# SYNTHESIS OF NEW 4-ALLYL-4-N-BENZYLAMINOPIPERIDINES AND THEIR SPIROCYCLIC PRODUCTS

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**Abstract:** A new series of N-substituted 4-allyl-4-N-benzylaminopiperidines and spiro[3H-2-benzazepine-3,4'-piperidines] have been prepared as potential psychotic agents from readily available 4-iminopiperidines, by a sequence of reactions that included nucleophilic addition of Grignard reagents and acid-mediated intramolecular cyclisation. Some of the compounds prepared have been tested in albine mice for the spontaneous motor activity.

## Introduction

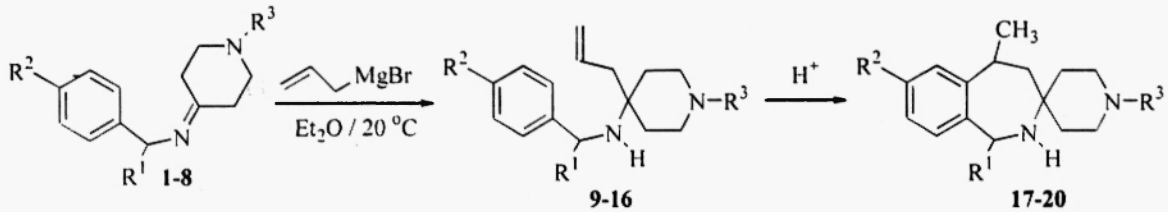
4-Iminopiperidines have received much attention owing to their obvious use in fine organic synthesis[1]. They are useful in design and subsequent synthesis of several medicinal agents, containing 4-substituted and 4,4'-disubstituted or C-4 spiroannulated piperidine rings[2]. As a part of our continuing interest in developing biologically active compounds with the piperidine ring[3], containing the amine group at C-4, that could act as analgesics, we report herein the synthesis of a new series of 4-allyl-4-N-benzylaminopiperidines and the results of studies on some of their psychoactive properties. We also describe the preparation of several new spiro[3H-2-benzazepine-3,4'-piperidines], by intramolecular cyclisation of the above mentioned 4-N-benzylaminopiperidines.

## Results and Discussion

The compounds described in this paper were synthesized by the route shown in scheme **1**. Initially, the imines **1-8** have been prepared in 41-90% yield by condensation of the corresponding benzylamines and N-substituted 4-piperidones as described in the literature[4]. The C=N double bond presence in ketimines **1-8** was confirmed by IR ($\nu_{C=N}$ 1661-1664 $cm^{-1}$). C-Allylation of the C=N bond of ketimines **1-8** was achieved with allylmagnesium bromide, prepared from allyl bromide and magnesium activated with $I_2$. All these reactions were run in dry ether at 20 °C. This way, the 4-allyl-4-N-benzylaminopiperidines **9-16** have been obtained as viscous oils with high yields after standard work-up and distillation at reduced pressure. The simplicity of the procedure and accessibility of the starting materials allowed us to prepare these homoallylamines in large quantities. Structural elucidation of piperidines **9-16** was carried out by IR and $^1H$ NMR spectroscopies and mass spectrometry (table 1).

Subsequent intramolecular allyl cyclisation of the aminopiperidines **9-11** and **13** was readily accomplished using concentrated sulfuric acid according to our method of spirocyclisation[5,6] (Scheme1). This allowed to obtain N-substituted 1,2,4,5-tetrahydrospiro[3H-2-benzazepine-3,4'-piperidines] **17-20** in 54-90% yield. These new spiropiperidines were isolated by column chromatography as maroon viscous oils. Under the conditions chosen, the cyclisation of **12**, and **14-16** did not take place.

The structural assignments proposed for the tetrahydrospiro[2-benzazepine-3,4'-piperidines] **17-20** were consistent with their $^1$H NMR spectra and were supported by the mass spectrometric data (table 1). In contrast with mass spectra of compounds **9-16**, intensities of molecular ion peaks ($M^+$) in the mass spectra of spirotetrahydrobenz-2-azepines **17-20** varied between 7 and 42%. The chemical shifts of the methyl (doublet at δ 1.30-1.36 ppm) and methine (multiplet at δ 3.22-3.50 ppm) protons at the C-5 position in $^1$H NMR spectra were used as the best evidences that the cyclisation of **9-11**, and **13** did take place.




