

Synthesis of Novel 3,7-Diazabicyclo[3.3.1]nonane Derivatives

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Abstract

A series of 3-(3-ethoxypropyl)-7-heterocyclalkyl-3,7-diazabicyclo[3.3.1]nonan-9-ones have been prepared by Mannich cyclocondensation of 1-(3-ethoxypropyl)-4-oxopiperidine with paraformaldehyde and primary amines followed by Wolff-Kischner reduction of the obtained bispidinones. The starting 1-(3-ethoxypropyl)-4-oxopiperidine was synthesized by Dickmann condensation of 3-ethoxypropylamine with ethylacrylate. The 3,7-diazabicyclo[3.3.1]nonanones were obtained in acceptable yields by condensation of 1-(3-ethoxypropyl)piperidin-4-one with primary amines: 1-(3-aminopropyl)imidazole or 1-(2-aminoethyl)piperazine and formaldehyde in the presence of acetic acid in methanol medium. Reduction of the obtained bispidinones with hydrazine hydrate was carried out in the presence of KOH in triethylene glycol at 160-170 °C for 5 hours. The syntheses were performed under the atmosphere of N₂. As the reaction products are viscous oils, the column chromatography (on III activity aluminum oxide, eluent – benzene: dioxane 5:1) was used for purification of novel bicyclic ketones and bicyclic nonanes. The completion of the reactions was monitored by TLC. Methods of ¹H and ¹³C NMR spectroscopy were used to determine the structures of the substances synthesized. The prior studies have demonstrated that variation on the substituents at nitrogen atoms in 3- and 7-positions of bispidine cycle could result in the increase of biological activity and effect on compound spectral characteristics. Spatial structures of bispidinones and related bispidines were determined on the basis of the data of the ¹³C and ¹H NMR spectra. A doublet of doublets of equatorial protons at C_{2,4} and C_{6,8} with large geminal constants of 10.5-11 Hz and vicinal constants of 3.0-6.0 Hz in ¹H NMR spectrum revealed that those 3,7-diazabicyclo[3.3.1]nonane derivatives have a "chair-chair" conformation of both piperidine rings.

Keywords: piperidone, 3,7-diazabicyclo[3.3.1]nonan-9-ones, 3,7-diazabicyclo[3.3.1]nonanes, Dieckman condensation, double Mannich reaction, Wolff-Kischner reduction.

Introduction

Chemistry of piperidine compounds is one of the most promising and rapidly developing areas of modern heterocyclic chemistry. Bicyclic piperidine analogs are of great interest due to a broad spectrum of pharmacological action. In addition, derivatives of 3,7-diazabicyclo[3.3.1]nonane are convenient models for studying the structure of six-membered cyclic compounds, mechanisms and stereochemistry of reactions and conformational analysis [1-7].

Bispidine chemistry began in 1930 with Mannich and Mohs's discovery that simple mixing of 4-piperidone 3,5-diester with aqueous formaldehyde and methylamine in hot methanol leads to

formation of bicyclic diamine. Mannich condensation is the simplest and most convenient way of preparative synthesis of 3-aza-, and 3,7-diazabicyclo[3.3.1]nonan-9-ones. Upon the reaction of aldehyde with primary amines, compounds exhibiting C-H acidity are necessary that the used amine was more nucleophilic than that participating in the reaction of C-H-acidic compound. Otherwise, aldehyde is reacted with preferably methylene component of aldol-type reaction. In some cases, instead of the expected ketone diazabicyclic ketone was obtained. The most common reason for this was that the reaction was carried out in highly concentrated solutions and in the components formaldehyde is used as aldehyde.

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Generally, the main routes of obtaining 3,7-diazabicyclo[3.3.1]nonane derivatives are (i) ring-cleavage reaction of diazaadamantane, (ii) intermolecular cyclization of piperidines and (iii) Mannich reaction [8]. Depending upon the substitution pattern of bispidine derivatives, several synthetic approaches are possible. N-alkoxyalkyl-piperidon-4-es were successfully used as a starting product of a novel 3,7-diazabicyclo[3.3.1]nonan-9-ones synthesis [9-11].

