HETEROCYCLES, Vol. 78, No. 8, 2009, pp. 2021 - 2032. © The Japan Institute of Heterocyclic Chemistry
Received, 9th March, 2009, Accepted, 14th April, 2009, Published online, 15th April, 2009.
DOI: 10.3987/COM-09-11701

PREPARATION OF 5-AMINO-1,2-DIHYDRO-4-(1-METHYL-4-PIPERIDINYL)PYRROL-3-ONES

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Abstract – Acylation of (1-methyl-4(1*H*)-pyridinylidene)acetonitrile with chloroacetyl chloride was found to occur at the exocyclic carbon atom leading to 4-chloro-2-(1-methyl-4(1*H*)-pyridinylidene)-3-oxobutanenitrile. Its reaction with primary amines furnished 4-(2-amino-4,5-dihydro-4-oxo-1*H*-pyrrol-3-yl)-1-methylpyridinium chlorides. Hydrogenation of these quaternary salts afforded 5-amino-1,2-dihydro-4-(1-methyl-4-piperidinyl)-3*H*-pyrrol-3-ones in nearly quantitative yields.

INTRODUCTION

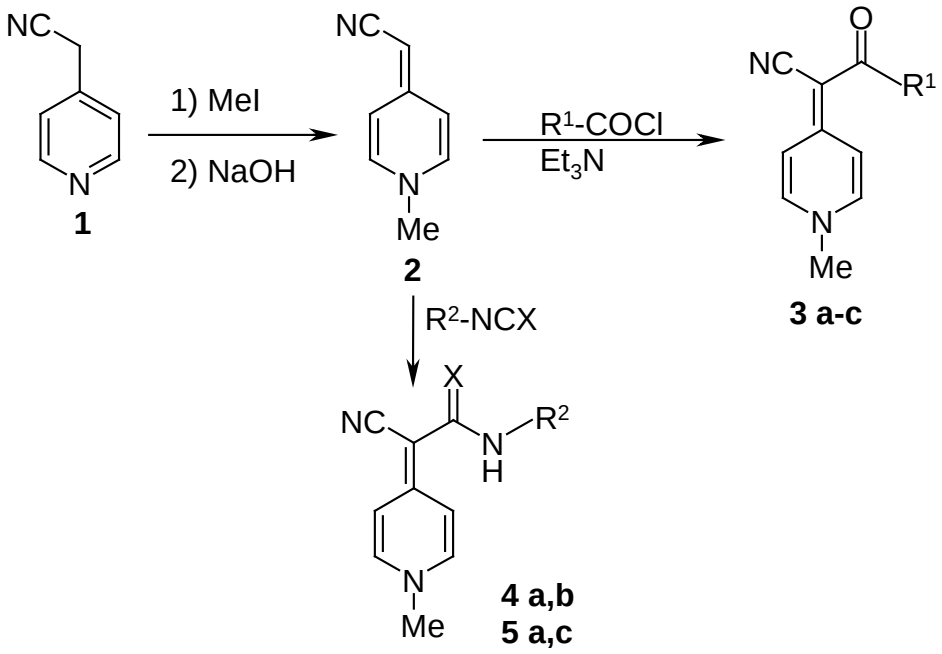
Piperidine core is a part of enormous number of natural products and synthetic drugs. Over the last 10 years thousands of piperidine derivatives were mentioned in clinical and preclinical studies and a plenty of synthetic methods for their preparations were published.[1] Among them 4-hetarylpiperidines, and particularly 4-pyrrolylpiperidines, have caught a due attention. Owing to the availability of 4-aminopiperidines synthesis and properties of 4-(pyrrol-1-yl)piperidine derivatives have been investigated extensively. Thus, nowadays the 4-(1-pyrrolidinyl)piperidine moiety has become one of the most popular pharmacophores.[2,3,4,5] It is the fragment of several compounds aimed for obesity treatment,[2] and is also comprised into certain anti-ischemic,[3] anti-asthmatic[4] and other drug candidates[5] currently being at different stages of preclinical studies. At the same time piperidine derivatives bearing pyrrole substituents adjacent through a carbon atom are little known. There are at about 10 papers only describing both 4-(pyrrol-2-yl)- and 4-(pyrrol-3-yl)piperidines.[6,7,8,9] Nevertheless, even within this limited set of compounds derivatives with potent anti-coccidial[6] and anti-arthritis[7] activities have been discovered. So, elaboration of new approaches to this type pyrrolylpiperidines, especially containing additional functionalities in the pyrrole ring seems to be promising.

The known methods of 2- and 3-(4-piperidinyl)pyrroles preparation utilize addition of lithiated pyrrole species to 4-piperidinone derivatives,[7,8] formation of pyrroles from ammonia and acyclic precursors already bearing desired piperidine substituent,[6] and hydrogenation of pyridinylpyrroles.[9] The former two methods have some shortcomings. Thus, the lithiation conditions do not tolerate most of functionalities therefore requiring multiple protections. In turn, the second approach despite the excellent final heterocyclization step necessitates vary laborious preparation of the suitable acyclic precursor. So, the hydrogenation seems to be the best way to the target compounds because, firstly, it is compatible with a number of functionalities like amino group, and secondly, there are many available pyridine derived building blocks applicable to the synthesis of pyridinylpyrroles. Generally speaking, reduction of pyridines or their quaternary salts into piperidines is the well known synthetic tool,[10] which has been successfully used in the total syntheses of several natural products.[11]

Over the last years the chemistry and synthetic utility of various hetarylideneacetonitriles was actively studied in our laboratory.[12] Continuing the research in the field we report herein preparation of the hitherto unknown (1-methyl-4(1*H*)-pyridinylidene)acetonitrile (**2**) and its application to the synthesis of piperidinylpyrroles.

