NEW METHOD FOR PREPARATION OF 1-AZABICYCLO[2.2.2]OCTANE-4-CARBONITRILE AND 1-AZABICYCLO[3.2.2]NONANE-5-CARBONITRILE

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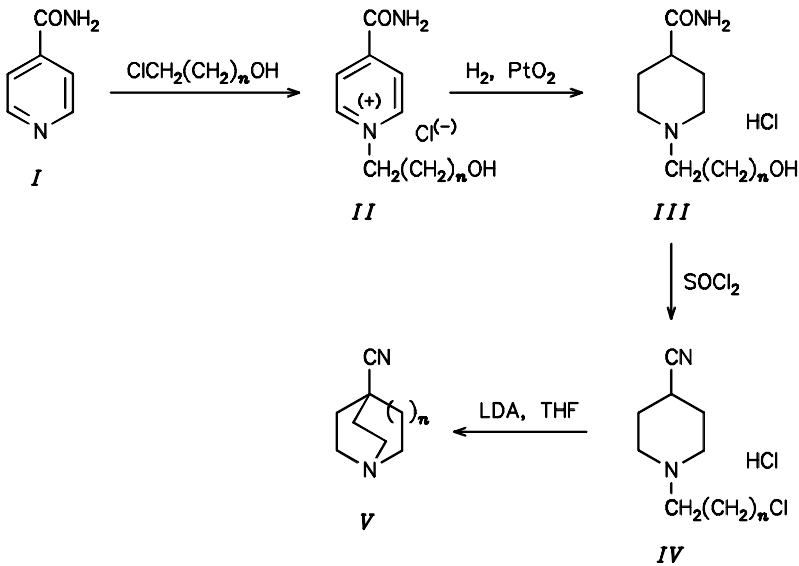
The title compounds were prepared from pyridine-4-carboxamide. Its alkylation with 2-chloroethanol or 3-chloropropanol, followed by hydrogenation gave 1-substituted piperidine-4-carboxamides *IIIa* and *IIIb*, respectively, which on treatment with thionyl chloride were converted into the respective 1-substituted halogenoalkylpiperidine-4-carbonitriles *IVa* and *IVb*. On cyclization, compounds *IVa* and *IVb* afforded 1-azabicyclo[2.2.2]octane-4-carbonitrile and 1-azabicyclo[3.2.2]nonane-5-carbonitrile, respectively.

Many biologically active substances contain substituted 1-azabicycloalkane moieties, the most frequent being 1-azabicyclo[2.2.2]octane (quinuclidine) residue[1]. Therefore, much attention is paid to this group of compounds, particularly quinuclidine and its 4-substituted derivatives, both from the chemical[2–7] and pharmacological[8,9] point of view. It has been found recently[10,11] that a change of the symmetrical azabicyclo-[2.2.2]octane system to the unsymmetrical azabicyclo[3.2.2]nonane skeleton results in change of biological properties. However, the preparation of compounds containing the 1-azabicyclo[3.2.2]nonane moiety has so far been relatively difficult[11–15]. The recently published[16] synthesis of quinuclidine-4-carbonitrile (*Va*) prompted us to make use of our experience[6,7] not only for simplified preparation of the nitrile *Va* but also for an analogous preparation of the hitherto undescribed 1-azabicyclo[3.2.2]nonane-5-carbonitrile (*Vb*) which represents key intermediate in the synthesis of the corresponding 5-substituted derivatives.

Our approach is depicted in Scheme 1. As the starting compound we used the easily accessible pyridine-4-carboxamide (*I*). Its alkylation with an excess of 2-chloroethanol or 3-chloropropanol (which also served as a solvent) at elevated temperatures afforded 4-aminocarbonyl-1-(2-hydroxyethyl)- (*IIa*) and 4-aminocarbonyl-1-(3-hydroxypropyl)-pyridinium chloride (*IIb*), respectively, in high yield. The advantage of these reaction conditions consists in a markedly shorter reaction time compared with reaction in ethanol (reflux for 2 h instead of 48 h). Low-pressure hydrogenation of the pyridinium salts *IIa* or *IIb* over Adams catalyst in methanol at 40 °C gave in practically quantitative

yield the corresponding hydrochlorides of 1-(2-hydroxyethyl)- (*IIIa*) or 1-(3-hydroxypropyl)piperidine-4-carboxamide (*IIIb*) which could be used without purification in the next step. The dehydration of the amide group and replacement of the hydroxyl by chlorine in compounds *IIIa* and *IIIb* was performed in one step[16] by heating with thionyl chloride in acetonitrile, affording hydrochlorides of 1-(2-chloroethyl)- (*IVa*) and 1-(3-chloropropyl)piperidine-4-carbonitrile (*IVb*), respectively.