**1, 9,17 $R^1$=$R^2$=H, $R^3$=$C_2H_5$; 2,10,18 $R^1$=$CH_3$, $R^2$=H, $R^3$=$C_2H_5$;**
**3,11,19 $R^1$=H, $R^2$=$CH_3$, $R^3$=$C_2H_5$; 4,12 $R^1$=H, $R^2$=Cl, $R^3$=$C_2H_5$;**
**5,13,20 $R^1$=$CH_3$, $R^2$=H, $R^3$=$CH_2C_6H_5$; 6,14 $R^1$=H, $R^2$=$CH_3$, $R^3$=$CH_2C_6H_5$;**
**7,15 $R^1$=H, $R^2$=Cl, $R^3$=$CH_2C_6H_5$; 8,16 $R^1$=$R^2$=H, $R^3$=$CH_2C_6H_5$**

**Scheme 1**

**Table 1:** Yields and some physical and spectral properties of the piperidines **9-16** and spiropiperidines **17-20.**

| N° | B.p. °C/mm Hg | IR. $cm^{-1}$; $\nu_{NH}$ | Yield (%) | Molecular Formula | MS m/z (%) |
|---|---|---|---|---|---|
| **9** | 165-181/10 | 3322 | 61 | $C_{17}H_{26}N_2$ | 258 ($M^+$<1), 217 (27), 160 (33), 153 (14), 138 (8), 125 (12), 110 (100), 91 (70), 84 (32), 72 (23), 65 (13), 58 (27) |
| **10** | 171-175/10 | 3339 | 60 | $C_{18}H_{28}N_2$ | 272 ($M^+$<1), 231 (32), 174 (8), 153 (13), 127 (15), 110 (100), 105 (60), 103 (9), 84 (29), 79 (15), 70 (19) |
| **11** | 180-188/10 | 3325 | 39 | $C_{18}H_{28}N_2$ | 272 ($M^+$<1), 231 (27), 174 (25), 153 (21), 138 (10), 125 (14), 110 (100), 105 (80), 84 (35), 72 (21) |
| **12** | 196-207/10 | 3327 | 47 | $C_{17}H_{25}ClN_2$ | 292* ($M^+$<1), 251 (17), 194 (19), 153 (15), 138 (11), 125 (61), 110 (100), 84 (30), 72 (20) |
| **13** | 165-185/10 | 3342 | 51 | $C_{23}H_{30}N_2$ | 334 ($M^+$<1), 293 (31), 172 (71), 105(59), 91 (100), 65 (11) |
| **14** | 195-208/10 | 3326 | 32 | $C_{23}H_{30}N_2$ | 334 ($M^+$<1), 293 (23), 172 (64), 105 (69), 91 (100), 65 (11) |
| **15** | ** | 3325 | 57 | $C_{22}H_{27}ClN_2$ | 354* ($M^+$<1), 313 (13), 172 (58), 125 (38), 91 (100), 65 (10) |
| **16** | ** | 3322 | 89 | $C_{22}H_{28}N_2$ | 320 ($M^+$<1), 279 (15), 172 (39), 91 (100), 65 (10) |
| **17** | ** | 3306 | 82 | $C_{17}H_{26}N_2$ | 258 ($M^+$, 35), 240 (28), 226 (21), 186 (23), 172 (9), 158 (14), 124 (100), 117 (30), 110 (50), 91 (25), 84 (30), 72 (36) |
| **18** | ** | 3315 | 90 | $C_{18}H_{28}N_2$ | 272 ($M^+$, 35), 254 (48), 240 (25), 228 (9), 200 (28), 186 (10), 172 (20), 131 (36), 124 (100), 117 (21), 110 (46), 91 (28), 84 (51), 72 (42) |
| **19** | ** | 3320 | 55 | $C_{18}H_{28}N_2$ | 272 ($M^+$, 33), 254 (36), 240 (22), 200 (26), 186 (11), 172 (12), 131 (20), 124 (100), 110 (45), 91 (12), 84 (36), 72 (39) |
| **20** | ** | 3318 | 54 | $C_{23}H_{30}N_2$ | 334 ($M^+$, 11), 316 (9), 243 (9), 226 (6), 200 (9), 186 (27), 172 (18), 146 (20), 131 (15), 117 (9), 91 (100), 65 (10) |

* Relative to $^{35}$Cl; ** These compounds were isolated by column chromatography

The spontaneous motor activity assay[7] showed significant differences ($p<0.001$) between the vehicle effect (distilled water, 1 mL/100 g, IP) and that of compounds **9,11,16** and **18** at a dose of 10 mg/kg. None of these compounds

was active at lower doses. In the subsequent assay of the amphetamine-induced hyperactivity antagonism the molecule **9** with representative structure of the compounds tested did not show any activity at a dose of 10 mg/kg (figure 1). No deaths were produced by any of these compounds, at any doses tested (10, 5 and 2 mg/kg).