RESULTS AND DISCUSSION

Compound **2** was obtained in 76 % yield from the pyridine **1**[13] through the quaternization with CH_3I followed by the treatment with NaOH (Scheme 1). It appeared to be brownish solid stable towards storage



Scheme 1. R^1 = **a:** Ph; **b:** 2-thienyl; **c:** CH_2Cl. X = **4:** O; **5:** S. R^2 = **a:** Ph; **b:** 4-ClC_6H_4; **c:** Me.

during several weeks without any special precautions from air. Since certain related hetarylideneacetonitriles were reported to react with electrophiles at exocyclic carbon atom,[12,14] corresponding behavior of derivative **1** was examined. Indeed, it underwent easy acylation with acid chlorides yielding derivatives **3a-c** and was added smoothly to iso(thio)cyanates giving amides **4** and thioamides **5**. The structure of the prepared compounds **3-5** was confirmed by ^{1}H and ^{13}C NMR spectra. It should be noted that the spectral data exhibited no inversion of the exocyclic double bond configuration in compounds **2** and **4**. Both the protons and carbon atoms at positions 3 and 5 (as well as 2 and 6) of the pyridine moiety were observed as magnetically non-equivalent. At the same time the spectra of derivatives **3,5** showed a slow rotation of the double bond in the NMR time scale. Thus in their ^{13}C NMR spectra the two two-carbon signals of 2,6-C (139.9-142.1 ppm) and 3,5-C (114.9-116.7 ppm) of the pyridine moiety were present, whereas the more quick ^{1}H NMR experiment revealed the two-proton signal of 2,6-H (7.74-8.12 ppm) of the pyridine and two one-proton significantly broadened signals of the 3-H (6.88-7.12 ppm) and 5-H (8.72-9.00 ppm) being “on the way” to the coalescence. Apparently, inversion of the double bond configuration occurs through the canonic structure **6** with the separated charges (Fig. 1). The greater ability of carbonyl and thioamide groups to accept the negative charge comparing to the carboxamide causes different behavior of derivatives **3,5** and **2,4**. Furthermore, the double bond inversion was facilitated by acids. Thus, for the all compounds **2-5** the both ^{1}H and ^{13}C NMR spectra recorded in CF_3COOD solutions exhibited magnetical equivalence of the mentioned pairs of carbons and protons.

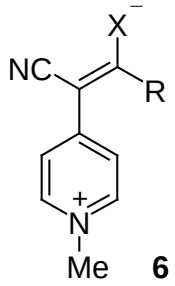


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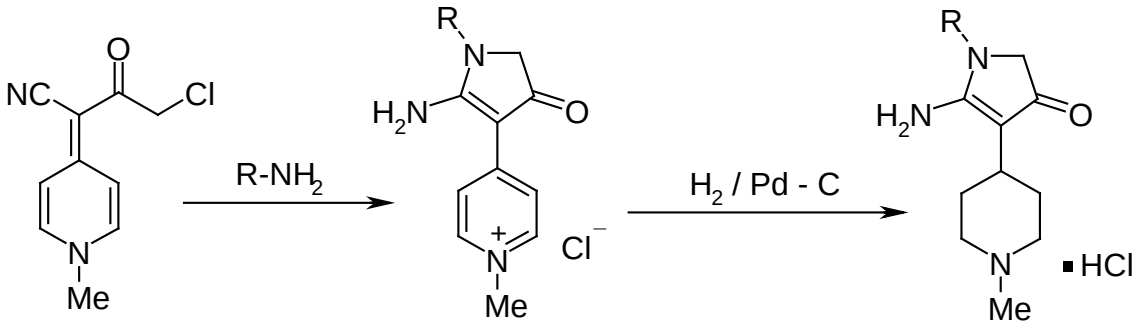
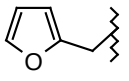
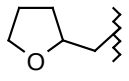
Figure 1. X = O, S. R = R^1, NHR^2.

The reaction of 4-halobutanenitrile derivatives with primary amines is known as a convenient method of aminopyrroles synthesis.[12,15,16] With this implication in mind the chloroacetyl chloride was selected among the acids chlorides used for the acylation of the compound **2**. Thus, the 4-chlorobutanenitrile derivative **3c** was prepared in 63 % yield. Its reaction with primary amines in DMF afforded aminopyrroles **7a-g** in 75-95 % yields (Scheme 2). Compounds **7** were assumed to be formed through initial alkylation of amines with the chloride **3c** and further hydrogen chloride assisted intramolecular addition of the secondary amine obtained to the nitrile group. The latter was accompanied with the positive charge transfer to the pyridine moiety. Thus, the equivalent amount of HCl liberated on the first step of the reaction was then utilized in the second one.



3c **7 a-g** **8 a-f, h**

Scheme 2. R = **a:** $PhCH_2$; **b:** 4-$MeOC_6H_4$; **c:** Ph; **d:** 4-MeC_6H_4; **e:** CH_2CH_2OH; **f:** CH_2CH_2OMe; **g:**  ; **h:**  .

Further, reduction of the quaternary salts **7** was examined. It was found that hydrogenation of derivatives **7** at atmospheric pressure with Pd on carbon catalyst resulted in the target piperidines **8 a-f,h** in the form of hydrochlorides in nearly quantitative yields. Noteworthy, during hydrogenation of certain pyridinylpyrroles bearing *N*-benzyl substituent partial or complete debenzylation was observed.[9] In the present case the benzyl group of compound **7a** appeared to be intact after the reduction and remained in the product **8a**. Furthermore, the furan moiety of the derivative **7g** turned out to undergo hydrogenation together with the pyridinium salt, thus leading to the completely reduced compound **8h**.

