Chemistry of Heterocyclic Compounds, Vol. 37, No. 10, 2001

SYNTHESIS AND CONVERSIONS OF SUBSTITUTED 4,5-DIHYDRO-3H-SPIRO[BENZ-2-AZEPINE-3,1'-CYCLOHEXANES]

A. V. Varlamov, F. I. Zubkov, E. V. Lazareva, A. I. Chernyshev, and D. G. Grudinin

On oxidizing substituted 1,2,4,5-tetrahydro-3H-spiro[benz-2-azepine-3,1'-cyclohexanes] with potassium permanganate under phase-transfer catalysis conditions the corresponding 4,5-dihydro derivatives are formed in quantitative yield. By the action of allyl- and benzylmagnesium halides 5-methyl-4,5-dihydro-3H-spiro[benz-2-azepine-3,1'-cyclohexane] is converted into 5-methyl-1,2,4,5-tetrahydro-1-allyl(benzyl)-3H-spiro[benz-2-azepine-3,1'-cyclohexane], and by reaction with phenoxyketene and dichlorocarbene into the corresponding 2-oxoazetidino[4,1-a]- and 1,1-dichloroaziridino[3,1-a]benz-2-azepines.

Keywords: benz-2-azepines, cyclic imines, phase-transfer catalysis, oxidation, cycloaddition.

Cyclic Schiff's bases of the pyrrolidine and piperidine series, being relatively easily available, are used widely in the synthesis of polycyclic nitrogen-containing systems [1,2]. The Bischler-Napieralski reaction enables the simplest condensed imines of the 3,4-dihydroisoquinoline series to be obtained [3,4]. The interaction of the latter with nucleophilic reagents gave a large number of biologically active compounds including the alkaloids apomorphine, cryptaustoline, and berberine.

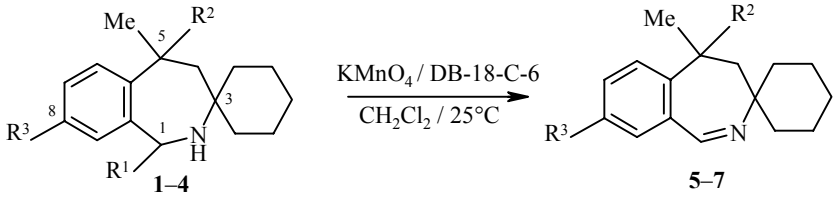
The synthesis and chemistry of azomethines containing an azepine ring have been studied significantly less and there is extremely limited information in the literature on the synthesis of cyclic imines of the benz-2-azepine series [5-7]. Meanwhile these difficultly available compounds are interesting for obtaining analogs of alkaloids of the tetrahydroisoquinoline and homoberberine series.

A report has been published recently on the possibility of oxidizing 1,2,3,4-tetrahydroisoquinolines to the corresponding 3,4-dihydro derivatives under phase transfer catalysis conditions [8]. This method was used in the present work to obtain imines of the benz-2-azepine series, *viz*. substituted 4,5-dihydro-3H-spiro[benz-2-azepine-3,1'-cyclohexanes]. 5-Methyl- (**1**), 5-methyl-8-nitro- (**2**), 5,5-dimethyl- (**3**), and 1,5-dimethyl- (**4**) 1,2,4,5-tetrahydro-3H-spiro[benz-2-azepine-3,1'-cyclohexanes] synthesized by us previously, were studied in the oxidation reaction [9-11].

The oxidation of compounds **1-3** was carried out with a 1.5 to 2 molar excess of $KMnO_4$ and DB-18-C-6 (5-10 mol.%) was used as phase-transfer catalyst. The azomethines **5-7** were formed in this way in 90-95% yield. They were viscous bright yellow oils (**5**, **7**) or yellow crystals (**6**), extremely stable on storage.

Russian Peoples Friendship University, Moscow 117198; e-mail: avarlamov@sci.pfu.edu.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1368-1375, October, 2001. Original article submitted November 17, 1999.

0009-3122/01/3710-1251$25.00



1–4 **5–7**

1–3 R^1 = H; **4** R^1 = Me; **1**, **2**, **4–6** R^2 = H; **3**, **7** R^2 = Me;
1, **3**, **4**, **5**, **7** R^3 = H; **2**, **6** R^3 = NO_2

The oxidation of azepine **3**, having two methyl groups at $C_{(5)}$, occurs 3-4 times more rapidly than its monosubstituted analogs **1** and **2**. This is evidently linked with the flattening of the benzylamino fragment of the molecule which makes easier the approach of permanganate anion to it.

One of the common methods of obtaining N-benzylideneamines is the decomposition of the corresponding N-tosylbenzylamines by the action of base [12]. However we were unable to effect the analogous conversion of the tosylate **8** of benzazepine **1** to aldimine **5**. On refluxing the sulfamide **8** in *o*-xylene with an excess of sodium ethylate only the initial compound **8** was isolated from the reaction mixture together with a small quantity of resinified products.