Typically, bispidinone derivatives are obtained via a modified Mannich condensation, where ketone, having acidic α -hydrogens, primary amine and aldehyde react in the presence of acid.

If conformationally homogeneous cyclic ketones are used in the Mannich reaction, the major product of the reaction yields are increased.

Experimental

Methods and Instrumentation

IR spectra were taken on a «Nicolet 5700FT-IR» spectrometer as a thin film (ν in cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a Jeol JNM-ECA-400 spectrometer with ^1H and ^{13}C being observed at 400 and 100.8 MHz, respectively. Chemical shifts (in δ values or ppm) for ^1H and ^{13}C NMR spectra are taken in CDCl_3 , downfield from TMS [$(\text{CH}_3)_4\text{Si}$], and coupling constants are reported as J in Hz. Thin layer and column chromatography were carried out on alumina of III activity. All reactions were performed in nitrogen atmosphere. Methanol was dehydrated with the Na metal. The reagents were used as received from commercial suppliers unless otherwise stated (Aldrich).

3-(3-Ethoxypropyl)-7-(3-imidazolopropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (2). Methanol (65 ml) was deoxygenized under nitrogen atmosphere for 30 min, then the mixture of 1 - (3-aminopropyl)imidazol (9.54 g, 80 mmol), paraformaldehyde (9.6 g, 640 mmol), concentrated hydrochloric acid (4.2 mL) and glacial acetic acid (6.15 mL) was added. Ice bath was removed and a solution of 1-(3-ethoxypropyl)-4-oxopiperidine (14.24 g, 80 mmol) and glacial acetic acid (6.15 mL) in methanol (20.8 mL) was added dropwise to the mixture. After initial 10 h of heating, another equivalent of added paraformaldehyde (9.6 g, 640 mmol) was added in one portion to the mixture after which reflux was continued (10 h). After cooling to RT, the solution was concentrated under vacuum and gave an orange oil which was redissolved in H_2O (125 mL). Extracts (ether, 2×100) thereof were discarded. The aqueous layer was chilled (5°C) and made basic (pH~12, NaOH pellets). Extraction (CHCl_3 , 3×25 mL) gave solution which was dried (MgSO_4),

filtered, and concentrated to give a viscous, reddish-orange oil. The solvent was filtered and concentrated in vacuum, and purified by column chromatography (eluent – benzene : dioxane 5:1). A light yellow oil 17.15 g (66%) was obtained. Elemental analysis: found (calculated for $\text{C}_{18}\text{H}_{30}\text{N}_4\text{O}_2$): C 64.62 (64.67); H 8.95 (8.98); N 16.72 (16.76).

3-(3-Ethoxypropyl)-7-(2-piperazinoethyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (3). Methanol (65 ml) was deoxygenized under nitrogen atmosphere for 30 min, then the mixture of 1 - (2-aminoethyl) piperazine (8.77 g, 670 mmol), paraformaldehyde (8.20 g, 536 mmol), concentrated hydrochloric acid (3.5 mL) and glacial acetic acid (5.16 mL) was added. Ice bath was removed and a solution of 1-(3-ethoxypropyl)-piperidin-4-one (12.47 g, 670 mmol) and glacial acetic acid (5.16 mL) in methanol (19.45 mL) was added dropwise to the mixture. After initial 10 h of heating, another equivalent of added paraformaldehyde (8.2 g, 536 mmol) was added in one portion to the mixture after which reflux was continued (10 h). After cooling to RT, the solution was concentrated under vacuum and gave an orange oil which was redissolved in H_2O (105.66 mL). Extracts (ether, 2×100) thereof were discarded. The aqueous layer was chilled (5°C) and made basic (pH~12, NaOH pellets). Extraction (CHCl_3 , 3×25 mL) gave solution which was dried (MgSO_4), filtered, and concentrated to give a viscous, reddish-orange oil. The solvent was filtered and concentrated in vacuum, and purified by column chromatography (eluent – benzene: dioxane 5:1). A light yellow oil (8.75 g, 38%) was obtained. Elemental analysis: found (calculated for $\text{C}_{18}\text{H}_{34}\text{N}_4\text{O}_2$): C 63.95 (63.90); H 10.01 (H 10.05); N 15.95 (15.97).

