dihydropyridines as intermediates.

We recently reported[4] the preparation of models of the novel indole alkaloid tangutorine[5] by the Fry reaction[6] (KCN, HCl, $NaBH_4$) of salt **1a** followed by acid treatment (Scheme 1). In addition to the expected isomeric mixture **4**, also the unexpected α-amino nitrile **5a** was formed. We assumed that nitrile **5a** could be derived from compound **3a**. However, at that time, intermediates **2a** (major) and **3a** (minor) were not isolated. Repeating the experiment, side product **3a** was isolated in 16% yield. This interesting dicyano product **3a** led us to focus our attention to the formation of such substituted dicyano derivatives in the Fry reactions in general.

Bearing in mind the reaction mechanism for sodium borohydride reduction of pyridinium and related salts,[7] the formation of dicyano compounds in the Fry reactions can be explained. Both a 1,2-dihydropyridine and to some extent also a 1,4-dihydropyridine intermediate are formed (Scheme 2). Under acidic conditions, the major 1,2-dihydropyridine is protonated to give an iminium ion which reacts with a cyanide ion, leading to *N*-alkyl-2-cyano-1,2,3,6-tetrahydropyridine. Similarly, the minor 1,4-dihydropyridine is protonated and reacted with cyanide. This is followed by a second protonation, leading to a 2,6-dicyanopiperidine.



Scheme 1. (i) KCN, 6N HCl, $NaBH_4$, Et_2O, 0°Crt, yield **2a** 22%, **3a** 16%; (ii) aq AcOH, yield **4** 20%, **5a** 10%.

To confirm the formation of the desired 2,6-dicyano product via the 1,4-dihydropyridine intermediate in the Fry reaction and to improve the yields, we decided to use sodium

Keywords: amino nitriles; cyano compounds; indole alkaloids; reduction.

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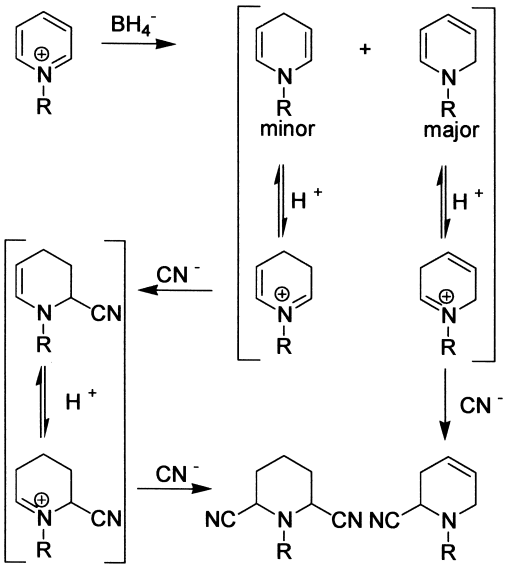
PII: S0040-4020(02)00896-7



Scheme 2.

dithionite as reductant. The dithionite reduction[7] of *N*-alkyl pyridinium salts bearing electron-withdrawing substituents at C-3 and/or C-5 to give 1,4-dihydropyridines is a well-known procedure. For a long time, an apparent limitation of this reaction was the reported failure of the reduction of pyridinium salts devoid of substituents or containing only an alkyl substituent. Recently, a simple modification to reduce pyridinium salts of this kind has been reported.[8]