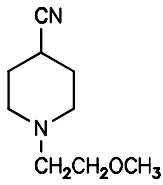
Unfortunately, we were not able to reproduce the cyclization of nitrile *IVa* to compound *Va* under conditions reported in the literature[16], i.e. with lithium diisopropylamide at –78 °C or sodium amide at room temperature; in all cases we recovered only the starting nitrile *IVa*. Therefore, we studied this cyclization reaction using various bases. Heating the nitrile *IVa* with phenyl sodium in benzene[6], potassium in toluene or sodium hydride in toluene afforded the desired nitrile *Va* in only low yields (5–10%). With potassium methoxide in toluene we isolated 1-(2-methoxyethyl)piperidine-4-carbonitrile (*VI*) as the result of substitution of chlorine in the nitrile *IVa*. Only when using lithium diisopropylamide in tetrahydrofuran at 0 °C we obtained quinuclidine-4-carbonitrile (*Va*) in a good yield (76%).



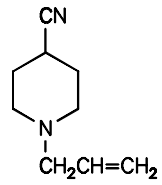
In formulae *IIa*–*Va*, $n = 1$; in formulae *IIb*–*Vb*, $n = 2$

SCHEME 1

These conditions were then applied to the cyclization of nitrile *IVb*. Workup of the reaction mixture afforded only a complex polymeric material which we assume was the result of intermolecular reactions of the starting compound *IVb*. However, when working at high dilution, we suppressed these undesired reactions and obtained, after chromatography, the desired product *Vb* in the yield of 32%. As an elimination side product we isolated also 1-allylpiperidine-4-carbonitrile (*VII*) (17%).



VI



VII

The obtained results show that the described synthetic sequence can be successfully applied to the preparation of compounds containing a 1-azabicyclo[3.2.2]nonane grouping.

EXPERIMENTAL

The temperature data were not corrected. The melting points were determined on a Boetius block. Infrared spectra were measured on a Nicolet 740 instrument, ^{1}H NMR spectra (δ, ppm; *J*, Hz) on a Bruker 300 spectrometer in deuteriochloroform. Mass spectra were obtained with a Jeol DX 300 instrument (electron energy 70 eV).

4-Aminocarbonyl-1-(2-hydroxyethyl)pyridinium Chloride (*IIa*)

A mixture of pyridine-4-carboxamide (48.8 g, 0.4 mol) and 2-chloroethanol (126 g, 1.6 mol) was refluxed for 2 h. The solid was filtered and crystallized from methanol to give 69.6 g (86%) of compound *IIa*, m.p. 228–229 °C. For $C_8H_{11}ClN_2O_2$ (202.6) calculated: 47.42% C, 5.47% H, 17.49% Cl, 13.82% N; found: 47.27% C, 5.46% H, 17.31% Cl, 13.66% N. IR spectrum (KBr, cm^{-1}): 3 350 (NH_2), 1 650 (CO). ^{1}H NMR spectrum: 3.44 t, 2 H, *J* = 6.0 (CH_2N); 4.06 s, 2 H (NH_2); 4.68 t, 2 H, *J* = 6.3 (CH_2OH); 8.48 d, 2 H, *J* = 6.6 (arom.); 9.28 d, 2 H (arom.).