Unlike to 5,5-dimethyl substituted benz-2-azepine **3** the oxidation of its 1,5-disubstituted analog **4** occurs with significantly more difficulty (it requires about a 20 fold excess of potassium permanganate) and ambiguously. A complex mixture of crystalline products was formed. We link the difficulty of oxidation both with steric hindrance of the proton at $C_{(1)}$ and with the possibility of side oxidation of the 1-CH_3 group of the 1,5-dimethyl-4,5-dihydrobenz-2-azepine formed initially.

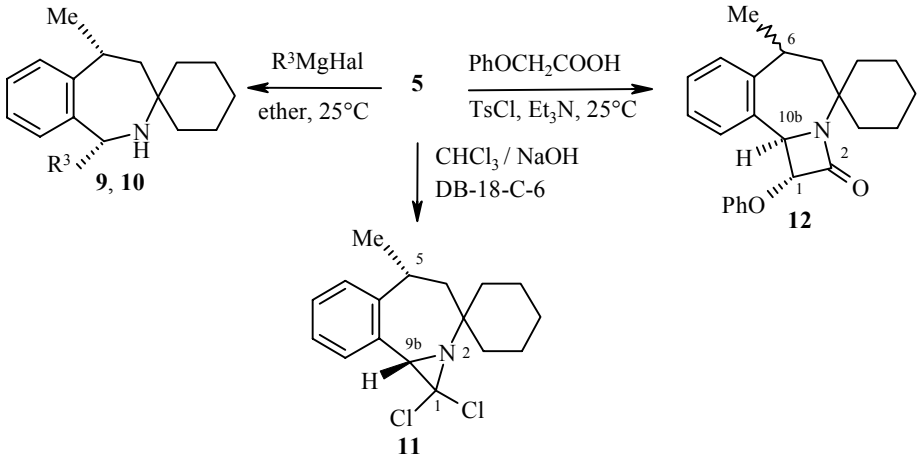
The structure of the synthesized Schiff's bases **5-7** was confirmed by a combination of spectral and chemical data. A narrow band was observed in the IR spectra of aldimines **5-7** at 1630-1640 cm^{-1} for the stretching vibrations of the C=N bond and the band for the stretching vibrations of the NH group at 3320-3350 cm^{-1}, characteristic of the initial amines, disappeared. The mass spectra were characterized by the presence of peaks for the molecular ions of medium intensity corresponding to the empirical formulas of the dihydroazepines **5-7**. The main direction of decomposition of their molecular ions was linked with the ejection of methyl, ethyl, and propyl radicals as a result of decomposition of the cyclohexane fragment with the formation of fragment ions of *m/z* [M^+-15], [M^+-29], and [M^+-43] respectively.

Unlike the ^{1}H NMR spectra of benz-2-azepines **1-3** [9,10] characteristic doublet signals for the 1-CH_AH_B protons at 3.62-4.20 ppm with a geminal coupling constant $^2J_{AB}$ = 15.1 Hz (**1,2**), and a singlet for the 1-CH_2 group with a chemical shift of 4.01 ppm (**3**) were absent from the spectra of Schiff's bases **5-7**. A narrow singlet signal for the HC=N proton with shift 8.31-8.41 ppm was observed at low field in the spectra of aldimines **5-7**. Pair comparison of the chemical shifts of the signals of corresponding protons in the spectra of benz-2-azepines **1-3** and of the compounds **5-7** obtained from them showed that the presence of an endocyclic azomethine double bond was displayed in a shift of the signals for the 4*a*-H and 4*e*-H protons towards low field by 0.3-0.5 ppm. The signals for the 5*a*-H protons in the spectra of compounds **5** and **6** were shifted towards high field, but to a lesser extent, Δ = -0.16-0.17 ppm.

We have studied certain chemical conversions of cyclic imines of the benz-2-azepine series using as example the most available 5-methyl-4,5-dihydro-3H-spiro[benz-2-azepine-3,1'-cyclohexane] (**5**) with a pseudoequatorial disposition of the 5-CH_3 group.