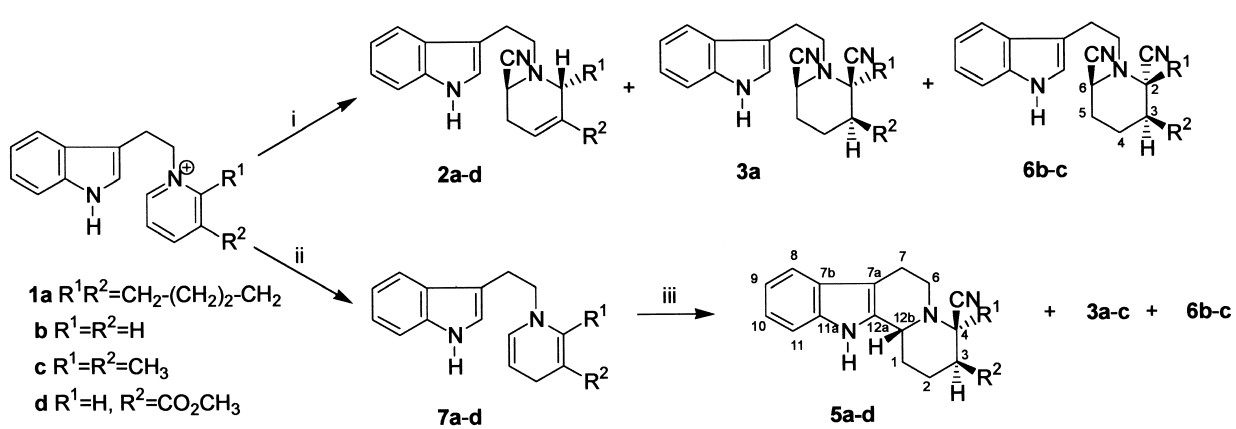
Four pyridinium salts, 1-[2-(3-indolyl)ethyl]-5,6,7,8-tetrahydroquinolinium bromide **1a**, an unsubstituted pyridinium salt (1-[2-(3-indolyl)ethyl]pyridinium bromide **1b**), one without electron-withdrawing substituents (2,3-dimethyl-1-[2-(3-indolyl)ethyl]pyridinium bromide **1c**) resembling the quinolinium salt **1a**, and one with an electron-withdrawing substituent (3-methoxycarbonyl-1-[2-(3-indolyl)-ethyl]pyridinium bromide **1d**), were chosen to study the assumed formation of 2,6-dicyanopiperidines under the Fry reaction conditions or using sodium dithionite as reductant.

2. Results and discussion

When salts **1a**–**d** were subjected to the Fry reaction conditions (KCN, HCl, $NaBH_4$), three identifiable products in different ratios were formed in every reaction. The main product each time was the expected monocyano compound (**2a**–**d**). In addition, the desired 2,6-dicyano compound (**3a**, **6b**, **6c**) was separated. In the reaction of salt **1d**, only traces of a dicyano compound were observed, however. In this reaction, the ester group stabilizes more the 1,2- than the 1,4-dihydropyridine intermediate. Therefore, the yield of dicyano compounds was very low, and the only isolated product was the monocyano compound **2d**. Moreover, tetrahydropyridine derivatives (and the corresponding octahydroquinoline) without a cyano substituent were formed as side products.

Salts **1a**–**d** were chosen as starting material for the $Na_2S_2O_4$/KCN reaction also: the reduction with sodium dithionite was followed by the addition of KCN under acidic conditions. In the reaction of salt **1a**, a dicyano product **3a** and a monocyano product **5a** were formed (total yield 40%). The reaction of salt **1b** gave three different aminonitriles **3b**, **5b**, **6b** (total yield 14%), and the reaction of salt **1c** gave the corresponding aminonitriles **3c**, **5c**, **6c** and minor amounts of other dicyano stereoisomers (total yield 67%) (Scheme 3). In the reduction of salt **1d**, only the cyclized monocyano compound **5d** was formed (yield 48%). In this reaction, the 1,4-dihydropyridine intermediate is more stable than with other salts (**1a**–**c**) because of the stabilizing ester group. Under acidic conditions, the nucleophilic attack by the indole is faster than the addition of a cyanide ion to C-6, leading to the cyclized monocyano product **5d**. The small coupling constant of C(4)H (J=4 Hz) indicates that the cyano and ester groups are *cis* in **5d**. Overreduction to 1,2,3,4-tetrahydropyridine and piperidine stages was observed, especially with salt **1b**.[9]

To determine the configuration of the cyano groups, we examined the NMR spectroscopic data of compounds **3a**–**c** and **6b**–**c**. The absence of a large coupling constant for C(6)H in the ^{1}H NMR spectra of compounds **3b** and **3c** indicates that the C-6 cyano substituents are axial. The ^{13}C NMR chemical shifts of C-4 for *N*-methyl piperidine and *N*-methyl *trans*-2,3-dimethylpiperidine are 23.8 and 34.0 ppm, respectively.[10] Comparison of these values with those of compounds **3b** and **3c**, respectively, and taking into account the γ-effect produced by an axial cyano group (approximately −4 ppm)[11] confirm that also the C-2 cyano



Scheme 3. (i) KCN, HCl, $NaBH_4$, Et_2O, 0°Crt; (ii) $Na_2S_2O_4$, aq K_2CO_3, toluene, 100°C or $Na_2S_2O_4$, aq $NaHCO_3$, MeOH, rt; (iii) KCN, HCl, MeOH, rt.