The structures of the prepared compounds **7,8** were confirmed by ^1H and ^{13}C NMR spectra. For selected derivatives **8** the APT experiments were performed to facilitate the signals assignments in the aliphatic region. As for the spectral data, disappearance of the nitrile group signal (122.7 ppm) of compound **3c** and the presence of the signal of 2′-C (165.5-166.5 ppm) in the ^{13}C NMR spectra of derivatives **7**, as well as the amino group signal observed in their ^1H NMR spectra at 7.8-8.5 ppm deserve to be mentioned as the most remarkable attributes of the heterocyclization reaction.

To resume, the present research has resulted in preparation of the new pyridine building block **2** and its application to the synthesis of piperidinylpyrroles **8**. The method seems to be tempting due to the use of readily available starting materials and simple procedures. Once again, the hydrogenation of pyridine has been shown to be an important and helpful tool in piperidines chemistry. The potential of compound **2** for the synthesis of interesting piperidine derivatives is believed not to be exhausted by the present example, and hence the further studies in the field are being undertaken.

EXPERIMENTAL

The starting compound **1** was prepared from the commercially available 4-(chloromethyl)pyridine according to the reported procedure.[13] Other reagents were commercially available and were used without extra purification. Commercial dioxane was dried with Na. Commercial DMF was kept over P_2O_5

overnight and then distilled under reduced pressure. All melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity plus 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) in DMSO-d_6 solutions, if otherwise not stated. ^{13}C NMR spectra of the quaternary salts **7** and hydrochlorides **8** were recorded in D_2O because of their better solubility comparing to DMSO. Chemical shifts (δ) are given in ppm downfield from internal Me_4Si. *J* values are in Hz. The purity of all compounds obtained was checked by ^{1}H NMR and LC/MS on an Agilent 1100 instument.

(1-Methyl-4(1*H*)-pyridinylidene)acetonitrile (2): MeI (18.1 g, 0.1275 mol) was added in one portion to a solution of the pyridine **1** (10.0 g, 0.085 mol) in 2-propanol (40 mL) and the mixture was left at rt for 1 day. The precipitate of the quaternary salt formed was filtered and dissolved in water (30 mL). Aqueous NaOH (4.0 g in 20 mL of water) was added to this solution in one portion resulting in the separation of oil, which quickly solidified. The solid was filtered and washed with water to give compound **2** (8.5 g, 76 %) sufficiently pure for further use. The analytical sample was additionally purified by recrystallization from 2-propanol. mp 68 °C (*i*-PrOH). ^{1}H NMR: δ = 3.39 (s, 3H, CH_3), 3.79 (s, 1H, CHCN), 6.09 (dd, J^3 = 7.0, J^4 = 2.0, 1H, 3-H), 6.18 (dd, J^3 = 7.0, J^4 = 2.0, 1H, 5-H), 6.94 (dd, J^3 = 7.0, J^4 = 1.5, 1H, 2-H), 7.07 (dd, J^3 = 7.0, J^4 = 1.5, 1H, 6-H). ^{13}C NMR: δ = 42.4 (CH_3), 60.0 (<u>*CH*</u>CN), 109.9 (5-C), 111.8 (3-C), 123.6 (CN), 137.1 (6-C), 138.2 (2-C), 151.8 (4-C). Anal. Calcd for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.83; H, 6.20; N, 21.04.

Nitriles 3a-c. General Procedure: Appropriate acid chloride (7 mmol) was added to a solution of compound **2** (0.92 g, 7 mmol) and triethylamine (0.71 g, 7 mmol) in dioxane (10 mL) and resulting mixture was refluxed for 1 h. After cooling the precipitate formed was filtered, thoroughly washed with water to remove triethylamine hydrochloride, and recrystallized from an appropriate solvent yielding derivatives **3a-c**.

α-(1-Methyl-4(1*H*)-pyridinylidene)-β-oxobenzenepropanenitrile (3a): (1.21 g, 73 %). mp 230 °C (dioxane). ^{1}H NMR: δ = 3.91 (s, 3H, CH_3), 7.11 (br s, 1H, 3-H), 7.41 (m, 3H, H_{R1}), 7.60 (d, *J* = 6.5, 2H, H_{R1}), 8.10 (d, *J* = 6.5, 2H, 2,6-H), 8.89 (br s, 1H, 5-H). ^{13}C NMR: δ = 45.0 (CH_3), 78.5 (α-C), 116.6 (3,5-C), 124.1 (CN), 127.9 (3,5-C_{R1}), 128.2 (2,6-C_{R1}), 130.2 (4-C_{R1}), 141.8 (2,6-C), 142.9 (1-C_{R1}), 154.2 (4-C), 188.3 (CO). Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.30; H, 5.12; N, 11.73.

α-(1-Methyl-4(1*H*)-pyridinylidene)-β-oxo-2-thiophenepropanenitrile (3b): (1.07 g, 63 %). mp 266 °C (DMF-H_2O). ^{1}H NMR: δ = 3.91 (s, 3H, CH_3), 7.12 (m, 2H, 3-H, 5-H_{R1}), 7.72 (s, 1H, 4-H_{R1}), 7.94 (s, 1H, 3-H_{R1}), 8.12 (d, *J* = 6.0, 2H, 2,6-H), 8.84 (br s, 1H, 5-H). ^{13}C NMR: δ = 45.0 (CH_3), 76.6 (α-C), 116.7 (3,5-C), 124.1 (CN), 128.1 (4-C_{R1}), 129.4 (5-C_{R1}), 131.2 (3-C_{R1}), 141.9 (2,6-C), 148.0 (2-C_{R1}), 154.5

(4-C), 177.7 (CO). Anal. Calcd for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56; S, 13.23. Found: C, 64.67; H, 3.95; N, 11.40; S, 13.26.