The addition of allylmagnesium bromide and benzylmagnesium chloride to azomethine **5** occurs stereoselectively with the formation of one geometric isomer. The yields of compounds **9** and **10** were 78 and 68% respectively. The structure of 1-substituted benz-2-azepines **9** and **10** was established by ^{1}H NMR spectroscopy. Analysis of the spectra measured previously for 1,5-dimethyl-1,2,4,5-tetrahydro-3H-spiro[benz-2-azepine-3,1'-cyclopentane] and 1,5-dimethyl-1,2,4,5-tetrahydro-3H-spiro[benz-2-azepine-3,1'-cyclohexane] (**4**)

with pseudoequatorial-equatorial and equatorial-axial disposition of the 5-CH_3 and 1-CH_3 methyl groups [9] shows the stereospecificity of the $^3J_{4e,5a}$ vicinal coupling constants. For isomers with an axial-axial disposition of the 5*a*-H and 1*a*-H protons this constant is 1.1 and 1.0 Hz, and for compounds with axial-equatorial 5*a*-H and 1*e*-H protons it is significantly greater – 4.6 and 4.8 Hz. In the spectra of compounds **9** and **10** the $^3J_{4e,5a}$ coupling constant was 1.5 and 0 Hz respectively, which suggests a pseudoequatorial orientation for the bulky substituents at $C_{(1)}$ in these derivatives.



9 $R^3 = CH_2CH{=}CH_2$; **10** $R^3 = CH_2Ph$

We note that due to the facile elimination of allyl and benzyl radicals from the molecular ions the mass spectra of amines **9** and **10** gave little information.

Cycloaddition reactions at the C=N bond of cyclic Schiff's bases are interesting from the point of view of both the stereochemistry of the process and the practical value of the resulting heterocycles (condensed aziridines and β-lactams). 4,5-Dihydrobenz-2-azepines have still not been studied in similar reactions.

The interaction of azomethine **5** with dichlorocarbene under conditions of the Makoshi reaction [13] leads to the bicyclic product **11** in low yield (19%). The presence of chlorine atoms in the molecule was confirmed qualitatively by a positive Beilstein test for halogen, and quantitatively by data of mass spectrometry. The cluster of peaks for the molecular ion of polycycle **11** with *m/z* 309, 311, and 313 has a distribution of intensities of 9 : 6 : 1 respectively, typical of dichloro substituted compounds.

The addition reaction of dichlorocarbene was also stereoselective. This follows from the presence in the ^{1}H NMR spectrum of aziridine **11** of one set of signals corresponding to the 9b-H, 4*a*-H, 4*e*-H, 5*a*-H, and 5*e*-CH_3 protons, which indicates the formation of a single geometric isomer according to the disposition of substituents at $C_{(5)}$ and $C_{(9b)}$. Applying arguments analogous to those given above in the analysis of the ^{1}H NMR spectra of compounds **9** and **10** it is possible to suggest an equatorial-equatorial linking of the aziridine and azepine rings for aziridine **11** (coupling constant $J_{4e,5a}$ = 0 Hz).

The [2+2] cycloaddition reaction of azomethine **5** to phenoxyketene generated in situ (Staudinger reaction) [14] leads to a new heterocyclic system, *viz*. azetidino[4,1-*a*]benz-2-azepine (**12**) in good yield (68%). The structure of bicyclic azetidinone **12** was confirmed by spectral methods. An intense band was observed in the IR spectrum for the stretching vibrations of the C=O bond at 1737 cm^{-1}, characteristic of the β-lactam fragment. The mass spectrum of compound **12** is characterized by the presence of an intense peak for the molecular ion with *m/z* 361 (100%), and also by the presence of peaks of fragment ions with *m/z* 268 [M^+-PhO] (22%) and 256 [M^+-PhCO] (6%). The stereochemistry of azetidino[4,1-*a*]benzazepine **12** was established by ^{1}H NMR spectroscopy.

The ^{1}H NMR spectrum of β-lactam **12** contains a double set of signals for each individual proton which indicates the formation of a mixture of two geometric isomers during the reaction. The ratio of the isomers, measured by the relative integrated intensities of the signals of corresponding protons was 52:48. In the 4.85-5.41 ppm region of the spectrum two pairs of doublet signals were recorded with chemical shifts 5.41, 5.07, and 5.15, 4.85 ppm and coupling constants ^3J = 2.1 and 1.8 Hz respectively. These signals are assigned to the 1-H and 10b-H protons of the β-lactam ring. There are many data in the literature on the ^{1}H NMR spectra of various classes of compounds containing a β-lactam fragment. It is possible to cite examples of compounds with N-methyl, N-benzyl [15], and N-phenyl [16] substituents, with methyl or phenyl substituents [15,16] and bromine atoms at the α-carbon atom relative to nitrogen, with alkyl or phenyl groups at the β-carbon atom [15,16], and also β-lactams annelated with various heterocycles [17,18]. Analysis of the values of the vicinal coupling constants between the α and β protons of the β-lactam shows their high stereospecificity. The coupling constant ^3J between protons occupying a *cis* orientation is 4.4-6.0, and between *trans* protons is 1.3-2.8 Hz. The values of the coupling constant $^3J_{1,10b}$ = 2.1 and 1.8 Hz in the spectrum of the mixture of isomers of compound **12** indicates a trans disposition of the 1-H and 10b-H protons in both isomers. Consequently the isomers must differ in the orientation of the β-lactam ring relative to the azepine ring. Direct measurement of the stereospecific coupling constants $^3J_{5e,6a}$ is difficult since the signals of the 6α-H of both isomers are complex multiplets and the 5*e*-H protons are masked by the complex multiplets of the cyclohexane ring protons. None the less, if the distance between the extreme components of the multiplets of the 6α-protons is equal to the sum of the coupling constants $^3J_{6a,\mathrm{Me}} + {}^3J_{5a,6a} + {}^3J_{5e,6a}$, then the greater value of the sum of the constants will apply to the multiplet signal of the isomer with a pseudoaxial orientation and the lesser to the equatorial orientation of the β-lactam ring (the $^3J_{6a,\mathrm{Me}}$ and $^3J_{5a,6a}$ constants have closely similar values for both isomers but $^3J_{5e,\,6a}$ differs by 3.5-3.8 Hz, which was mentioned above).

