4-N-ARYL(BENZYL)AMINO-4-HETEROARYL-1-BUTENES AS BUILDING BLOCKS IN HETEROCYCLIC SYNTHESIS. 2. SYNTHESIS OF NEW TETRAHYDRO-2-BENZAZEPINE DERIVATIVES AND RELATED COMPOUNDS CONTAINING A PYRIDINE RING

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Abstract: Chemical transformations of the aminobutenes (**1,2**) were studied. Their allyl cationic intramolecular cyclisation led to the preparation of new tetrahydro-2-benzazepines containing a pyridine ring (**3,4**). The acylation and oxidation reactions of these aminobutenes gave several amides (**5,6,8**) and nitrone (**7a**), which was converted into the 6-phenyl-2-(3-pyridyl)-7-oxa-1-azabicyclo[2.2.1]heptane (**9a**).

Introduction

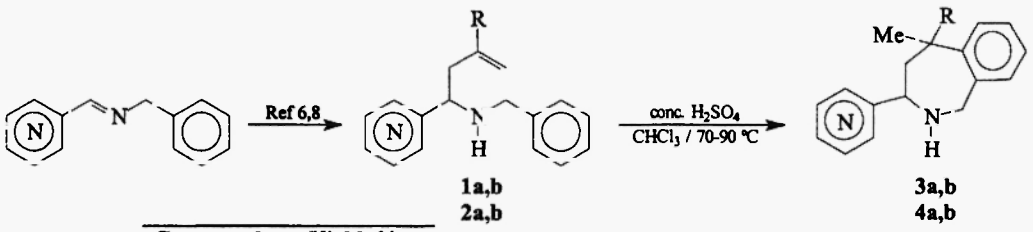
The synthesis of pyridine and benzazepine derivatives has long been an area of intense for organic chemistry due to the presence of these scaffolds within the framework of numerous biologically interesting natural products.[1-3] Many drugs based on a pyridine nucleus are used successfully in the medicinal practice. The development of new compounds, which could be agonists of neuronal acetylcholine receptors is important task. That is the reason that medicinal chemistry needs to search for new nicotinic acetylcholine receptors as selective drug candidates against senile dementia of the Alzheimer's type, Parkinson's disease, dyslexia etc. Both types of heterocycles and their derivatives have been evaluated for their interaction at specific receptors.[4]

During our investigations on the N-substituted homoallylamines[5,6] we noted that these homoallylamines containing a pyridine ring at the C-4 of butene chain could be very useful as intermediates in straightforward synthesis of new heterocycles which serve as potential bioactive agents. Herein, we wish to describe the transformation of 4-N-benzylamino-4-(pyridyl)-1-butenes and 4-N-benzylamino-2-methyl-4-(pyridyl)-1-butenes to produce new hydrogenated 2-benzazepines and related compounds containing a pyridine nucleus.

Results and Discussion

Homoallylamines have attracted the attention of a wide range of organic, heterocyclic and medicinal chemists, which address often to prepare bioactive N-heterocycles.[7] Our starting compounds, 4-N-benzylamino-4-(pyridyl)-1-butenes (**1a,b**) and 4-N-benzylamino-2-methyl-4-(pyridyl)-1-butenes (**2a,b**), were obtained in common way adding the allyl organometallic reagents (CH_2=CH-CH_2MgBr and CH_2=C(CH_3)-CH_2MgCl) to the double bond of respective aldimines.[6,8]

First we addressed to the synthesis of new methyl substituted hydrogenated 2-benzazepines using our experience in the methodology of allyl cationic intramolecular cyclisation.[9-11] This cyclisation of the aminobutenes **1,2** was readily achieved by heating (85-90°C) these compounds in chloroform in the presence of concentrate sulfuric acid affording the 5-methyl- or 5,5'-dimetyl-3-(pyridyl) hydrogenated 2-benzazepines (**3,4**) in 47-56 % yields (Scheme 1). According to the GC-MS and NMR analysis of the crude reaction product for mono methyl derivatives **3a,b**, a mixture of the two geometric isomers (cis-trans: 5-Me/3-Py) is observed in the ratio 70:30. Purification by column chromatography of this mixture led to the enrichment of cis-isomer (5e-Me/3e-Py).[12]