4-Chloro-2-(1-methyl-4(1*H*)-pyridinylidene)-3-oxobutanenitrile (3c): (0.92 g, 63 %). mp 212 °C (dioxane). ^{1}H NMR: δ = 3.91 (s, 3H, CH_3), 4.33 (s, 2H, CH_2), 7.07 (br s, 1H, 3-H), 8.11 (d, *J* = 6.0, 2H, 2,6-H), 8.72 (br s, 1H, 5-H). ^{13}C NMR: δ = 45.2 (CH_3), 48.1 (CH_2), 77.0 (*C*-CN), 116.3 (3,5-C), 122.7 (CN), 142.1 (2,6-C), 153.4 (4-C), 183.8 (CO). Anal. Calcd for $C_{10}H_9ClN_2O$: C, 57.57; H, 4.35; N, 13.43; Cl, 16.99. Found: C, 57.70; H, 4.19; N, 13.23; Cl, 16.79.

Amides 4a,b and Thioamides 5a,c. General Procedure: A solution of compound **2** (0.92 g, 7 mmol) and corresponding isocyanate or isothiocyanate (7 mmol) in dioxane (10 mL) was heated at reflux for 1.5 h. Upon cooling the solid separated was filtered and recrystallized from an appropriate solvent affording derivatives **4a,b 5a,c**.

2-Cyano-2-(1-methyl-4(1*H*)-pyridinylidene)-*N*-phenylacetamide (4a): (1.42 g, 81 %). mp 276 °C (DMF-H_2O). ^{1}H NMR: δ = 3.74 (s, 3H, CH_3), 6.81 (d, *J* = 7.0, 1H, 3-H), 6.96 (t, *J* = 8.0, 1H, 4-H_{R2}), 7.22 (t, *J* = 8.0, 2H, 3,5-H_{R2}), 7.56 (d, *J* = 8.0, 2H, 2,6-H_{R2}), 7.73 (d, *J* = 7.0, 1H, 6-H), 7.79 (d, *J* = 7.0, 1H, 2-H), 8.30 (d, *J* = 7.0, 1H, 5-H), 8.67 (s, 1H, NH). ^{13}C NMR: δ = 44.0 (CH_3), 70.0 (*C*-CN), 113.9 (3-C), 114.7 (5-C), 120.4 (2,6-C_{R2}), 122.6 (4-C_{R2}), 122.7 (CN), 128.8 (3,5-C_{R2}), 139.9 (2-C), 140.4 (1-C_{R2}), 140.5 (6-C), 153.7 (4-C), 165.4 (CO). Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.50; H, 5.22; N, 16.53.

***N*-(4-Chlorophenyl)-2-cyano-2-(1-methyl-4(1*H*)-pyridinylidene)acetamide (4b):** (1.54 g, 77 %). mp 290 °C (DMF-H_2O). ^{1}H NMR: δ = 3.75 (s, 3H, CH_3), 6.83 (dd, J^3 = 7.5, J^4 = 2.5, 1H, 3-H), 7.26 (d, *J* = 8.5, 2H, 2,6-H_{R2}), 7.60 (d, *J* = 8.5, 2H, 3,5-H_{R2}), 7.76 (d, *J* = 7.5, 1H, 6-H), 7.82 (d, *J* = 7.5, 1H, 2-H), 8.30 (dd, J^3 = 7.5, J^4 = 2.5, 1H, 5-H), 8.89 (s, 1H, NH). ^{13}C NMR: δ = 44.1 (CH_3), 69.9 (*C*-CN), 114.0 (3-C), 114.8 (5-C), 121.9 (2,6-C_{R2}), 122.5 (CN), 128.6 (3,5-C_{R2}), 139.5 (4-C_{R2}), 140.0 (2-C), 140.1 (1-C_{R2}), 140.7 (6-C), 153.8 (4-C), 165.4 (CO). Anal. Calcd for $C_{15}H_{12}ClN_3O$: C, 63.05; H, 4.23; N, 14.71; Cl, 12.41. Found: C, 62.84; H, 4.23; N, 14.53; Cl, 12.40.

Cyano(1-methyl-4(1*H*)-pyridinylidene)-*N*-phenylethanethioamide (5a): (1.64 g, 88 %). mp 194 °C (dioxane). ^{1}H NMR: δ = 3.78 (s, 3H, CH_3), 7.08 (t, *J* = 7.5, 1H, 4-H_{R2}), 7.29 (t, *J* = 7.5, 2H, 3,5-H_{R2}), 7.48 (d, *J* = 7.5, 2H, 2,6-H_{R2}), 7.84 (m, 4H, H_{Py}), 10.07 (d, 1H, NH). ^{13}C NMR: δ = 44.3 (CH_3), 83.2 (*C*-CN), 115.9 (3,5-C), 122.2 (CN), 124.4 (2,6-C_{R2}), 124.7 (4-C_{R2}), 128.6 (3,5-C_{R2}), 140.4 (2,6-C), 141.2 (1-C_{R2}), 152.1 (4-C), 189.7 (CS). Anal. Calcd for $C_{15}H_{13}N_3S$: C, 67.39; H, 4.90; N, 15.72; S, 11.99. Found: C, 67.42; H, 4.87; N, 15.73; S, 11.99.