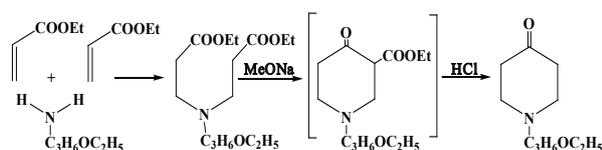
3-(3-Ethoxypropyl)-7-(3-imidazolopropyl)-3,7-diazabicyclo[3.3.1]nonane (4). To a solution of ketone (2) (4 g, 12 mmol) and anhydrous hydrazine (1.92 g, 60 mmol) in triethylene glycol (35.03 mL) KOH pellets (8.33 g, 148 mmol) were added at 60°C . The stirred mixture was heated at $160\text{--}170^\circ\text{C}$ for 5 h under N_2 . At a temperature of $190\text{--}200^\circ\text{C}$ water and the excess hydrazine hydrate were distilled. Cooling of the solution to RT (1 h) was followed by addition of ice-cold H_2O (57.2 mL) and was extracted with diethyl ether and dried (MgSO_4). The solvent was filtered and concentrated in vacuum, and purified by column chromatography. A light yellow oil (3.2 g, 83%) was obtained. Elemental analysis: found (calculated for $\text{C}_{18}\text{H}_{32}\text{N}_4\text{O}$): C 67.54 (67.50); H 9.96 (10.00); N 17.52 (17.50).

3-(3-Ethoxypropyl)-7-(2-piperazinoethyl)-3,7-diazabicyclo[3.3.1]nonane (5). To a solution of ketone (3) (3 g, 890 mmol) and anhydrous hydrazine (14 g, 44 mmol) in triethylene glycol (25.98 mL) KOH pellets (6.18 g, 110 mmol) were added at 60°C .

Then the temperature was raised to 160-170 °C and the reaction mixture was heated at this temperature with stirring for 5 hours under N₂. At a temperature of 190-200 °C water and the excess hydrazine hydrate were distilled. Cooling of the solution to RT (1 h) was followed by addition of ice-cold H₂O (44.27 mL) and was extracted with diethyl ether and dried (MgSO₄). The solvent was filtered and concentrated in vacuum, and purified by column chromatography. A light yellow oil (2.7 g, 94%) was obtained. Elemental analysis: found (calculated for C₁₈H₃₆N₄O): C 66.57 (66.66); H 11.04 (11.11); N 17.30 (17.28).

Results and Discussion

Piperidone for Mannich reaction was synthesized from 3-ethoxypropylamine by Dickmann condensation [12]. Thus, in step I of the process of the acrylate and the corresponding diesters 3-ethoxypropylamino-N,N-bis-(3-ethoxycarbonyl)ethyl)-N-ethoxypropylamine was obtained. Next, in process step III is carried out by saponification and decarboxylation is obtained in step II carbalkoxypiperidine derivative to form the corresponding 1-(3-ethoxypropyl)-4-oxopiperidine:



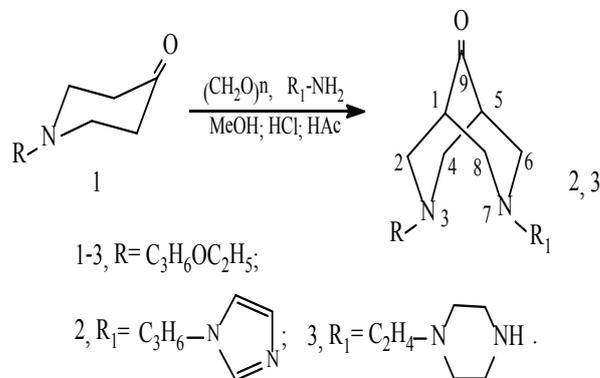
The main disadvantage of the Mannich approach is that it always gives a carbonyl group at the C-9 position which might induce some unfavorable properties relative to the corresponding bispidine. Reduction of the keto group is almost exclusively achieved by the Wolff-Kishner method.