The measurements showed that the distance between the extreme components of the 6a-H multiplet with chemical shift 3.35 ppm (35.4 Hz) is 5.4 Hz greater than that of the multiplet at 3.19 ppm (30.0 Hz). Consequently the first multiplet is assigned to the isomer with pseudoaxial-equatorial and the second to the pseudoequatorial-equatorial linkage of the β-lactam and azepine rings.

We have therefore proposed a convenient method for obtaining substituted 4,5-dihydro-3H-benz-2-azepines and also have studied certain conversions at the C=N bond of the synthesized aldimines.

EXPERIMENTAL

The IR spectra were obtained on a UR 20 spectrometer in KBr disks (for crystalline substances) or in a film (for liquids). The mass spectra were recorded on a Varian MAT 112 instrument with direct injection of the sample into the ion source at an ionizing voltage of 70 eV. The ^{1}H NMR spectra of 3% solutions of substances in $CDCl_3$ were recorded at 30°C on a Bruker WP 200 instrument (operating frequency 200 MHz). Chemical shifts were measured relative to TMS as internal standard. Silufol UV 254 plates were used for thin layer chromatography (visualization with iodine vapor), and Al_2O_3 of zero activity according to Brockmann was used for column chromatography.

5-Methyl-4,5-dihydro-3H-spiro[benz-2-azepine-3,1'-cyclohexane] (5) and 5-Methyl-8-nitro-4,5-dihydro-3H-spiro[benz-2-azepine-3,1'-cyclohexane] (6). Crown ether DB-18-C-6 (0.14 g, 0.42 mmol) and potassium permanganate (6.64 g, 0.042 mol) in 1/3 portions were added every 30 min to a solution of amine **1** or **2** (0.042 mol) in dichloromethane (100 ml) at 25°C. The mixture was stirred for 6 h and left overnight. The following day further $KMnO_4$ (0.042 mol) was added also in portions and the mixture was stirred for 8 h (check by TLC). The manganese dioxide was filtered off and washed with dichloromethane (500 ml). After distilling off the solvent the residue was dissolved in a mixture (20 ml) of 1:1 ether–hexane. The crown ether was filtered off and washed with hexane (2 × 10 ml). The filtrate was evaporated in vacuum, and imines **5** and **6** were obtained in a pure state.

Compound **5** was a viscous yellow oil, R_f 0.35 (ethyl acetate–hexane, 1:1). IR spectrum: 1633 cm^{-1} (C=N). Mass spectrum, *m/z* (I_{rel}, %): 227 (M^+, 20), 212 (13), 198 (24), 186 (36), 184 (100), 131 (50), 117 (12), 115 (9), 98 (17), 91 (56), 77 (22). ^{1}H NMR spectrum: δ, ppm, *J* (Hz): 8.31 (1H, s, 1-H); 7.20-7.35 (4H, m, C_6H_4); 3.12 (1H, m, $^3J_{5a,Me}$ = 6.7, $^3J_{5a,4a}$ = 11.1, $^3J_{5a,4e}$ = 3.7, 5*a*-H); 2.07 (1H, dd, $^2J_{4a,4e}$ = 14.4, $^3J_{4e,5a}$ = 3.7, 4*e*-H); 1.73 (1H, dd, $^2J_{4a,4e}$ = 14.4, $^3J_{4a,5}$ = 11.1, 4*a*-H); 1.30-1.80 (10H, m, C_6H_{10}); 1.34 (3H, d, $^3J_{5a,Me}$ = 6.7, 5-Me). Found, %: C 84.33; H 9.38; N 9.36. $C_{16}H_{21}N$. Calculated, %: C 84.58; H 9.69; N 6.17. Yield 95%.