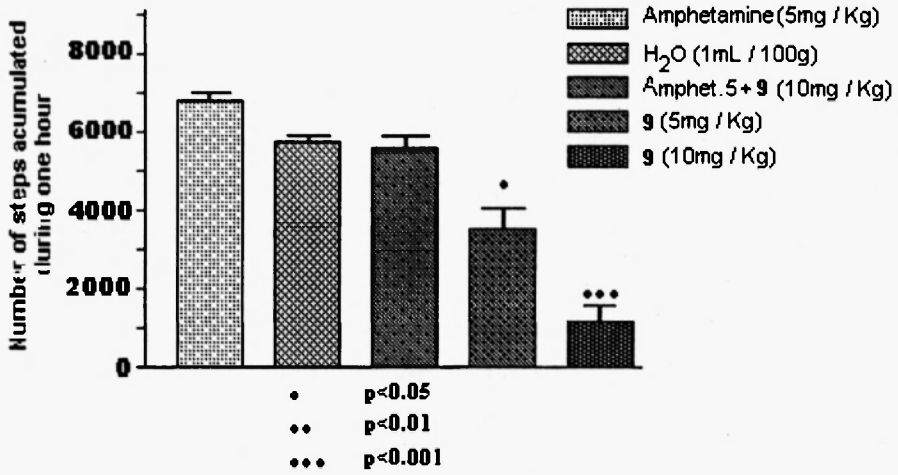



**Figure 1. Study of spontaneous motor activity of compound 9.**

**Experimental**

The purity of the obtained substances and the composition of the reaction mixtures were monitored by TLC over Alufol 60 and Silufol $UV_{254}$ plates. The final spiranes were isolated by column chromatography over aluminium oxide eluting with heptane. IR spectra were obtained from potassium bromide pellets on a Perkin Elmer 599B-FTIR spectrophotometer. The $^1H$ NMR spectra were recorded on a Bruker AC-300 spectrometers. $CDCl_3$ was used as a solvent and TMS as internal standard. Chemical shifts are reported in ppm and coupling constants are in Hz. A Hewlett-Packard (HP) 5890A Series II Gas Chromatograph interfaced to an HP 5972 Mass Selective Detector (MSD) with an HP MS ChemStation Data system was used for MS identification. The electron beam energy was 70 eV. Mass spectra and reconstructed chromatograms were obtained by automatic scanning in the mass range m/z 50-400 a.m.u.'s at 2.2 scan/s. Elemental analyses were performed on a Leco CHN-600 analyzer.

**4-Allyl-4-N-benzylaminopiperidines 9-16. General Procedure.**

A solution (0.10 moles) of the ketimines **1-8** dissolved in dry ether (30 mL) was added dropwise to a stirred solution of allylmagnesium bromide, prepared from allyl bromide (0.30 moles) and metallic magnesium (0.60 moles) in dry ether (100 mL). After the addition of the imines, the reaction mixture was heated to 35 °C and vigorously stirred for four hours. Work-up of the reaction mixture with a cold saturated solution of ammonium chloride, extraction with ether (3x100 mL), and vacuum distillation of the dried extracts afforded the corresponding 4-allyl-4-N-benzylamino-piperidines as yellow or brown oils (table 1). $^1H$ NMR data and elemental analysis of the products are given below.

**9**: $^1H$ NMR ($CDCl_3$) δ 1.08 (3H, t, J = 7.3 Hz, N-$CH_2\mathbf{CH_3}$), 1.40-1.55 (4H, m, β-H and β′-H), 2.24 (2H, d, J = 7.7 Hz, -$CH_2$ allyl protons), 2.38-2.48 (4H, m, α-H and α′-H), 2.42 (2H, q, J = 7.3 Hz, N-$\mathbf{CH_2}CH_3$), 3.60 (2H, s, 4-$CH_2$Ph), 5.09 (2H, m, =$CH_2$ allyl protons), 5.83 (1H, m, CH= allyl protons), 7.18-7.34 ppm (5H, m, phenyl protons); Anal. Calcd for $C_{17}H_{26}N_2$: C, 79.07; H, 10.08; N, 10.85. Found: C, 79.25; H, 10.30; N, 10.67.