group in compounds **3b** and **3c** is axial. In accordance with these results the chemical shift of C-4 (δ 25.3 ppm) for compound **3a** indicates that both cyano groups are axial. Two other facts support this conclusion: as the ring juncture is *trans*, the C-8a cyano group is axial. The two small coupling constants for C(2)H confirm that the C-2 cyano group is axial, too. The diaxial conformation is preferred, as in this conformation the molecule can benefit from the stabilizing anomeric effects between the anti-periplanar nitrile groups and the nitrogen lone pair of electrons.[3c,12]

The ^{13}C NMR chemical shift of C-4 for compound **6b** (δ 19.4 ppm) does not differ significantly from the one observed for compound **3b**. Since the γ-effect produced by an equatorial cyano group is only 0–2 ppm,[3c] the chemical shift of C-4 in compound **6b** should have a higher value if the cyano groups were diequatorial. In fact, the two coupling constants (J=4, 7 Hz) of both C(2)H and C(6)H in **6b** indicate that the molecule exists as an equilibrium mixture of conformers and the values determined are an average of axial and equatorial hydrogens.[12] The two small coupling constants of C(6)H for compound **6c** confirm that the C-6 cyano group is axial. In turn, the difference between the chemical shifts of C-4 for *N*-methyl *cis*-2,3-dimethylpiperidine (δ 29.3 ppm) and for compound **6c** (δ 24.3 ppm) indicates that one of the cyano groups is axial and the other equatorial. Thus, the C-2 cyano group is equatorial.

The dissimilar reaction temperatures could be one reason for stereochemically different products in the Fry and the $Na_2S_2O_4$/KCN reactions. Most likely, the dicyano products **6b** and **6c** are due to the kinetically controlled addition of cyanide whereas the diaxial dicyano compounds **3a–c** are formed under thermodynamic control.

We have shown for the first time that 2,6-dicyanopiperidines are formed in the Fry reaction. In order to show that 1,4-dihydropyridines are possible intermediates in this reaction, we changed the reducing agent to sodium dithionite. The cyanide addition then gave the expected compounds. This novel method makes it possible to synthesize various substituted *N*-alkyl 2,6-dicyanopiperidines. It seems that by careful adjustment of the reaction temperature, specific isomeric structures of 2,6-dicyanopiperidines can be prepared (Table 1).

3. Experimental

Infrared spectra were recorded on a Perkin–Elmer Spectrum One FT-IR. NMR spectra were recorded on a Bruker AV-400 spectrometer. Chemical shifts (δ) are reported in ppm relative to TMS (^{1}H NMR; δ_H=0.00 ppm) and $CDCl_3$ (^{13}C NMR; δ_C=77.000 ppm). Signal assignments are based on standard APT, DEPT, HSQC and ^{1}H–^{1}H COSY experiments. Abbreviations s, d, t, m, def and br are used to designate singlet, doublet, triplet, multiplet, deformed and broad, respectively. Mass spectra (EI and HRMS, 70 eV, m/z) were obtained on a Jeol DX 303/DA 5000 instrument. Compounds were purified by column chromatography (CH_2Cl_2/MeOH, 99:1) using Merck Kieselgel 60 (230–400 mesh).

3.1. General procedure for the Fry reaction

Potassium cyanide (10 mmol) was dissolved in water (0.60 mL) and cooled to 0°C. Hydrochloric acid (6N, 0.80 mL) was added dropwise and the mixture was layered with Et_2O (4.0 mL). MeOH (1.0 mL) and the pyridinium salt (1.7 mmol) were added. After 10 min of stirring, $NaBH_4$ (2.2 mmol) was added in small portions during 30 min, keeping the solution at 0°C. The reaction mixture was stirred at rt for 4 h. The ethereal layer was separated and the aqueous layer was extracted several times with CH_2Cl_2. The