Cyano-*N*-methyl(1-methyl-4(1*H*)-pyridinylidene)ethanethioamide (5c): (1.13 g, 79 %). mp 168 °C (dioxane). ^{1}H NMR: δ = 2.96 (d, *J* = 4.5, 3H, CH_3), 3.73 (s, 3H, CH_3), 6.88 (bs s, 1H, 3-H), 7.74 (d, *J* =

6.0, 2H, 2,6-H), 8.44 (q, *J* = 4.5, 1H, NH), 9.00 (br s, 1H, 5-H). ^{13}C NMR: δ = 32.3 (CH_3), 44.0 (CH_3), 79.8 (*C*-CN), 114.9 (3,5-C), 122.3 (CN), 139.9 (2,6-C), 152.0 (4-C), 190.2 (CS). Anal. Calcd for $C_{10}H_{11}N_3S$: C, 58.51; H, 5.40; N, 20.47; S, 15.62. Found: C, 58.33; H, 5.40; N, 20.50; S, 15.63.

Pyridinium Chlorides 7a-g. General Procedure: Corresponding amine (5 mmol) was added to a solution of compound **3c** (1.04 g, 5 mmol) in DMF (5 mL) and resulting mixture was heated at 110-120 °C for 2-3 h. After cooling the precipitate formed was filtered and recrystallized from DMF to give derivatives **7a-g**.

4-[2-Amino-4,5-dihydro-4-oxo-1-benzyl-1*H*-pyrrol-3-yl]-1-methylpyridinium chloride (7a): (1.47 g, 93 %). mp 258 °C (DMF). ^{1}H NMR: δ = 3.76 (s, 2H, CH_2), 4.06 (s, 3H, CH_3), 4.85 (s, 2H, CH_2), 7.29 (m, 3H, 2,6,4-H_R), 7.38 (t, *J* = 6.0, 2H, 3,5-H_R), 8.21 (d, *J* = 6.5, 2H, 3,5-H), 8.38 (s, 2H, NH_2), 8.41 (d, *J* = 6.5, 2H, 2,6-H). ^{13}C NMR: δ = 46.4 (CH_3), 47.9 (CH_2), 57.3 (CH_2), 95.3 (3-C_{Pyrr}), 121.1 (3,5-C), 127.5 (2,6-C_R), 128.3 (4-C_R), 129.3 (3,5-C_R), 135.0 (1-C_R), 143.4 (2,6-C), 148.6 (4-C), 166.2 (2-C_{Pyrr}), 190.8 (CO). Anal. Calcd for $C_{17}H_{18}N_3OCl$: C, 64.66; H, 5.75; N, 13.31; Cl, 11.23. Found: C, 64.77; H, 5.75; N, 13.09; Cl, 11.13.

4-[2-Amino-4,5-dihydro-1-(4-methoxyphenyl)-4-oxo-1*H*-pyrrol-3-yl]-1-methylpyridinium chloride (7b): (1.43 g, 86 %). mp 270 °C (DMF). ^{1}H NMR: δ = 3.79 (s, 3H, OCH_3), 4.09 (s, 3H, NCH_3), 4.21 (s, 2H, CH_2), 7.07 (d, *J* = 9.0, 2H, H_R), 7.39 (d, *J* = 9.0, 2H, H_R), 7.85 (s, 2H, NH_2), 8.24 (d, *J* = 7.5, 2H, 3,5-H), 8.48 (d, *J* = 7.5, 2H, 2,6-H). ^{13}C NMR: δ = 46.3 (NCH_3), 55.7 (OCH_3), 59.9 (CH_2), 95.0 (3-C_{Pyrr}), 115.5 (3,5-C_R), 120.9 (3,5-C), 127.6 (2,6-C_R), 128.5 (1-C_R), 143.3 (2,6-C), 148.3 (4-C), 159.0 (4-C_R), 165.8 (2-C_{Pyrr}), 190.7 (CO). Anal. Calcd for $C_{17}H_{18}N_3O_2Cl$: C, 61.54; H, 5.47; N, 12.66; Cl, 10.68. Found: C, 61.37; H, 5.47; N, 12.78; Cl, 10.55.

4-(2-Amino-4,5-dihydro-4-oxo-1-phenyl-1*H*-pyrrol-3-yl)-1-methylpyridinium chloride (7c): (1.24 g, 82 %). mp 294 °C (DMF). ^{1}H NMR: δ = 4.10 (s, 3H, CH_3), 4.29 (s, 2H, CH_2), 7.41 (t, *J* = 7.0, 1H, 4-H_R), 7.47 (d, *J* = 7.0, 2H, 2,6-H_R), 7.53 (t, *J* = 7.0, 2H, 3,5-H_R), 7.99 (s, 2H, NH_2), 8.26 (d, *J* = 7.0, 2H, 3,5-H), 8.51 (d, *J* = 7.0, 2H, 2,6-H). ^{13}C NMR: δ = 46.4 (CH_3), 59.6 (CH_2), 95.2 (3-C_{Pyrr}), 121.1 (3,5-C), 125.7 (2,6-C_R), 128.8 (4-C_R), 130.4 (3,5-C_R), 135.8 (1-C_R), 143.4 (2,6-C), 148.3 (4-C), 165.6 (2-C_{Pyrr}), 190.8 (CO). Anal. Calcd for $C_{16}H_{16}N_3OCl$: C, 63.68; H, 5.34; N, 13.92; Cl, 11.75. Found: C, 63.59; H, 5.28; N, 14.08; Cl, 11.72.