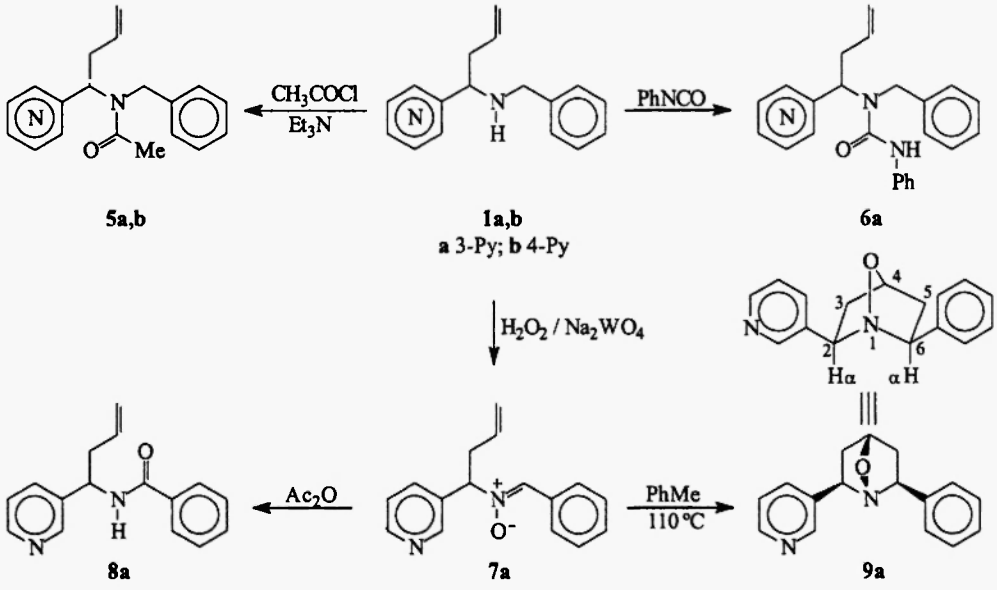


Compound	Yield, %
3a	48
3b	47
4a	56
4b	54

Scheme 1.

Next, seeking substances with potential bioactivity among other derivatives of homoallylamines containing a pyridine nucleus, we prepared several oxygenated derivatives of chosen aminobutenes: acetamides **5a,b**, urea **6a** and benzamide **8a** (Scheme 2). The amides **5a,b** were obtained by N-acetylation reaction of the compounds **1a,b** and acetyl chloride in the presence of a catalytic amounts of Et_3N. Compound **6a** was prepared by treating the homoallylic amine **1a** with phenyl isocyanate in benzene at 80°C for 10 h. Benzamide **8a** was synthesized (acetic anhydride, 60°C) from nitrone **7a**, which is available by oxidation of the aminobutene **1a** with 50% H_2O_2 in the presence of a catalytic amounts of Na_2WO_4 in a mixture of acetone-water (9:1) at room temperature.[8] The obtained amides showed in the IR spectra the characteristic C=O bands appearing in the region of 1660-1646 cm^{-1}. Their structures were also consistent with their ^1H- and ^{13}C-NMR spectra and supported by the mass spectrometric data.[13]

Finally, nitrone **7a** was subjected (toluene, reflux, 72 h) to 1,3-dipolar intramolecular cycloaddition that afforded the 6-phenyl-2-(3-pyridyl)-7-oxa-1-azabicyclo[2.2.1]heptane (**9a**) in good yield (Scheme 2).



Scheme 2.

Due to the structural symmetry of molecule **9a**, its ^1H NMR spectrum has a very few signals. The values of coupling constants $J_{2,3}$ ($J_{2\alpha,3\alpha}$ = 8.3 and $J_{2\alpha,3\beta}$ = 4.5 Hz) and $J_{5,6}$ ($J_{5\alpha,6\alpha}$ = 8.3 and $J_{5\alpha,6\beta}$ = 4.5 Hz) displayed the *exo* relative stereochemistry of C-2 pyridine and C-6 phenyl groups in this bicycle.[14] Electronic density of

pyridine and phenyl rings of rigid molecule **9a** affect equally on the protons at C-2 and C-6, which resonate at 4.10 ppm. A triplet proton at C-4 appears at 5.10 ppm. We wondered the geometry parameters of bicycle **9a**, in particular, the values of dihedral angle (α). To calculate these geometry parameters we used a semi-empirical method (PM3) (Table 1). Calculated data correlate well with found values of vicinal coupling constants, which are agreed with those determined previously.[8 15]

Table 1.