Compound **6** formed yellow crystals; mp 78-80°C (hexane–ethyl acetate), R_f 0.59 (ethyl acetate–hexane 1 : 1). IR spectrum, ν, cm^{-1}: 1636 (C=N), 1352 (NO_2 sym.), 1519 (NO_2 asym.). Mass spectrum, *m/z* (I_{rel}, %): 272 (M^+, 9), 267 (90), 253 (48), 239 (65), 228 (35), 217 (52), 203 (100), 200 (78). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 8.41 (1H, s, 1-H), 8.26 (1H, d, $^4J_{9,7}$ = 2.4, 9-H); 8.16 (1H, d, $^4J_{7,9}$ = 2.4, $^3J_{7,6}$ = 8.5, 7-H); 7.47 (1H, d, $^3J_{7,6}$ = 8.5, 6-H); 3.17 (1H, m, $^3J_{5,Me}$ = 7.0, $^3J_{4e,5a}$ = 3.4, $^3J_{4a,5a}$ = 10.7, 5-H); 2.13 (1H, dd, $^2J_{4a,4e}$ = 14.7, $^3J_{4e,5a}$ = 3.4, 4*e*-H); 1.76 (1H, dd, $^2J_{4a,4e}$ = 14.7, $^3J_{4a,5a}$ = 10.7, 4*a*-H); 1.41 (3H, d, $^3J_{5,Me}$ = 7.0, 5-Me); 1.30-1.80 (10H, m, C_6H_{10}). Found, %: C 70.61; H 7.33; N 9.97. $C_{16}H_{20}N_2O_2$. Calculated, %: C 70.59; H 7.35; N 10.29. Yield 91%.

5,5-Dimethyl-4,5-dihydro-3H-spiro[benz-2-azepine-3,1'-cyclohexane] (7). Crown ether DB-18-C-6 (0.18 g, 0.50 mmol) was added to a solution of compound **3** (2.43 g, 0.01 mol) in dichloromethane (50 ml) at 25°C and then potassium permanganate (1.58 g, 0.01 mol) was added in three equal portions every 30 min. The mixture was stirred for 6 h (check by TLC). The manganese dioxide was filtered off, and washed with dichloromethane (200 ml). The crown ether was separated as described above. After distilling off the solvent compound **7** (2.16 g, 90%) was obtained as a viscous yellow oil, R_f 0.55 (ethyl acetate–hexane, 1:1). IR spectrum, ν: 1638 cm^{-1} (C=N). Mass spectrum, *m/z* (I_{rel}, %): 241 (M^+, 70), 226 (36), 212 (20), 198 (30), 186 (36), 145 (100), 129 (54), 117 (20), 115 (38), 105 (2), 102 (12), 98 (10), 91 (36), 77 (26). ^{1}H NMR spectrum, δ, ppm: 8.41 (1H, s, 1-H); 7.15-7.45 (4H, m, C_6H_4); 2.08 (2H, s, 4-CH_2); 1.37 (6H, s, 5-Me_2); 1.15-1.80 (10H, m, C_6H_{10}). Found, %: C 84.47; H 9.29; N 5.62. $C_{17}H_{23}N$. Calculated, %: C 84.65; H 9.54; N 5.81.

5-Methyl-2-tosyl-1,2,4,5-tetrahydro-3H-spiro[benz-2-azepine-3,1'-cyclohexane] (8). Tosyl chloride (4.75 g, 24.9 mmol), Na_2CO_3 (3.95 g, 37.26 mmol), and water (20 ml) were added to a solution of amine **1** (3.03 g, 13.23 mmol) in dichloromethane (50 ml). The mixture was boiled for 6 h. Further tosyl chloride (2.50 g, 12.0 mmol) and sodium hydroxide (1.0 g, 25 mmol) were added and the mixture was refluxed for 24 h (check by TLC). The mixture was poured into water, extracted with dichloromethane (4 × 50 ml), the extract was washed with saturated sodium carbonate solution (2 × 100 ml), and dried over magnesium sulfate. After distilling off the dichloromethane the residue was recrystallized twice from hexane. Compound **8** (2.62 g, 57%) was obtained as white crystals of mp 126-128°C, R_f 0.58 (ethyl acetate–hexane, 1:1). IR spectrum, ν, cm^{-1}: 1161 (SO_2 sym.), 1334 (SO_2 asym.). Mass spectrum, *m/z* (I_{rel}, %): 273 (19), 240 (35), 228 (36), 202 (100). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 7.27 (2H, AA', α-H); 7.10-7.25 (4H, m, C_6H_4); 7.05 (2H, BB', β-H); 4.82 (2H, s, 1-CH_2); 2.96 (1H, m, $^3J_{Me,5a}$ = 7.0, $^3J_{4e,5a}$ = 2.4, $^3J_{4a,5a}$ = 11.0, 5*a*-H); 2.33 (3H, s, Me-Tos); 2.24 (1H, dd, $^2J_{4a,4e}$ = 15.3, $^3J_{4e,5a}$ = 2.4, 4*e*-H); 1.76 (1H, dd, $^2J_{4e,4a}$ = 15.3, $J_{4a,5a}$ = 11.0, 4*a*-H); 1.34 (3H, d, $^3J_{Me,5a}$ = 7.0, 5-Me); 1.20-2.30 (10H, m, C_6H_{10}). Found, %: C 71.85; H 7.68; N 3.94. $C_{23}H_{29}NO_2S$. Calculated, %: C 72.06; H 7.57; N 3.66.