Table 1. ^{13}C-values

Carbon[a]	**3a**	Carbon[a]	**3b**	**3c**	**6b**	**6c**	Carbon[b]	**5a**	Carbon[a]	**5b**	**5c**	**5d**
2	50.1	2	48.9	60.4	50.8	61.5	2	134.6	1	29.8	30.0*	29.2
3	28.6	3	28.3	40.2	29.0	38.9	3	56.6	2	20.6	29.9*	23.2
4	44.9	4	17.1	26.8	19.4	24.3	5	44.1	3	28.8	40.0	44.1
4a	25.3	5	28.3	28.2	29.0	27.6	6	22.0	4	54.9	63.0	56.5
5	29.7	6	48.9	49.9	50.8	47.5	7	108.1	6	51.7	45.7	51.5
6	24.9	α	22.9	25.0	23.3	24.7	8	127.0	7	21.5	22.2	21.6
7	22.7	β	54.8	51.1	54.5	52.2	9	118.1	7a	107.9	108.2	108.1
8	35.7	2′	121.6	121.7	121.8	121.9	10	119.5	7b	127.1	127.0	126.9
8a	62.8	3′	112.7	113.1	112.9	112.9	11	121.5	8	118.5	118.2	118.2
α	24.9	3a′	127.2	127.2	127.9	127.6	12	110.8	9	119.6	119.5	119.7
β	49.7	4′	118.2	118.6	118.7	118.8	13	136.1	10	121.7	121.6	121.9
2′	121.8	5′	119.6	119.5	119.6	119.6	14	30.0	11	110.8	110.8	110.8
3′	112.9	6′	122.3	122.2	122.3	122.2	15	28.5*	11a	136.1	136.2	136.2
3a′	127.2	7′	111.2	111.2	111.2	111.1	16	24.9	12a	133.8	134.6	133.1
4′	118.6	7a′	136.1	136.2	136.2	136.2	17	23.5	12b	54.9	56.4	54.2
5′	119.4	2-Me		25.2		14.7	18	34.5	3-Me		18.2	
6′	122.1	3-Me		17.9		16.6	19	65.1	4-Me		23.5	
7′	111.3						20	44.5	CO_2Me			170.7
7a′	136.2						21	30.3*	CO_2*Me*			52.5
CN	116.8	CN	115.9	116.4	117.3	116.6	CN	117.7	CN	116.7	117.9	114.8
CN	117.1	CN	115.9	117.4	117.3	117.8						

[a] IUPAC numbering.
[b] Numbering proposed by Berner et al.[4]

combined organic layers were dried over Na_2SO_4 and evaporated.

3.2. General procedure for the $Na_2S_2O_4$/KCN reaction

Reduction of salts **1a**–**c** was carried out according to the following procedure.[8] To a two-phase solution of toluene (5 mL) and water (6 mL) containing sodium dithionite (3.0 mmol) and potassium carbonate (6.0 mmol), pyridinium or quinolinium salt (1.0 mmol) was added. The mixture was heated at 100°C for 12 min. The organic phase was separated, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4 and evaporated.

Reduction of salt **1d** was performed as follows. Sodium dithionite (3.0 mmol) was added in small portions during 10 min to a solution of pyridinium salt **1d** (0.5 mmol) in 40 mL of aqueous methanol (H_2O/MeOH, 1:2) containing $NaHCO_3$ (9.0 mmol). The mixture was stirred for 18 h at rt and filtered. Methanol was evaporated and the residue extracted with CH_2Cl_2. The extracts were washed with brine, dried over Na_2SO_4 and evaporated.

Due to their instability, the 1,4-dihydropyridines were used as such in the following reaction. The yields given are integrated from ^{1}H NMR spectra. The crude $Na_2S_2O_4$ reduction product (see above) (~0.5 mmol) in methanol (6.5 mL) was added to a solution of potassium cyanide (5 mmol) in water (1 mL). Hydrochloric acid (6N, 1 mL) was added and the mixture was stirred at rt for 4 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and evaporated.

3.3. Reactions of 1-[2-(3-indolyl)ethyl]-5,6,7,8-tetrahydroquinolinium bromide 1a

The Fry reaction of salt **1a** (605 mg, 1.7 mmol) gave 530 mg of crude product comprising 115 mg (22%) of compound **2a** and 90 mg (16%) of **3a**.

Reduction of salt **1a** (400 mg, 1.1 mmol) with sodium dithionite gave compound **7a** in 45% yield. Addition of potassium cyanide to **7a** gave 45 mg of compound **3a** and 20 mg of **5a** (total yield 40%).