**10:** $^1$H NMR ($CDCl_3$) δ 0.92 (3H, t, J = 7.3 Hz, N-$CH_2\mathbf{CH_3}$), 1.19 (3H, d, J = 6.9 Hz, 4-$CH\mathbf{CH_3}$), 1.45-1.53 (4H, m, β-H and β′-H), 2.14-2.29 (4H, m, α-H and α′-H), 2.16 (2H, d, J = 7.7 Hz, -$CH_2$ allyl protons), 2.23 (2H, q, J = 7.3 Hz, N-$\mathbf{CH_2}CH_3$), 3.83 (1H, q, J = 6.8 Hz, 4-$\mathbf{CH}CH_3$), 4.94 (2H, m, =$CH_2$ allyl protons), 5.65 (1H, m, CH= allyl protons), 7.04-7.28 ppm (5H, m, phenyl protons); Anal. Calcd for $C_{18}H_{28}N_2$: C, 79.41; H, 10.29; N, 10.29. Found: C, 79.17; H, 10.42; N, 10.41.

**11:** $^1$H NMR ($CDCl_3$) δ 0.99 (3H, t, J = 7.3 Hz, N-$CH_2\mathbf{CH_3}$), 1.53-1.58 (4H, m, β-H and β′-H), 2.16 (2H, d, J = 7.7 Hz, -$CH_2$ allyl protons), 2.23 (3H, s, *p*-CH3), 2.26-2.38 (4H, m, α-H and α′-H), 2.32 (2H, q, J = 7.3 Hz, N-$\mathbf{CH_2}CH_3$), 3.50 (2H, s, 4-$CH_2$Ph), 5.01 (2H, m, =$CH_2$ allyl protons), 5.76 (1H, m, CH= allyl protons), 7.02 (2H, d, J = 8.2 Hz, *ortho*-H), 7.15 (2H, d, J = 8.2 Hz, *meta*-H); Anal. Calcd for $C_{18}H_{28}N_2$: C, 79.41; H, 10.29; N, 10.29. Found: C, 79.09; H, 10.03; N, 10.50.

**12:** $^1$H NMR ($CDCl_3$) δ 0.98 (3H, t, J = 7.3 Hz, N-$CH_2\mathbf{CH_3}$), 1.54-1.62 (4H, m, β-H and β′-H), 2.15 (2H, d, J = 7.7 Hz, -$CH_2$ allyl protons), 2.33 (2H, q, J = 7.3 Hz, N-$\mathbf{CH_2}CH_3$), 2.37-2.53 (4H, m, α-H and α′-H), 3.58 (2H, s, 4-$CH_2$Ph), 5.02 (2H, m, =$CH_2$ allyl protons), 5.73 (1H, m, CH= allyl protons), 7.14 (2H, d, J = 8.2 Hz, *ortho*-H), 7.22 (2H, d, J = 8.2 Hz, *meta*-H); Anal. Calcd for $C_{17}H_{25}ClN_2$: C, 69.74; H, 8.55; N, 9.57. Found: C, 69.53; H, 8.41; N, 9.39.

**13:** $^1$H NMR ($CDCl_3$) δ 1.29 (3H, d, J = 6.8 Hz, 4-$CH\mathbf{CH_3}$), 1.44-1.58 (4H, m, β-H and β′-H), 2.22-2.32 (4H, m, α-H and α′-H), 2.25 (2H, d, J = 7.7 Hz, -$CH_2$ allyl protons), 3.43 (2H, s, N-$\mathbf{CH_2}$Ph), 3.85 and 3.95 (1H, 2q, each, J = 6.8 Hz, 4-$\mathbf{CH}CH_3$), 5.02 (2H, m, =$CH_2$ allyl protons), 5.75 (1H, m, CH= allyl protons), 7.15-7.37 (10H, m, arom. protons); Anal. Calcd for $C_{23}H_{30}N_2$: C, 82.63; H, 8.98; N, 8.38. Found: C, 82.45; H, 8.87; N, 8.26.