4-Aminocarbonyl-1-(3-hydroxypropyl)pyridinium Chloride (*IIb*)

Pyridine-4-carboxamide (12.21 g, 0.1 mol) was treated with 3-chloropropanol (18.90 g, 0.2 mol) as described for the preparation of *IIa*. Crystallization from methanol afforded 18.92 g (87%) of compound *IIb*, m.p. 167–169 °C. For $C_9H_{13}ClN_2O_2$ (216.7) calculated: 49.89% C, 6.05% H, 16.36% Cl, 12.93% N; found: 49.63% C, 6.17% H, 16.09% Cl, 12.77% N. IR spectrum (KBr, cm^{-1}): 3 350 (NH_2), 1 650 (CO). ^{1}H NMR spectrum: 2.10 m, 2 H, *J* = 6.1 (CH_2); 3.46 t, 2 H, *J* = 5.8 (CH_2N); 3.99 s, 2 H (NH_2); 4.74 t, 2 H (CH_2OH); 8.51 d, 2 H, *J* = 6.6 (arom.); 9.30 d, 2 H (arom.).

4-Aminocarbonyl-1-(2-hydroxyethyl)piperidinium Chloride (*IIIa*)

A suspension of compound *IIa* (11.0 g, 54.3 mmol) and PtO_2 (0.73 g) in dry methanol (150 ml) was vigorously stirred in an atmosphere of hydrogen at 40 °C. After consumption of the calculated amount of hydrogen, the mixture was filtered and the filtrate was taken down. Yield 11.1 g (98%) of

hydrochloride *IIIa*, m.p. 180–183 °C. For spectral measurements the base was liberated by addition of aqueous potassium hydroxide and taken up in ether. The ethereal extract was dried over magnesium sulfate and the solvent was evaporated. The spectral data of *IIIa* agreed with those given in the literature[16].

4-Carbamoyl-1-(3-hydroxypropyl)piperidinium Chloride (*IIIb*)

Pyridinium salt *IIb* (17.55 g, 81 mmol) was hydrogenated as described in the preceding experiment. Yield 17.56 g (97%) of hydrochloride *IIIb*, m.p. 178–180 °C. For $C_9H_{19}ClN_2O_2$ (222.7) calculated: 48.54% C, 8.60% H, 15.92% Cl, 12.58% N; found: 48.26% C, 8.84% H, 15.66% Cl, 12.31% N. Base *IIIb*: IR spectrum ($CHCl_3$, cm^{-1}): 3 360 (NH_2), 1 652 (CO). ^1H NMR spectrum: 1.56 m, 1 H (CH); 1.89 t, J = 6.1 (CH_2); 2.32 m, 2 H, 2.48 t, 2 H (2 × CH_2); 2.84 m, 2 H, 3.12 m, 2 H, 3.43 t, 2 H, J = 6.1 (3 × CH_2); 4.78 t, 2 H (CH_2OH); 6.91 s and 7.42 s, 2 H (NH_2).

4-Cyano-1-(3-chloropropyl)piperidinium Chloride Hydrochloride (*IVb*)

A mixture of hydrochloride *IIIb* (12.05 g, 54.1 mmol), thionyl chloride (50.0 g, 420 mmol) and dry acetonitrile (130 ml) was refluxed for 3 h. The solvent was evaporated and the residue crystallized from isopropyl alcohol to give 8.80 g (73%) of hydrochloride *IVb*, m.p. 162–164 °C. For $C_9H_{16}Cl_2N_2$ (223.1) calculated: 48.44% C, 7.23% H, 31.78% Cl, 12.55% N; found: 48.18% C, 7.36% H, 31.40% Cl, 12.22% N.

Base *IVb* was liberated by aqueous potassium hydroxide and taken up in chloroform (3 × 50 ml). After drying over anhydrous magnesium sulfate and evaporation of the solvent, the base *IVb* was isolated as an oil. IR spectrum ($CHCl_3$, cm^{-1}): 2 240 (CN). ^1H NMR spectrum: 1.89 m, 3 H (CH + CH_2); 1.91 t, 2 H, J = 6.1; 2.31 t, 2 H, 2.43 t, 2 H, J = 7.0; 2.62 m, 4 H (5 × CH_2); 3.58 t, 2 H, J = 6.5 (CH_2Cl).

Hydrochloride *IVa* was prepared according to ref.[16]; m.p. 176–178 °C (reported[16] m.p. 176–178 °C).