4-[2-Amino-4,5-dihydro-1-(4-methylphenyl)-4-oxo-1*H*-pyrrol-3-yl]-1-methylpyridinium chloride (7d): (1.48 g, 94 %). mp 280 °C (DMF). ^{1}H NMR: δ = 2.35 (s, 3H, CH_3), 4.09 (s, 3H, NCH_3), 4.24 (s, 2H, CH_2), 7.34 (m, 4H, H_R), 7.90 (s, 2H, NH_2), 8.23 (d, *J* = 7.0, 2H, 3,5-H), 8.48 (d, *J* = 7.0, 2H, 2,6-H). ^{13}C NMR: δ = 20.3 (CH_3), 46.3 (NCH_3), 59.6 (CH_2), 95.2 (3-C_{Pyrr}), 121.0 (3,5-C), 125.6 (2,6-C_R), 130.7

(3,5-C_R), 132.9 (4-C_R), 139.3 (1-C_R), 143.3 (2,6-C), 148.3 (4-C), 165.5 (2-C_{Pyrr}), 190.7 (CO). Anal. Calcd for $C_{17}H_{18}N_3OCl$: C, 64.66; H, 5.75; N, 13.31; Cl, 11.23. Found: C, 64.66; H, 5.71; N, 13.44; Cl, 11.27.

4-[2-Amino-4,5-dihydro-1-(2-hydroxyethyl)-4-oxo-1*H*-pyrrol-3-yl]-1-methylpyridinium chloride (7e): (1.05 g, 78 %). mp 286 °C (DMF). ^{1}H NMR: δ = 3.33 (m, 2H, NCH_2), 3.59 (m, 2H, OCH_2), 3.94 (s, 2H, CH_2), 4.03 (s, 3H, NCH_3), 5.06 (t, *J* = 8.5, 1H, OH), 7.95 (s, 2H, NH_2), 8.15 (d, *J* = 7.0, 2H, 3,5-H), 8.36 (d, *J* = 7.0, 2H, 2,6-H). ^{13}C NMR: δ = 46.3 (CH_3), 46.8 (NCH_2), 57.9 (CH_2), 59.0 (OCH_2), 95.2 (3-C_{Pyrr}), 120.6 (3,5-C), 143.3 (2,6-C), 148.4 (4-C), 166.5 (2-C_{Pyrr}), 190.9 (CO). Anal. Calcd for $C_{12}H_{16}N_3O_2Cl$: C, 53.44; H, 5.98; N, 15.58; Cl, 13.14. Found: C, 53.44; H, 5.90; N, 15.44; Cl, 13.27.

4-[2-Amino-4,5-dihydro-1-(2-methoxyethyl)-4-oxo-1*H*-pyrrol-3-yl]-1-methylpyridinium chloride (7f): (1.26 g, 89 %). mp 224 °C (DMF). ^{1}H NMR: δ = 3.27 (s, 3H, OCH_3), 3.53 (t, *J* = 5.0, 2H, NCH_2), 3.73 (t, *J* = 5.0, 2H, OCH_2), 3.91 (s, 2H, CH_2), 4.04 (s, 3H, NCH_3), 8.12 (s, 2H, NH_2), 8.17 (d, *J* = 7.0, 2H, 3,5-H), 8.39 (d, *J* = 7.0, 2H, 2,6-H). ^{13}C NMR: δ = 44.5 (NCH_2), 46.3 (NCH_3), 57.9 (CH_2), 58.5 (OCH_3), 69.6 (OCH_2), 95.3 (3-C_{Pyrr}), 120.9 (3,5-C), 143.3 (2,6-C), 148.5 (4-C), 166.5 (2-C_{Pyrr}), 190.9 (CO). Anal. Calcd for $C_{13}H_{18}N_3O_2Cl$: C, 55.03; H, 6.39; N, 14.81; Cl, 12.49. Found: C, 55.10; H, 6.39; N, 14.93; Cl, 12.62.

4-[2-Amino-1-(2-furanylmethyl)-4,5-dihydro-4-oxo-1*H*-pyrrol-3-yl]-1-methylpyridinium chloride (7g): (1.42 g, 93 %). mp 270 °C (DMF). ^{1}H NMR: δ = 3.80 (s, 2H, CH_2), 4.06 (s, 3H, CH_3), 4.89 (s, 2H, CH_2), 6.43 (dd, *J* = 3.0, *J* = 1.5, 1H, 4-H_R), 6.51 (d, *J* = 3.0, 1H, 5-H_R), 7.65 (d, *J* = 1.5, 1H, 3-H_R), 8.19 (d, *J* = 7.0, 2H, 3,5-H), 8.42 (d, *J* = 7.0, 2H, 2,6-H), 8.46 (s, 2H, NH_2). ^{13}C NMR: δ = 40.9 (CH_2), 46.3 (CH_3), 57.1 (CH_2), 95.0 (3-C_{Pyrr}), 109.6 (4-C_R), 110.8 (3-C_R), 120.6 (3,5-C), 143.2 (2,6-C), 143.7 (5-C_R), 148.1 (2-C_R), 148.2 (4-C), 165.8 (2-C_{Pyrr}), 190.7 (CO). Anal. Calcd for $C_{15}H_{16}N_3O_2Cl$: C, 58.92; H, 5.27; N, 13.74; Cl, 11.59. Found: C, 58.83; H, 5.17; N, 13.74; Cl, 11.41.