1-Allyl-5-methyl-1,2,4,5-tetrahydro-3H-spiro[benz-2-azepine-3,1'-cyclohexane] (9). A solution of imine **5** (4.04 g, 17.66 mmol) in absolute ether (10 ml) was added with stirring to allylmagnesium bromide, obtained from magnesium shavings (1.28 g, 52.67 mmol) and allyl bromide (2.30 ml, 26.49 mmol) in absolute ether (40 ml). The mixture was boiled for 1 h, then cooled, and poured onto crushed ice (20 ml). The resulting emulsion was decomposed with saturated ammonium chloride solution, extracted with ether (5 × 20 ml), and dried over magnesium sulfate. After removing the solvent the residue was purified on a column (2 × 3 cm) of aluminum oxide, eluting with ether. The ether was distilled off. The residue, a viscous yellow oil, was dissolved in absolute ether, and converted into the hydrochloride with dioxane hydrochloride. The hydrochloride was filtered off, and washed with ethyl acetate (3 × 50 ml). Compound **9** hydrochloride (4.04 g) was obtained as white crystals of mp 162-169°C. On decomposing the hydrochloride with 5% ammonia solution amine **9**

(3.70 g, 78%) was obtained as a colorless oil, R_f 0.69 (ethyl acetate–hexane, 1:3). IR spectrum, ν, cm^{-1}: 1634 (C=C), 3331 (N-H). Mass spectrum, *m/z* (I_{rel}, %): 228 (100), 211 (2), 200 (5), 129 (18), 115 (18), 105 (16), 99 (27), 91 (32), 81 (18), 77 (38). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 7.05-7.30 (4H, m, C_6H_4); 5.98 (1H, m, $^3J_{2',1'A}$ = 5.8, $^3J_{2',1'B}$ = 7.9, $^3J_{2',3'\text{-}trans}$ = 15.9, $^3J_{2',3'\text{-}cis}$ = 10.1, 2'-H); 5.20 (1H, d, $^3J_{2',3'\text{-}trans}$ = 15.9, 3'-*trans*-H), 5.13 (1H, d, $^3J_{2',3'\text{-}cis}$ = 10.1, 3'-*cis*-H); 4.07 (1H, dd, $^3J_{1a,1'A}$ = 4.9, $^3J_{1a,1'B}$ = 9.2, 1*a*-H); 3.33 (1H, m, $^3J_{5a,Me}$ = 7.0, $^3J_{5a,4e}$ = 1.5, $^3J_{5a,4a}$ = 11.0, 5*a*-H); 2.75 (1H, m, $^3J_{2',1'A}$ = 5.8, $^3J_{1a,1'A}$ = 4.9, $^2J_{1'A,1'B}$ = 13.7, 1'A-H); 2.54 (1H, m, $^3J_{2',1'B}$ = 7.9, $^3J_{1a,1'B}$ = 9.2, $^2J_{1'A,1'B}$ = 13.7, 1'B-H); 1.64 (1H, dd, $^3J_{5a,4e}$ = 1.5, $^2J_{4e,4a}$ = 13.7, 4*e*-H); 1.35 (3H, d, $^3J_{5a,Me}$ = 7.0, 5-Me); 1.11 (1H, dd, $^3J_{5a,4a}$ = 11.0, $^2J_{4a,4e}$ = 13.7, 4*a*-H); 1.20-2.00 (10H, m, C_6H_{10}). Found, %: C 84.44; H 9.90; N 5.38. $C_{19}H_{27}N$. Calculated, %: C 84.76; H 10.04; N 5.20.