3.3.1. Compound 3a. Amorphous; ν_{max}/cm^{-1} 3410 (NH) and 2220 (CN); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.3–1.4 (1H, m, 6_{ax}-H), 1.35 (1H, ddd, J=4, 12, 13 Hz, 8_{ax}-H), 1.44 (1H, dddd, J=3, 3, 12, 12 Hz, 4a-H), 1.5–1.6 (4H, m, 2×4-H, and 2×5-H), 1.7–1.8 (3H, m, 6_{eq}-H, and 2×7-H), 1.83 (1H, dddd, J=4, 5, 12, 13 Hz, 3_{ax}-H), 2.01 (1H, dddd, J=2.5, 3, 3, 13 Hz, 3_{eq}-H), 2.33 (1H, ddd, J=3, 3, 13 Hz, 8_{eq}-H), 2.9–3.0 (3H, m, 2×α-H and β-H), 3.3–3.4 (1H, m, β-H), 4.04 (1H, d (def), J=5 Hz, 2-H), 7.02 (1H, d, J=2 Hz, 2′-H), 7.12 (1H, t, J=8 Hz, 5′-H), 7.19 (1H, t, J=8 Hz, 6′-H), 7.36 (1H, d, J=8 Hz, 7′-H), 7.57 (1H, d, J=8 Hz, 4′-H), 8.08 (1H, br s, NH); m/z (EI) 332 (M^+), 305, 278, 251, 202, 175, 148, 130 (100%). Exact mass: 332.2054 (calcd for $C_{21}H_{24}N_4$: 332.2001).

3.3.2. Compound 5a. Amorphous; ν_{max}/cm^{-1} 3400 (NH) and 2215 (CN); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.30 (1H, ddddd, J=3, 4, 12, 12, 12 Hz, 16_{ax}-H), 1.46 (1H, dddd, J=4, 12, 12, 12 Hz, 21_{ax}-H), 1.48 (1H, ddd, J=4, 12, 13 Hz, 18_{ax}-H), 1.6–1.7 (5H, m, 14_{ax}-H, 2×15-H, 17_{ax}-H and 20_{ax}-H), 1.7–1.8 (2H, m, 16_{eq}-H and 21_{eq}-H), 1.91 (1H, br d, J=13 Hz, 17_{eq}-H), 2.13 (1H, dddd, J=2.5, 3, 6, 12 Hz, 14_{eq}-H), 2.50 (1H, ddd, J=4, 11, 11 Hz, 5_{ax}-H), 2.52 (1H, ddd, J=3, 3, 13 Hz, 18_{eq}-H), 2.76 (1H, dddd, J=1.5, 2, 4, 15.5 Hz, 6_{eq}-H), 2.88 (1H, dddd, J=2.5, 5.5, 11, 15.5 Hz, 6_{ax}-H), 3.53 (1H, ddd, J=1.5, 5.5, 11 Hz, 5_{eq}-H), 3.84 (1H, br d, J=9 Hz, 3-H), 7.09 (1H, t, J=8 Hz, 10-H), 7.14 (1H, t, J=8 Hz, 11-H), 7.31 (1H, d, J=8 Hz, 12-H), 7.46 (1H, d, J=8 Hz, 9-H), 7.74 (1H, br s, NH); m/z (EI) 305 (M^+, 100%), 278, 251, 169. Exact mass: 305.1885 (calcd for $C_{20}H_{23}N_3$: 305.1892).

3.4. Reactions of 1-[2-(3-indolyl)ethyl]pyridinium bromide 1b

The Fry reaction of salt **1b** (500 mg, 1.7 mmol) gave 405 mg of crude product comprising 145 mg (35%) of compound **2b** and 10 mg (2%) of **6b**.

Sodium dithionite reduction of salt **1b** (600 mg, 2.0 mmol) gave compound **7b** in 24% yield. Addition of potassium cyanide to **7b** gave 10 mg of compound **3b**, 5 mg of **5b** and 3 mg of **6b** (total yield 14%).

3.4.1. Compound 3b. Amorphous; ν_{max}/cm^{-1} 3410 (NH) and 2225 (CN); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.5–2.2 (6H, m, 2×3-H, 2×4-H and 2×5H), 2.9–3.0 (2H, m, 2×α-H), 3.12 (2H, t, J=7 Hz, 2×β-H), 4.02 (2H, d (def), J=5 Hz, 2_{eq}-H and 6_{eq}-H), 7.05 (1H, d, J=2 Hz, 2′-H), 7.12 (1H, t, J=8 Hz, 5′-H), 7.21 (1H, t, J=8 Hz, 6′-H), 7.37 (1H, d, J=8 Hz, 7′-H), 7.59 (1H, d, J=8 Hz, 4′-H), 8.02 (1H, br s, NH); m/z (EI) 278 (M^+), 251, 224, 148, 144, 130 (100%), 121. Exact mass: 278.1538 (calcd for $C_{17}H_{18}N_4$: 278.1531).