Protons	Dihedral angle, α	J found, Hz
2α,3α	6.348	4.48
2α,3β	126.442	8.31
3α,4β	83.175	0.00
3β,4β	36.706	4.92
4β,5α	83.372	0.00
4β,5β	36.501	4.92
5α,6α	5.883	4.50
5β,6α	125.995	8.31

In conclusion, we have obtained a new series of potentially bioactive pyridine and 2-benzazepine derivatives. Their biological activities are under investigation and the results will be published elsewhere.

Experimental

Experimental conditions were described in previous communication of this series. Elemental analyses were in satisfying agreement with the calculated data. The allylation reactions of starting aldimines and the subsequent intramolecular cyclisations of obtained homoallylamines **1,2** were carried out using known procedures.[1,8] Preparation of acetamides **5a,b**, urea **6a**, nitrone **7a** and benzamide **8a** from aminobutene **1a** were made by the known methods.

Acknowledgements

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References

1. Communication No.1 of this series : Vargas Méndez, L.Y., Kouznetsov, V., Stashenko, E., Bahsas, A., Amaro-Luis, J., *Heterocycl. Commun.*, 7, 323, (2001).

2. Jones, G., Pyridines and Their Benzo Derivatives: (v). Synthesis, in Comprehensive Heterocyclic Chemistry, Katritzky, A.R., ed., Pergamon Press, Oxford, 1984, V. 2, pp. 395.

3. Kouznetsov, V., Palma, A., Ewert C., *Curr. Org. Chem.*, 5, 519, (2001).

4. Schmitt, J.D., Bencherif M., Targeting Nicotinic Acetylcholine Receptors: Advances in Molecular Design and Therapies, in *Ann. Rep. Med. Chem.*, Doherty A.M., ed., Academic Press, New York, 2000, V. 35, pp. 41.

5. Kuznetsov, V.V., Aliev, A.E., Prostakov, N.S., *Khim. Geterotsikl. Soedin.*, 73 (1994). Chem. Abst. 121, 300.738, (1994).

6. Kouznetsov, V.V., Palma, A.R., Aliev, A.E., *Anales de Química. Int. Ed.*, 94, 132 (1998). Chem. Abst. 130. 52.317, (1999).

7. Ochoa, P.C., Kouznetsov, V., *J. Heterocycl. Chem.*, (2002), in press.

8. Varlamov, A., Kouznetsov, V., Zubkov, F., Chernyshev A., Shurupova, O., Vargas Méndez, L.Y., Palma A.R., Rivero Castro, J., Rosas-Romero, F.J., *Synthesis*, (2002), in press.

9. Kouznetsov, V., Ocal N., Turgut, Zh., Zubkov, F., Kaban, Ş., Varlamov, A., *Mon. Chem.*, 129, 671 (1998).

10. Palma A.R., Salas S., Kouznetsov V., Stashenko E., Montenegro G.N., Fontela A.G., *J. Heterocycl. Chem.*, 38, 837 (2001).

11. Palma A., Carrillo C., Stashenko E., Kouznetsov V., Bahsas A., Amaro-Luis J., *Tetrahedron Lett.*, 42, 6247 (2001).

12. Compound **3a**: yield 48%; a yellow oil; IR (neat): ν = 3273, 3029, 1490, 1376, 1300 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 8.55 (1H, d, J = 1.9 Hz, 2-H_{Py}), 8.46 (1H, dd, J = 6.6 and 1.7 Hz, 6-H_{Py}), 7.7 (1H, t, J = 7.6 Hz, 5-H_{Py}), 7.6 (1H, dt, J = 7.9 and 1.9 Hz, 4-H_{Py}), 7.28-7.17 (4H, m, Ph), 5.61 (1H, t, J = 5.8 Hz, 3-H), 4.21 (1H, d, J = 15.7 Hz, 1-H_A), 3.96 (1H, d, J = 15.7 Hz, 1-H_B), 3.32 (1H, m, 5-H), 2.07 (1H, s, NH), 1.91 (1H, m, 4-H_e), 1.41 (3H, d, J = 6.9 Hz, 5-CH_3), 1.24 (1H, m, 4-H_a); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.6, 148.9, 148.7, 145.5, 141.5, 134.4, 128.6, 127.6, 126.4, 124.9, 123.6, 65.2, 53.8, 45.3, 35.5, 20.5; CG-MS: t_R: 26.63 min.; m/z, (%) = 238 (M^+, 5), 223 (8), 195 (4), 146 (77), 132 (100), 117 (98), 107 (5), 91 (64).