**14:** $^1$H NMR ($CDCl_3$) δ 1.56-1.64 (4H, m, β-H and β′-H), 2.26 (2H, d, J = 7.7 Hz, -$CH_2$ allyl protons), 2.33 (3H, s, *p*-$CH_3$), 2.40-2.55 (4H, m, α-H and α′-H), 3.52 (2H, s, N-$\mathbf{CH_2}$Ph), 3.59 (2H, s, 4-$CH_2$Ph), 5.11 (2H, m, =$CH_2$ allyl protons), 5.86 (1H, m, CH= allyl protons), 7.11-7.34 (9H, m, arom. protons); Anal. Calcd for $C_{23}H_{30}N_2$: C, 82.63; H, 8.98; N, 8.38. Found: C, 82.42; H, 8.81; N, 8.33.

**15:** $^1$H NMR ($CDCl_3$) δ 1.52-1.63 (4H, m, β-H and β′-H), 2.27 (2H, d, J = 7.7 Hz, -$CH_2$ allyl protons), 2.35-2.53 (4H, m, α-H and α′-H), 3.55 (2H, s, N-$\mathbf{CH_2}$Ph), 3.62 (2H, s, 4-$CH_2$Ph), 5.14 (2H, m, =$CH_2$ allyl protons), 5.87 (1H, m, CH= allyl protons), 7.26-7.36 (9H, m, arom. protons); Anal. Calcd for $C_{22}H_{27}ClN_2$: C, 74.47; H, 7.62; N, 7.90. Found: C, 74.19; H, 7.41; N, 7.78.

**16:** $^1$H NMR ($CDCl_3$) δ 1.70-1.90 (4H, m, β-H and β′-H), 2.24 (2H, d, J = 7.7 Hz, -$CH_2$ allyl protons), 2.55-2.80 (4H, m, α-H and α′-H), 3.71 (2H, s, N-$\mathbf{CH_2}$Ph), 3.81 (2H, s, 4-$CH_2$Ph), 5.30 (2H, m, =$CH_2$ allyl protons), 6.05 (1H, m, CH= allyl protons), 7.35-7.65 (10H, m, arom. protons); Anal. Calcd for $C_{22}H_{28}N_2$: C, 82.50; H, 8.75; N, 8.75. Found: C, 82.67; H, 8.49; N, 8.55.

**N-Substituted 1,2,4,5-tetrahydrospiro[3H-2-benzazepine-3,4′-piperidines] 17-20. General Procedure.**

To a stirred and cooled (0 °C) solution of homoallylamines **9-11** and **13** (1.0 g) and dichloromethane (2.0 mL) was added concentrated sulfuric acid (2.0 mL) dropwise for five minutes. The reaction mixture was heated at 80 °C and vigorously stirred for three hours, and monitored by TLC. Neutralisation of the reaction mixture with a concentrated solution of ammonium hydroxide (pH≈ 9-10) in the cold, extraction with ether (2x50 mL), and purification by column chromatography of the dried extracts gave the corresponding spiranes **17-20** as brown viscous oils (table 1). $^1$H NMR data and elemental analysis of the products are given below.

**17:** $^1$H NMR ($CDCl_3$) δ 1.10 (3H, t, J = 7.2 Hz, N-$CH_2$**$CH_3$**), 1.27 (1H, dd, J = 12.8 Hz, 4-$H_{ax}$), 1.36 (3H, d, J = 7.2 Hz, 5-$CH_3$), 1.56-1.82 (4H, m, 3'/5'-H ), 2.15-2.60 (4H, m, 2'/6'-H ), 2.45 (2H, q, J = 7.2 Hz, N-**$CH_2$**$CH_3$), 3.26 (1H, m, 5-H), 3.67 (1H, d, $J_{AB}$ = 15.5 Hz, 1-$H_A$), 4.09 (1H, d, $J_{BA}$ = 15.5 Hz, 1-$H_B$), 7.10-7.33 (4H, m, phenyl protons); Anal. Calcd for $C_{17}H_{26}N_2$: C, 79.07; H, 10.08; N, 10.85. Found: C, 79.33; H, 9.93; N, 10.57.