Piperidinylpyrrole Hydrochlorides 8a-f, h. General Procedure: Pd on carbon (0.13 g, 10 % of Pd) was added to a solution of the appropriate quaternary salt **7a-g** (2.5 mmol) in methanol (20 mL) and obtained mixture was degassed. Then it was vigorously stirred at 40 °C under hydrogen atmosphere until the hydrogen absorption was completely finished (usually at about 2 days). The catalyst was removed by filtration, the solvent was evaporated to dryness in vacuo, and the residue was triturated with anhydrous MeCN and filtered. Recrystallization from the suitable solvent afforded compounds **8a-f, h**.

5-Amino-1,2-dihydro-4-(1-methyl-4-piperidinyl)-1-benzyl-3*H*-pyrrol-3-one hydrochloride (8a): (0.74 g, 92 %). mp 245 °C (*i*-PrOH). ^{1}H NMR: δ = 1.58 (m, 2H, H_{Pip}), 2.35 (m, 3H, H_{Pip}), 2.71 (s, 3H, CH_3), 2.81 (m, 2H, H_{Pip}), 3.33 (m, 4H, CH_2, H_{Pip}), 4.52 (s, 2H, CH_2Ph), 7.18 (d, *J* = 7.5, 2H, 2,6-H_R), 7.27 (m, 3H, NH_2, H_R), 7.35 (t, *J* = 7.5, 2H, 3,5-H_R), 8.57 (s, 1H, N·HCl). ^{13}C NMR: δ = 27.5 (3,5-C_{Pip}), 28.7 (4-C_{Pip}), 43.5 (CH_3), 47.8 ($\underline{CH_2}$Ph), 55.3 (2,6-C_{Pip}), 56.9 (2-CH_2), 97.6 (4-C), 127.3 (2,6-C_R), 128.1

(4-C_R), 129.2 (3,5-C_R), 136.2 (1-C_R), 156.7 (5-C), 169.0 (CO). Anal. Calcd for $C_{17}H_{23}N_3O \cdot HCl$: C, 63.44; H, 7.52; N, 13.06; Cl, 11.02. Found: C, 63.48; H, 7.58; N, 12.99; Cl, 10.83.

5-Amino-1,2-dihydro-1-(4-methoxyphenyl)-4-(1-methyl-4-piperidinyl)-3*H*-pyrrol-3-one hydrochloride (8b): (0.73 g, 87 %). mp 274 °C (DMF). ^{1}H NMR: δ = 1.61 (m, 2H, H_{Pip}), 2.36 (m, 3H H_{Pip}), 2.68 (s, 3H, NCH_3), 2.82 (m, 2H, H_{Pip}), 3.36 (m, 2H, H_{Pip}), 3.74 (s, 3H, OCH_3), 3.85 (s, 2H, CH_2), 6.86 (s, 2H, NH_2), 6.96 (d, *J* = 8.0, 2H, H_R), 7.19 (d, *J* = 8.0, 2H, H_R), 10.39 (br s, 1H, N·HCl). ^{13}C NMR: δ = 27.3 (3,5-C_{Pip}), 28.6 (4-C_{Pip}), 43.4 (NCH_3), 55.1 (2,6-C_{Pip}), 55.7 (OCH_3), 59.4 (2-CH_2), 97.6 (4-C), 115.3 (3,5-C_R), 127.3 (2,6-C_R), 130.0 (1-C_R), 158.3 (4-C_R), 168.3 (5-C), 186.7 (CO). Anal. Calcd for $C_{17}H_{23}N_3O_2 \cdot HCl$: C, 60.44; H, 7.16; N, 12.44; Cl, 10.49. Found: C, 60.66; H, 7.12; N, 12.40; Cl, 10.50.

5-Amino-1,2-dihydro-4-(1-methyl-4-piperidinyl)-1-phenyl-3*H*-pyrrol-3-one hydrochloride (8c): (0.72 g, 94 %). mp 268 °C (DMF). ^{1}H NMR: δ = 1.63 (m, 2H, H_{Pip}), 2.41 (m, 2H, H_{Pip}), 2.55 (m, 1H, H_{Pip}), 2.73 (s, 3H, CH_3), 2.83 (m, 2H, H_{Pip}), 3.41 (m, 2H, H_{Pip}), 3.92 (s, 2H, CH_2), 7.00 (s, 2H, NH_2), 7.19 (t, *J* = 7.5, 1H, 4-H_R), 7.28 (d, *J* = 7.5, 2H, 2,6-H_R), 7.40 (t *J* = 7.5, 2H, 3,5-H_R), 10.11 (br s, 1H, N·HCl). ^{13}C NMR: δ = 27.3 (3,5-C_{Pip}), 28.6 (4-C_{Pip}), 43.5 (NCH_3), 55.2 (2,6-C_{Pip}), 59.0 (2-CH_2), 97.9 (4-C), 125.1 (2,6-C_R), 127.7 (4-C_R), 130.1 (3,5-C_R), 137.1 (1-C_R), 167.9 (5-C), 187.1 (CO). Anal. Calcd for $C_{16}H_{21}N_3O \cdot HCl$: C, 62.43; H, 7.20; N, 13.65; Cl, 11.52. Found: C, 62.43; H, 7.29; N, 13.62; Cl, 11.63.