13. Compound **5a**: yield 62%; a red oil; IR (neat): ν = 3064, 3031, 1646, 1496, 919 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.50- 6.93 (9H, m, phenyl and pyridine), 5.91 (1H, t, J = 5.4 Hz, 4-H), 5.63 (1H, m, 2-H), 4.99 (2H, m, 1-H), 4.39 (1H, d, J = 17.8 Hz, H_A ,-CH_2-N), 4.26 (1H, d, J = 17.6 Hz, H_B ,-CH_2-N), 2.66 (2H, t, J = 7.3 Hz, 3-H), 2.03 (1H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 150.0, 149.3, 137.1, 136.4, 134.2, 131.0, 128.7, 127.4, 123.3, 118.1, 54.8, 48.7, 34.9, 22.7; CG-MS: t_R: 29.22 min.; m/z, (%) = 280 (M^+, 2), 239 (26), 197 (45), 147 (5), 91 (100), 65 (13), 77 (5). Compound **6a**: yield 60%; a yellow oil; IR (neat): ν = 3413, 1651, 1597, 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.30-7.00 (14H, m, phenyls and pyridine), 6.87 (1H, t, J = 7.2, 1-H), 6.15 (1H, s, NH), 5.85 (1H, m, 4-H), 5.08 (2H, m, 1-H), 4.33 (1H, d, J = 17.0 Hz, H_A ,-CH_2-N), 4.20 (1H, d, J = 17.0 Hz, H_B ,-CH_2-N), 2.72 (2H, m, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 139.8, 137.3, 135.9, 135.0, 129.0, 128.6, 128.3, 127.9, 126.9, 122.9, 119.7, 117.6, 116.8, 57.2, 47.3, 35.4; CG-MS: t_R: 25.65 min.; m/z, (%) = 238 (M+, 2), 197 (62), 91 (100), 65 (7), 51 (4). Compound **8a**: yield 68%; a white solid, m.p. 96-98°C; IR (KBr): ν = 3354, 1646, 1642, 1603, 919 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.61 (1H, d, J = 2.2 Hz, 2-H_{Py}), 8.50 (1H, dd, J = 6.4 and 1.5 Hz, 6-H_{Py}), 7.65 (1H, dt, J = 7.9 and 1.9 Hz, 4-H_{Py}), 7.42 (1H, t, J = 6.9 Hz, 5-H_{Py}), 7.39-7.10 (4H, m, Ph), 6.53 (1H, d, J = 6.9 Hz, NH), 5.73 (1H, m, 2-H), 5.28 (1H, q, J = 7.0 Hz, 4-H), 5.19 (1H, ddd, J = 26.6, 2.9 and 1.4 Hz, 1-H_{trans}), 5.18 (1H, d, J = 1.4, 1-H_{cis}), 2.65 (2H, t, J = 7.0 Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 148.7, 148.1, 137.2, 134.2, 134.0, 133.1, 131.7, 128.6, 126.8, 123.4, 119.2, 50.8, 40.2; CG-MS: t_R: 28.30 min.; m/z, (%) = 252 (M^+, 2), 211 (24), 120 (5), 105 (100), 77 (40), 51 (11).

14. Compound **9a**: yield 50%; a yellow solid, m.p. 79-81°C; IR (KBr): ν = 2973, 1023 cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$): δ 7.50-7.10 (9H, m, phenyl and pyridine), 5.10 (1H, t, J = 4.9 Hz, 4-H), 4.09 (1H, dd, J = 8.3 and 4.5 Hz, 2-Hα), 4.09 (1H, dd, J = 8.3 and 4.5 Hz, 6-Hα), 2.27 (2H, dd, J = 8.3 and 4.9 Hz, 3-Hα /5-Hα), 2.08 (2H, dd, J = 8.3 and 4.9 Hz, 3-Hβ/5-Hβ); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.1, 128.4, 126.8, 126.7, 79.1, 70.2, 42.6; CG-MS: t_R: 28.13 min; m/z, (%) = 252 (1), 208 (38), 131 (100), 118 (66), 104 (71), 91 (90), 77 (65), 65 (21), 51 (33).

15. Varlamov, A.V., Zubkov, F.I., Chernyshev, A.I., Kouznetsov, V.V., Palma, A.R., *Khim. Geterotsikl. Soedin.*, 77 (1998). Chem. Abst. 129, 260.609, (1998).

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