**18:** $^1$H NMR ($CDCl_3$) δ 1.07 and 1.11 (3H, 2t, each, J = 7.2 Hz, N-$CH_2$**$CH_3$**), 1.22 (1H, dd, J = 10.9, 13.6 Hz, 4-$H_{ax}$), 1.35 and 1.36 (3H, 2d, each, J = 7.2 Hz, 5-$CH_3$), 1.48 and 1.50 (3H, 2d, each, J = 6.8 Hz, 1-$CH_3$), 1.53-1.74 (4H, m, 3'/5'-H ), 2.20-2.56 (4H, m, 2'/6'-H), 2.41 (2H, q, J = 7.2 Hz, N-**$CH_2$**$CH_3$), 3.33 and 3.50 (1H, 2m, each, 5-H), 4.21 and 4.35 (1H, 2q, each, J = 6.8 Hz, 1-H), 7.11-7.26 (4H, m, phenyl protons); ); Anal. Calcd for $C_{18}H_{28}N_2$: C, 79.41; H, 10.29; N, 10.29. Found: C, 79.60; H, 9.99; N, 10.11.

**19:** $^1$H NMR ($CDCl_3$) δ 1.17 (3H, t, J = 7.1 Hz, N-$CH_2$**$CH_3$**), 1.25 (1H, dd, J = 10.6, 14.1 Hz, 4-$H_{ax}$), 1.30 (3H, d, J = 7.0 Hz, 5-$CH_3$), 1.54-1.79 (4H, m, 3'/5'-H), 2.37 (3H, s, 7-$CH_3$), 2.40-2.63 (4H, m, 2'/6'-H), 2.43 (2H, q, J = 7.1 Hz, N-**$CH_2$**$CH_3$), 3.22 (1H, m, 5-H), 3.59 (1H, d, $J_{AB}$ = 15.3 Hz, 1-$H_A$), 3.62 (1H, d, $J_{BA}$ = 15.3 Hz, 1-$H_B$), 6.90-7.20 (3H, m, phenyl protons); Anal. Calcd for $C_{18}H_{28}N_2$: C, 79.41; H, 10.29; N, 10.29. Found: C, 78.89; H, 10.58; N, 10.47.

**20:** $^1$H NMR ($CDCl_3$) δ 1.26 (1H, dd, J = 10.9, 13.6 Hz, 4-$H_{ax}$), 1.32 and 1.34 (3H, 2d, each, J = 7.1 Hz, 5-$CH_3$), 1.46 and 1.49 (3H, 2d, each, J = 6.9 Hz, 1-$CH_3$), 1.55-1.74 (4H, m, 3'/5'-H), 2.30-2.60 (4H, m, 2'/6'-H), 3.31 (1H, m, 5-H), 3.46 and 3.51 (2H, 2s, each, N-**$CH_2$**Ph), 4.20 and 4.34 (1H, 2q, each, J = 6.9 Hz, 1-H), 7.07-7.35 (9H, m, arom. protons); Anal. Calcd for $C_{23}H_{30}N_2$: C, 82.63; H, 8.98; N, 8.38. Found: C, 82.80; H, 8.69; N, 8.50.

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**References**

1 Kuznetsov V.V., *Khim. Farm. Zh.*, 25, 61 (1991), C.A., 115, 118826 (1991).

2 Kuznetsov V.V., Prostakov N.S., *Khim. Geterotsikl. Soedin.*, 1, 3 (1994), C.A., 121, 255518 (1994).

3 a) Kuznetsov V.V., Naumov Yu.I., Minaev L. I., Andreeva E. I., Prostakov N. S., *Khim. Farm. Zh.*, 25, 24 (1991), C.A., 115, 135887 (1991); b) Kuznetsov V.V., Lantsetov S. V., Andreeva E. I., Prostakov N. S., *Khim. Farm. Zh.*, 28, 21 (1994), C.A., 122, 55272 (1995); c) Kouznetsov V., *Rev. Latinoamer. Quím.*, 25, 132 (1997).

4 Kuznetsov V.V., Lantsetov S.V., Aliev A., Varlamov A.V., Prostakov N.S., *Khim. Geterotsikl. Soedin.*, 11, 1528 (1991), C.A., 117, 233881 (1992).

5 Kouznetsov V., Palma A., Salas S., Vargas L., Zubkov F., Varlamov A., Martínez J., *J. Heterocycl. Chem.*, 34, 1591 (1997).

6 Kouznetsov V.V., Lantsetov S.V., Aliev A., Varlamov A.V., Prostakov N.S., *Zh. Org. Khim.*, 28, 74 (1992), C.A., 117, 171194 (1992).

7 The detailed results from these studies will be published elsewhere.

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