5-Amino-1,2-dihydro-1-(4-methylphenyl)-4-(1-methyl-4-piperidinyl)-3*H*-pyrrol-3-one hydrochloride (8d): (0.73 g, 91 %). mp 280 °C (DMF). ^{1}H NMR: δ = 1.62 (m, 2H, H_{Pip}), 2.29 (s, 3H, CH_3), 2.38 (m, 3H, H_{Pip}), 2.72 (s, 3H, NCH_3), 2.81 (m, 2H, H_{Pip}), 3.37 (m, 2H, H_{Pip}), 3.85 (s, 2H, CH_2), 6.88 (s, 2H, NH_2), 7.15 (d, *J* = 8.0, 2H, H_R), 7.20 (d, *J* = 8.0, 2H, H_R), 9.93 (br s, 1H, N·HCl). ^{13}C NMR: δ = 20.3 (CH_3), 27.4 (3,5-C_{Pip}), 28.6 (4-C_{Pip}), 43.4 (NCH_3), 55.2 (2,6-C_{Pip}), 59.1 (2-CH_2), 97.8 (4-C), 125.0 (2,6-C_R), 130.6 (3,5-C_R), 134.3 (4-C_R), 138.1 (1-C_R), 168.0 (5-C), 186.9 (CO). Anal. Calcd for $C_{17}H_{23}N_3O \cdot HCl$: C, 63.44; H, 7.52; N, 13.06; Cl, 11.02. Found: C, 63.51; H, 7.52; N, 13.20; Cl, 10.96.

5-Amino-1,2-dihydro-1-(2-hydroxyethyl)-4-(1-methyl-4-piperidinyl)-3*H*-pyrrol-3-one hydrochloride (8e): (0.66 g, 96 %). mp 154 °C (acetonitrile). ^{1}H NMR: δ = 1.54 (m, 2H, H_{Pip}), 2.35 (m, 2H H_{Pip}), 2.44 (m, 1H, H_{Pip}), 2.69 (s, 3H, NCH_3), 2.79 (m, 2H, H_{Pip}), 3.34 (m, 4H, 2H_R, H_{Pip}), 3.49 (t, *J* = 5.5, 2H, CH_2O), 3.58 (s, 2H, CH_2), 4.97 (br s, 1H, OH), 7.11 (s, 2H, NH_2), 9.94 (br s, 1H, N·HCl). ^{13}C NMR: δ = 27.4 (3,5-C_{Pip}), 28.6 (4-C_{Pip}), 43.4 (NCH_3), 46.5 (1-C_R), 55.2 (2,6-C_{Pip}), 57.3 (2-CH_2), 59.4 (OCH_2), 97.8 (4-C), 169.3 (5-C), 185.6 (CO). Anal. Calcd for $C_{12}H_{21}N_3O_2 \cdot HCl$: C, 52.26; H, 8.04; N, 15.24; Cl, 12.86. Found: C, 52.30; H, 8.03; N, 15.46; Cl, 12.73.

5-Amino-1,2-dihydro-1-(2-methoxyethyl)-4-(1-methyl-4-piperidinyl)-3*H*-pyrrol-3-one hydrochloride (8f): (0.62 g, 85 %). mp 168 °C (acetonitrile). ^{1}H NMR: δ = 1.54 (m, 2H, H_{Pip}), 2.35 (m, 3H, H_{Pip}), 2.69 (s, 3H, NCH_3), 2.78 (m, 2H, H_{Pip}), 3.24 (s, 3H, OCH_3), 3.33 (m, 2H, H_{Pip}), 3.41 (m, 4H,

H_R), 3.49 (s, 2H, CH_2), 6.99 (s, 2H, NH_2), 10.34 (br s, 1H, N·HCl). ^{13}C NMR: δ = 27.4 (3,5-C_{Pip}), 28.6 (4-C_{Pip}), 43.4 (1-C_R), 44.3 (NCH_3), 55.3 (2,6-C_{Pip}), 57.3 (2-CH_2), 58.4 (OCH_3), 69.9 (OCH_2), 97.6 (4-C), 169.2 (5-C), 185.9 (CO). Anal. Calcd for $C_{13}H_{23}N_3O_2$ · HCl: C, 53.88; H, 8.35; N, 14.50; Cl, 12.23. Found: C, 53.98; H, 8.40; N, 14.65; Cl, 12.39.

5-Amino-1,2-dihydro-4-(1-methyl-4-piperidinyl)-1-[(tetrahydro-2-furanyl)methyl]-3*H*-pyrrol-3-one hydrochloride (8h): (0.68 g, 86 %). mp 232 °C (acetonitrile). ^{1}H NMR: δ = 1.43 (m, 1H, H_R), 1.55 (m, 2H, H_{Pip}), 1.80 (m, 2H, H_R), 1.90 (m, 1H, H_R), 2.35 (m, 3H, H_{Pip}), 2.70 (s, 3H, NCH_3), 2.77 (m, 2H, H_{Pip}), 3.22 (m, 2H, H_R), 3.40 (m, 2H, H_{Pip}), 3.49 (d, J = 17.5, 1H, CH_2), 3.56 (d, J = 17.5, 1H, CH_2), 3.63 (m, 1H, H_R), 3.75 (m, 1H, H_R), 3.92 (m, 1H, H_R), 6.98 (s, 2H, NH_2), 10.05 (br s, 1H, N·HCl). ^{13}C NMR: δ = 25.3 (4-C_R), 28.2 (4-C_{Pip}), 28.7 (3,5-C_{Pip}), 30.0 (3-C_R), 44.5 (NCH_3), 48.6 (α-C_R), 55.3 (2,6-C_{Pip}), 58.0 (2-CH_2), 68.2 (5-C_R), 77.7 (2-C_R), 99.4 (4-C), 169.6 (5-C), 185.5 (CO). Anal. Calcd for $C_{15}H_{25}N_3O_2$ · HCl: C, 57.04; H, 8.30; N, 13.30; Cl, 11.22. Found: C, 56.99; H, 8.40; N, 13.30; Cl, 11.05.

ACKNOWLEDGEMENTS

The authors wish to thank Dr. Vitaliy V. Polovinko (Enamine Ltd.) for the recording ^{1}H and ^{13}C NMR spectra.

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