3.4.2. Compound 5b. Amorphous; ν_{max}/cm^{-1} 3400 (NH) and 2225 (CN); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.5–2.1 (6H, m, 2×1-H, 2×2-H and 2×3-H), 2.7–3.1 (4H, m, 2×6-H and 2×7-H), 3.78 (1H, dd, J=2, 11 Hz, 12b-H), 4.06 (1H, dd, J=3, 4 Hz, 4_{eq}-H), 7.10 (1H, t, J=7.5 Hz, 9-H), 7.15 (1H, t, J=7.5 Hz, 10-H), 7.32 (1H, d, J=7.5 Hz, 11-H), 7.47 (1H, d, J=7.5 Hz, 8-H), 7.74 (1H, br s, NH); m/z (EI) 251 (M^+), 224, 197 (100%), 169. Exact mass: 251.1416 (calcd for $C_{16}H_{17}N_3$: 251.1422).

3.4.3. Compound 6b. Amorphous; ν_{max}/cm^{-1} 3410 (NH), 2250 (CN) and 2225 (CN); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.7–1.8 (2H, m, 2×4-H), 1.9–2.0 (4H, m, 2×3-H and 2×5-H), 2.9–3.0 (1H, m, α-H), 3.0–3.1 (2H, m, β-H and α-H), 3.4–3.5 (1H, m, β-H), 3.80 (2H, dd, J=4, 7 Hz, 2-H and 6-H), 7.11 (1H, d, J=2 Hz, 2′-H), 7.14 (1H, t, J=7.5 Hz, 5′-H), 7.21 (1H, t, J=7.5 Hz, 6′-H), 7.37 (1H, d, J=7.5 Hz, 7′-H), 7.63 (1H, d, J=7.5 Hz, 4′-H), 8.01 (1H, br s, NH); m/z (EI) 278 (M^+), 251, 224, 144, 130, 121 (100%). Exact mass: 278.1539 (calcd for $C_{17}H_{18}N_4$: 278.1531).

3.5. Reactions of 2,3-dimethyl-1-[2-(3-indolyl)ethyl]-pyridinium bromide 1c

The Fry reaction of salt **1c** (565 mg, 1.7 mmol) gave 445 mg

of crude product comprising 105 mg (22%) of compound **2c** and 15 mg (3%) of **6c**.

Reduction of salt **1c** (300 mg, 0.9 mmol) with sodium dithionite gave compound **7c** in 27% yield. Addition of potassium cyanide to **7c** gave 35 mg of compound **3c**, 5 mg of **5c** and 10 mg of other dicyano stereoisomers (total yield 67%).

3.5.1. Compound 3c. Amorphous; ν_{max}/cm^{-1} 3410 (NH) and 2225 (CN); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.17 (3H, d, J=6.5 Hz, 3-CH_3), 1.53 (3H, s, 2-CH_3), 1.55–1.65 (1H, m, 3_{ax}-H), 1.65–1.85 (3H, m, 2×4-H and 5_{ax}-H), 1.97 (1H, br d, J=12 Hz, 5_{eq}-H), 2.85–2.95 (1H, m, α-H), 2.95–3.05 (2H, m, α-H and β-H), 3.3–3.4 (1H, m, β-H), 4.01 (1H, def, 6-H), 7.04 (1H, br s, 2′-H), 7.13 (1H, t, J=8 Hz, 5′-H), 7.21 (1H, t, J=8 Hz, 6′-H), 7.37 (1H, d, J=8 Hz, 7′-H), 7.58 (1H, d, J=8 Hz, 4′-H), 8.02 (1H, s, NH); m/z (EI) 306 (M^+), 279, 252, 179, 149, 130 (100%). Exact mass: 306.1820 (calcd for $C_{19}H_{22}N_4$: 306.1844).