1-Benzyl-5-methyl-1,2,4,5-tetrahydro-3H-spiro[benz-2-azepine-3,1'-cyclohexane] (10). Imine **5** (5.00 g, 22.03 mmol) dissolved in absolute ether (10 ml) was added with stirring to benzylmagnesium chloride, obtained from magnesium shavings (2.14 g, 88.0 mmol) and benzyl chloride (4.92 ml, 44.0 mmol) in absolute ether (70 ml), and the mixture was boiled for 1 h. The mixture was cooled, and poured onto crushed ice (40 ml). The resulting emulsion was decomposed with saturated ammonium chloride solution, extracted with ether (4 × 50 ml), and dried over magnesium sulfate. After distilling off the ether, the residue was recrystallized from a hexane–ethyl acetate mixture. Amine **10** (4.77 g, 68%) was obtained as white crystals; mp 122-125°C, R_f 0.49 (ethyl acetate–hexane, 1 : 3). IR spectrum, ν: 3355 cm^{-1} (N–H). Mass spectrum, *m/z* (I_{rel}, %): 228 (4), 227 (15), 213 (7), 212 (5), 207 (4), 194 (41), 180 (16), 128 (14), 107 (100), 94 (50), 91 (34), 77 (89). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 7.10-7.40 (9H, m, H arom.); 4.22 (1H, dd, $^3J_{1a,1'A}$ = 3.7, $^3J_{1a,1'B}$ = 10.7, 1*a*-H); 3.35 (1H, dd, $^2J_{1'A,1'B}$ = 13.1, $^3J_{1a,1'A}$ = 3.7, 1'A-H); 3.35 (1H, m, $^3J_{5a,Me}$ = 7.0, $^3J_{5a,4a}$ = 10.7, 5*a*-H); 2.99 (1H, dd, $^2J_{1'A,1'B}$ = 13.1, $^3J_{1a,1'B}$ = 10.7, 1'B-H); 1.48 (1H, d, $^2J_{4a,4e}$ = 13.7, $^3J_{5a,4e}$ = 0.0, 4*e*-H); 1.34 (3H, d, $^3J_{5a,Me}$ = 7.0, 5-Me); 1.14 (1H, dd, $^2J_{4a,4e}$ = 13.7, $^3J_{5a,4a}$ = 10.7, 4*a*-H); 0.80-1.70 (10H, m, C_6H_{10}). Found, %: C 86.41; H 9.29; N 4.18. $C_{23}H_{29}N$. Calculated, %: C 86.52; H 9.09; N 4.39.

1,1-Dichloro-5-methyl-2,4,5,9b-tetrahydro-3H-spiro[aziridino[3,1-*a*]benz-2-azepine-3,1'-cyclohexane] (11). Powdered sodium hydroxide (0.88 g, 22.00 mmol) was added with vigorous stirring to a solution of imine **5** (0.50 g, 2.20 mmol) and DB-18-C-6 (0.039 g, 0.11 mmol) in chloroform (10 ml). The mixture was boiled for 30 h (check by TLC). The solid inorganic salt was filtered off, and washed with chloroform (2 × 25 ml). After distilling off the chloroform the residue was chromatographed on aluminum oxide (1 × 30 cm), eluting with ethyl acetate–hexane, 1 : 30. Compound **11** (0.13 g, 19%) was isolated as a bright yellow oil, R_f 0.53 (ethyl acetate–hexane, 1 : 3). Mass spectrum, *m/z* (I_{rel}, %): 313 (7), 311 (59), 309 (M^+, 77), 229 (71), 228 (100), 208 (83), 179 (80), 131 (95), 129 (77), 115 (76), 103 (44), 91 (55), 81 (70), 77 (36). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 7.15-7.25 (4H, m, C_6H_4); 4.90 (1H, s, 9b(ax)-H); 3.30 (1H, m, $^3J_{5a,Me}$ = 7.0, $^3J_{5a,4a}$ = 11.0, $^3J_{5a,4e}$ = 0.0, 5*a*-H); 1.65 (1H, d, $^2J_{4a,4e}$ = 13.7, $^3J_{5a,4e}$ = 0.0, 4*e*-H); 1.37 (3H, d, $^3J_{5a,Me}$ = 7.0, 5-Me); 1.16 (1H, dd, $^2J_{4a,4e}$ = 13.7, $^3J_{5a,4a}$ = 11.0, 4*a*-H); 1.20-2.20 (10H, m, C_6H_{10}). Found, %: C 65.88; H 6.55; N 4.80. $C_{17}H_{21}Cl_2N$. Calculated, %: C 66.02; H 6.79; N 4.53.

6-Methyl-2-oxo-1-phenoxy-3,5,6,10b-tetrahydro-4H-spiro[azetidino[4,1-*a*]benz-2-azepine-4,1'-cyclohexane] (12). Phenoxyacetic acid (0.28 g, 1.85 mmol) and triethylamine (0.44 ml, 3.20 mmol) were added sequentially to a solution of tosyl chloride (0.35 g, 1.85 mmol) in dichloromethane (10 ml), and then after 10 min imine **5** (0.42 g, 1.85 mmol) dissolved in dichloromethane (2 ml) was added. The mixture was stirred for 3 h (check by TLC). A solution of tosyl chloride (0.35 g, 1.85 mmol), phenoxyacetic acid (0.28 g, 1.85 mmol), and triethylamine (0.44 g, 3.20 mmol) in dichloromethane (10 ml) prepared as described above was then added. The mixture was stirred for a further 4 h. The dichloromethane was distilled off, and the residue purified on a short column (1.5 × 4 cm) of aluminum oxide, eluting with ethyl acetate–hexane, 1 : 10. A mixture of isomers (ratio 52 : 48) of compound **12** (0.44 g, 68%) was obtained as a yellow oil of R_f 0.56 and 0.62 (ethyl acetate–hexane, 1 : 10). IR spectrum, ν: 1737 cm^{-1} (C=O). Mass spectrum, *m/z* (I_{rel}, %): 362 (84), 361 (M^+, 100), 270 (8), 268 (22), 256 (6), 243 (9), 226 (18), 225 (21), 211 (28), 200 (26), 196 (9), 183 (13), 172 (88), 169 (15), 155 (33), 144 (61), 143 (95), 142 (34), 131 (72), 130 (89), 129 (94), 128 (88), 124 (68), 115 (83), 105 (27),