The subjects investigated in the present work were 3-(3-ethoxypropyl)-7-heterocyclyl-3,7-diazabicyclo[3.3.1]nonan-9-ones. The results on the investigation of their spatial structure with the aid of ¹H and ¹³C NMR spectroscopy are given. On the basis of the data obtained on the vicinal coupling constants of protons, which bear important information on the geometry of the molecules [13], it was stated that the bispidinones studied exist in solution predominantly in a chair-chair conformation.

Synthesis of new 1-(3-ethoxypropyl)-7-heterocyclylalkyl-3,7-diazabicyclo [3.3.1] nonan-9-ones

Corresponding 3,7-diazabicyclo[3.3.1]nonan-9-ones (2, 3) with 66% and 38% yield were synthesized by Mannich condensation of 1-(3-ethoxypropyl)-

4-oxopiperidine (1) with paraformaldehyde and 1-(3-aminopropyl)imidazole or 1-(2-aminoethyl) piperazine in methanol medium in the presence of acetic acid:



It is necessary to note that the column chromatography (Al₂O₃, eluent – benzene : dioxane 5:1) was used for purification of novel bicyclic ketones (2, 3), the reaction products are viscous oils. The composition and structure of bispidinones (2, 3) were determined by TLC (Al₂O₃, eluent – benzene : isopropanol 6:1), IR and NMR spectroscopy (Tables 1, 2).

Table 1

Yields, physical and chemical characteristics of 3,7-diazabicyclo[3.3.1]nonan-9-ones (2, 3)

Compound	Yield, %	R _f [*]	Calculated Found, %		IR, cm ⁻¹	
			C	H	C=O	C-O-C
2	66	0.46	64.67 64.62	8.98 8.95	1737	1117
3	38	0.30	63.90 63.95	10.05 10.01	1736	1119

Note – Al₂O₃, eluent: benzene: isopropanol 6:1

In the IR spectrum of the synthesized 3,7-diazabicyclo[3.3.1]nonan-9-ones (2, 3) the characteristic absorption bands of the stretching vibrations of the carbonyl group (1737 and 1736 cm⁻¹) and the ether linkage (1117 and 1119 cm⁻¹) (Table 1) were identified.

The chemical shifts of carbon atoms in the spectrum of bispidinones (2, 3) are shown in Table 2. In the spectrum of carbon compounds (2, 3) the most low field singlet signals at 214.4 and 214.8 ppm belong to the carbon atom of the carbonyl group. In the spectrum doublet signal of the ring atoms C_{1,5} at 46.6 and 46.8 ppm and the signals of carbons of the substituents at the nitrogen atoms also indicated the formation of bicyclic products.

Table 2
Chemical shifts of carbons (δ , ppm) (2, 3) in CDCl_3

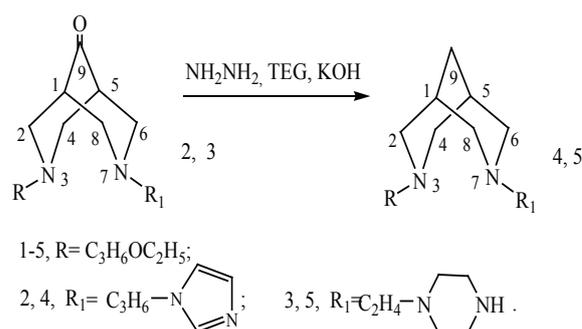
Compound	C _{1,5}	C ₉	C ₁₁	C ₁₂	C ₁₃	C ₁₅	C ₁₆	C ₁₇	C ₁₈	C ₁₉
2	46.6	214.4	68.5	66.2	15.2	28.2	43.9	137.6	129.1	119.1
3	46.8	214.8	68.6	66.2	15.3	27.5	58.7	53.5	67.04	

Spatial structure of bispidinones (2, 3) was determined on the basis of the data on the ^{13}C NMR spectrum. Two doublets of doublets at 2.94-2.91 and 2.47-2.71 ppm with constants 3.0 and 3.3 Hz belong to the geminal protons at 6- and 8-H occupying axial positions relative to the plane of the chair-form ring. Signal equatorial protons near C_{2,4} and C_{6,8} have the form of widened doublets and a doublet of doublets with $J^2 = 10.2-11.0$ and $J^3 = 3.0-6.0$ Hz was obtained in the low field of spectrum (3.26-3.12 and 3.19-3.10 ppm).