3.5.2. Compound 5c. Amorphous; ν_{max}/cm^{-1} 3400 (NH) and 2220 (CN); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.18 (3H, d, J=6 Hz, 3-CH_3), 1.5–1.9 (5H, m, 2×1-H, 2×2-H and 3-H), 1.67 (3H, s, 2-CH_3), 2.59 (1H, ddd, J=4, 11, 11 Hz, 6_{ax}-H), 2.7–3.0 (2H, m, 2×7-H), 3.54 (1H, ddd, J=1.5, 4, 11 Hz, 6_{eq}-H), 3.78 (1H, br d, J=11 Hz, 12b-H), 7.09 (1H, t, J=7.5 Hz, 9-H), 7.14 (1H, t, J=7.5 Hz, 10-H), 7.31 (1H, d, J=7.5 Hz, 11-H), 7.47 (1H, d, J=7.5 Hz, 8-H), 7.76 (1H, br s, NH); m/z (EI) 279 (M^+), 252, 237 (100%), 169. Exact mass: 279.1731 (calcd for $C_{18}H_{21}N_3$: 279.1735).

3.5.3. Compound 6c. Amorphous; ν_{max}/cm^{-1} 3410 (NH), 2240 (CN) and 2220 (CN); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.12 (3H, d, J=7 Hz, 3-CH_3), 1.47 (3H, s, 2-CH_3), 1.58 (1H, dddd, J=3.5, 4, 5, 11.5 Hz, 4_{eq}-H), 1.75 (1H, dddd, J=5, 11, 11, 11.5 Hz, 4_{ax}-H), 1.83 (1H, dddd, J=4, 5, 11, 12 Hz, 5_{ax}-H), 1.97 (1H, dddd, J=4, 4, 5, 12 Hz, 5_{eq}-H), 2.13 (1H, ddddd, J=3.5, 7, 7, 7, 11 Hz, 3_{ax}-H), 2.9–3.1 (2H, m, 2×α-H), 3.1–3.2 (1H, m, β-H), 3.3–3.4 (1H, m, β-H), 3.90 (1H, dd, J=4, 4 Hz, 6_{eq}-H), 7.08 (1H, d, J=2 Hz, 2′-H), 7.14 (1H, t, J=7.5 Hz, 5′-H), 7.20 (1H, t, J=7.5 Hz, 6′-H), 7.36 (1H, d, J=7.5 Hz, 7′-H), 7.67 (1H, d, J=7.5 Hz, 4′-H), 8.01 (1H, br s, NH); m/z (EI) 306 (M^+), 279, 252, 176, 149, 144, 130 (100%). Exact mass: 306.1836 (calcd for $C_{19}H_{22}N_4$: 306.1844).

3.6. Reactions of 3-methoxycarbonyl-1-[2-(3-indolyl)ethyl]pyridinium bromide 1d

The Fry reaction of salt **1d** (300 mg, 0.8 mmol) gave 250 mg of crude product mixture comprising 80 mg (30%) of compound **2d** without any observable amounts of dicyanopiperidine.

Reduction of salt **1d** (200 mg, 0.6 mmol) with sodium dithionite gave product **7d** in 70% yield. Addition of potassium cyanide to **7a** gave 55 mg (48%) of compound **5d**.

3.6.1. Compound 5d. Amorphous; ν_{max}/cm^{-1} 3390 (NH), 2225 (CN) and 1730 (C=O); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.58 (1H, dddd, J=4, 12, 12, 13 Hz, 1_{ax}-H), 1.95 (1H, dddd, J=4, 12, 12, 14 Hz, 2_{ax}-H), 2.22 (1H, dddd, J=3, 3, 4, 13 Hz, 1_{eq}-H), 2.35 (1H, dddd, J=3, 3, 4, 14 Hz, 2_{eq}-H), 2.78 (1H, br d, J=12 Hz, 7_{eq}-H) 2.9–3.0 (4H, m, 3-H, 2×6-H and 7_{ax}-H), 3.78 (1H, br d, J=12 Hz, 12b-H), 3.80 (3H, s, $-CO_2CH_3$), 4.44 (1H, d, J=4 Hz, 4_{eq}-H), 7.11 (1H, t, J=8 Hz, 9-H), 7.17 (1H, t, J=8 Hz, 10-H), 7.32 (1H, d, J=8 Hz, 11-H), 7.48 (1H, d, J=8 Hz, 8-H), 7.75 (1H, br s, NH); m/z (EI) 309 (M^+), 282, 250 (100%), 223, 169, 156. Exact mass: 309.1476 (calcd for $C_{18}H_{19}N_3O_2$: 309.1477).

Acknowledgements

The financial support of Helsinki University of Technology and the Finnish Foundation of Technology is gratefully acknowledged.

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