94 (42), 91 (44), 81 (79), 77 (41), 69 (13), 65 (29). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): a) predominant isomer: 6.90-7.40 (9H, m, H arom); 5.15 (1H, d, $^3J_{10b,1}$ = 1.8, 1-H); 4.85 (1H, d, $^3J_{10b,1}$ = 1.8, 10b-H); 3.35 (1H, m, 6-H); 1.38 (3H, d, $^3J_{6,Me}$ = 6.7, 6-Me); 1.20-2.00 (10H, m, C_6H_{10}); b) minor isomer: 6.90-7.40 (9H, m, H arom); 5.41 (1H, d, $^3J_{10b,1}$ = 2.1, 1-H); 5.07 (1H, d, $^3J_{10b,1}$ = 2.1, 10b-H); 3.19 (1H, m, 6-H); 1.45 (3H, d, $^3J_{6,Me}$ = 7.3, 6-Me); 1.20-2.00 (10H, m, C_6H_{10}). Found, %: C 83.40; H 8.03; N 4.13. $C_{24}H_{27}NO_2$. Calculated, %: C 83.48; H 7.82; N 4.06.

The work was carried out with the financial support of the Russian Fund for Fundamental Investigations, grant 99-03-32942a.

REFERENCES

1. K. Blaha and O. Cervinka, *Adv. Heterocycl. Chem.*, **6**, 147 (1966).
2. A. Giovannini, D. Savoia, and A. Umani-Ronchi, *J. Org. Chem.*, **54**, 228 (1989).
3. N. Itoh and S. Sugasawa, *Tetrahedron*, **1**, 45 (1957).
4. W. M. Whaley and W. H. Hartung, *J. Org. Chem.*, **14**, 650 (1949).
5. R. C. Bernotas, G. Adams, and A. A. Carr, *Tetrahedron*, **52**, 6519 (1996).
6. R. Alonso, K. Takahashi, B. Schönenberger, and A. Brossi, *Heterocycles*, **26**, 1595 (1987).
7. S. Kasparek, *Adv. Heterocycl. Chem.*, **17**, 45 (1974).
8. A. P. Venkov and S. M. Statkova-Abeghe, *Tetrahedron*, **52**, 1451 (1996).
9. V. V. Kuznetsov, S. V. Lantsetov, A. E. Aliev, A. V. Varlamov, and N. S. Prostakov, *Zh. Org. Khim.*, **28**, 74 (1992).
10. V. Kouznetsov, A. Palma, S. Salas, L. Y. Vargas, F. Zubkov, A. Varlamov, and I. R. Martinez, *J. Heterocycl. Chem.*, **34**, 1591 (1997).
11. V. V. Kuznetsov, S. V. Lantsetov, A. E. Aliev, A. V. Varlamov, and N. S. Prostakov, *Khim. Geterotsikl. Soedin.*, 1528 (1991).
12. G. Simson and H. G. Pollie, *J. Chem. Soc.*, 487 (1965).
13. A. F. Khlebnikov, T. Yu. Nikiforova, M. S. Novikov, and R. R. Kostikov, *Synthesis*, 677 (1997).
14. M. Miyake, N. Tokutake, and M. Kirisawa, *Synthesis*, 833 (1983).
15. K. D. Barrow and T. M. Spotswood, *Tetrahedron Lett.*, 3325 (1965).
16. H. B. Kagan, J.-J. Basselier, and J.-L. Luche, *Tetrahedron Lett.*, 941 (1964).
17. G. F. Lelyak, E. A. Povalyaeva, A. A. Filatova, A. S. Mezentsev, A. I. Chernyshev, M. G. Korotkov, and O. G. Kesarev, *Khim.-farm. Zh.*, **23**, 76 (1989).
18. T. Kametani, K. Kigasawa, M. Hiiragi, K. Wakisaka, H. Sugi, and K. Tanigawa, *Heterocycles*, **12**, 795 (1979).