Quinuclidine-4-carbonitrile (*Va*)

Hydrochloride *IVa* (5.0 g, 23.9 mmol) was added at –78 °C under nitrogen to a solution of lithium diisopropylamide in tetrahydrofuran, prepared from 12.5 ml of diisopropylamine and 37.5 ml of 2 M butyllithium in hexane. After stirring for 10 min, the cooling bath was removed and the mixture was slowly warmed to 0 °C (during 30 min) and held at this temperature for 2 h. Saturated solution of ammonium chloride (25 ml) was added, the organic layer was separated and the aqueous one washed with ether (25 ml). The combined organic solutions were washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate and the solvent was evaporated. Crystallization from hexane afforded 2.46 g (76%) of nitrile *Va*, m.p. 138–140 °C (reported[16] m.p. 133 °C).

1-Azabicyclo[3.2.2]nonane-5-carbonitrile (*Vb*)

Base *IVb* (1.82 g, 9.75 mmol) in dry tetrahydrofuran (1 200 ml) was cyclized analogously as described in the preceding experiment. Column chromatography on silica gel in chloroform–methanol afforded 0.48 g (32%) of compound *Vb*. For $C_9H_{14}N_2$ (150.2) calculated: 71.96% C, 9.39% H, 18.65% N; found: 71.71% C, 9.44% H, 18.37% N. IR spectrum (KBr, cm^{-1}): 2 231 (CN). ^1H NMR spectrum: 1.44 dt, 2 H, J = 3.6 and J = 13.0; 1.63 m, 4 H, 1.94 d, 2 H, J = 12.6; 2.23 t, 2 H, J = 12.0; 2.39 t, 2 H, J = 5.4; 2.80 d, 2 H, J = 12.1 (7 × CH_2). Mass spectrum (*m/z*, %): 150 (M^+, 40), 149 ($M^+ - 1$, 50), 135 (28), 123 (100), 122 (10), 121 (10), 96 (17), 82 (56), 84 (12), 69 (30), 68 (44), 67 (15), 56 (18), 55 (38), 54 (21).

1-Allylpiperidine-4-carbonitrile (*VII*) was isolated (0.25 g, 17%) as side product. For $C_9H_{14}N_2$ (150.2) calculated: 71.96% C, 9.39% H, 18.65% N; found: 71.49% C, 9.26% H, 18.46% N. IR spectrum ($CHCl_3$, cm^{-1}): 2 230 (CN). ^1H NMR spectrum: 1.91 m, 5 H; 2.50 m, 2 H; 2.70 m, 2 H; 3.10 d, 2 H, J = 6.1; 5.22 dd, 2 H, J = 7.0 and J = 14.0; 5.90 m, 1 H.

1-(2-Methoxyethyl)piperidine-4-carbonitrile (*VI*)

Hydrochloride *IIIa* (1.00 g, 4.78 mmol) was added under nitrogen to potassium methoxide in toluene (prepared by dropwise addition of dry methanol (0.61 ml) to potassium dust (0.59 g, 15 mmol) in dry toluene (15 ml)). The stirred mixture was boiled for 2 h, cooled and decomposed with saturated ammonium chloride solution (20 ml). The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated. Column chromatography on silica gel in hexane–ethyl acetate afforded 0.35 g (44%) of oily compound *VI*. For $C_9H_{16}N_2O$ (168.2) calculated: 64.25% C, 9.59% H, 16.65% N; found: 64.34% C, 9.64% H, 16.33% N. IR spectrum ($CHCl_3$, cm^{-1}): 2 232 (CN). ^1H NMR spectrum: 1.91 m, 4 H; 2.28 m, 1 H; 2.39 m, 2 H; 2.55 t, 2 H, J = 5.5 (CH_2N); 2.66 m, 2 H; 3.33 s, 3 H (CH_3O); 3.47 t, 2 H (CH_2O). Mass spectrum (*m/z*, %): 169 (M^+ + 1, 8), 168 (M^+, 5), 137 ($M^+ - CH_3O$, 5), 124 (10), 123 ($M^+ - C_2H_5O$, 100), 56 (12), 55 (11), 54 (12), 42 (26).

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