Synthesis of new 1-(3-ethoxypropyl)-7-heterocyclalkyl-3,7-diazabicyclo[3.3.1]nonanes

Finally, as part of this study, we re-evaluated the Wolff-Kishner reduction of bispidinone (2, 3) to bispidine (4, 5). In our work the reaction with hydrazine hydrate/KOH was carried out at 160-170 °C.

The reaction was completed after 5 hours, the yields were 83% and 94%:



It should be noted that purification of the products was performed by column chromatography on aluminum oxide of III activity. Yields and physical-chemical characteristics of the bispidines (4, 5) are presented in Table 3.

Table 3
Yields and elementary analysis data of 3,7-diazabicyclo[3.3.1]nonanes (4, 5)

Compound	Yield, %	R _f *	Formula	Calculated, %		Found, %	
				C	H	C	H
4	83	0.36	C ₁₈ H ₃₂ N ₄ O	67.50	10.00	67.54	9.96
5	94	0.26	C ₁₈ H ₃₆ N ₄ O	66.66	11.11	66.57	11.04

The composition and structure of 3,7-diazabicyclononanes (4, 5) are confirmed by elemental analysis, IR spectra and ^{13}C NMR spectra. Formation of bicyclic amines was indicated by the absence in the IR spectra of compounds (2, 3) of the absorption band of the carbonyl group. The

assignment of the signals of carbon atoms were in position and shape of the multiplets in the ^{13}C NMR spectra mono-resonance. The chemical shifts of carbon atoms in the ^{13}C NMR spectrum of 3,7-diazabicyclo[3.3.1]nonanes (4, 5) are listed in Table 4.

Table 4
Chemical shifts of carbons (δ , ppm) (4, 5) in CDCl_3

Compound	C _{1,5}	C _{2,4}	C _{6,8}	C ₉	C ₁₀	C ₁₁	C ₁₂	C ₁₃	C ₁₄	C ₁₅	C ₁₆	C ₁₇	C ₁₈	C ₁₉
4	29.9	58.5	58.3	32.0	56.5	27.3	69.3	66.1	15.1	56.5	27.5		138.2	128.9
5	27.4	58.5	58.8	33.9	56.2	27.5	66.1	72.7	15.2	56.1	52.7	55.1	46.3	

In the ^{13}C NMR spectrum of bispidines 2 pairs of doublet of doublets and fragment of 3,7-diazabicyclo[3.3.1]nonanes (4, 5) rings with large broadening coupling were observed. The ^{13}C NMR spectrum of 3,7-diazabicyclo[3.3.1]nonanes (4, 5) differ from the spectra of the initial bicyclic ketone (2, 3) in that they lack the signal of carbon atoms, characteristic of carbonyl group, wherein in heavily dipole part of the spectrum there is a triplet signal of carbon atom of the methylene group in the ninth position (32.0 and 33.9 ppm). It should also be noted that reduction of the carbonyl group to methylene leads to significant displacement of the signal node of carbon atoms $\text{C}_{1,5}$ in a stronger field (27.4 and 29.9 ppm). NMR ^1H spectrum analysis revealed that 3,7-diazabicyclo[3.3.1]nonane derivatives has a bicyclic unit in a chair-chair conformation.

Conclusion

A series of 3-(3-ethoxypropyl)-7-heterocyclilalkyl-3,7-diazabicyclo[3.3.1]nonanes have been prepared by Mannich cyclocondensation on 3-ethoxypropyl-4-piperidone followed by Wolff-Kischner reduction of the intermediate ketones. The structures were determined by IR and NMR spectroscopies, ^1H NMR spectrum analysis revealed that 3,7-diazabicyclo[3.3.1]nonane derivatives have a bicyclic unit in a chair-chair conformation.

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