Amino Acids (2012) 43:1225–1231
DOI 10.1007/s00726-011-1187-5

ORIGINAL ARTICLE

Synthesis of hydroxydiamines and triamines via reductive cleavage of N–N bond in substituted pyrazolidines

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Received: 18 October 2011 / Accepted: 24 November 2011 / Published online: 15 March 2012

Abstract Aliphatic polyamines, being a versatile class of organic compounds, are widely used in many fields of medicine and organic chemistry. However, the general approach to the synthesis of chiral aliphatic polyamines has been still undeveloped. Here, we describe a new method for the synthesis of chiral trifunctional amino compounds, namely hydroxydiamines and triamines. The initial compounds, namely substituted hydroxy- or aminopyrazolidines and pyrazolines, are readily available using convenient stereoselective methods developed earlier by us. The proposed method allows synthesizing of chiral diaminoalcohols and triamines, which are the analogs of a well-known anti-TB drug, namely ethambutol, and cannot be obtained alternatively. The key step of the synthesis is N–N bond cleavage in substituted hydroxy- or aminopyrazolidines and pyrazolines with borane-tetrahydrofuran complex; other known methods for N–N bond cleavage turned out to be ineffective. The main advantage of the proposed method is the retention of a certain configuration of stereocenters in the course of the reaction. Six new chiral diasteomerically pure substituted hydroxydiamines and triamines and the enantiomerically pure triamine with four chiral centers were synthesized and characterized using NMR, IR and mass spectroscopy, as well as elemental analysis.

Keywords Hydroxydiamines · Triamines · Ethambutol · Pyrazolines · Pyrazolidines · Diasteomerically pure polyamines

Abbreviations

Anti-TB drugs	Antituberculosis drugs
THF	Tetrahydrofuran

Introduction

Being effective complexing agents, polyamines are widely used as catalysts and chiral reagents in asymmetric organic synthesis (Kizirian 2008). Due to a broad spectrum of biological activities, aliphatic polyamines are applicable in medicine (Cooper et al. 2004, 2009; Agostinelli et al. 2007; Minarini et al. 2010). Polyamine metabolism is a rational target for drug design, especially for curing diseases connected with parasites or uncontrolled proliferation (Bergeron et al. 2001; Wallace and Niiranen 2007; Casero and Marton 2007; Casero and Woster 2009). For instance, a front-line antituberculous drug, ethambutol (Fig. 1), that is, dihydroxydiamine [(2*S*,2′*S*)-2,2′-(ethane-1,2-diyldiimino)dibutan-1-ol] (Yendapally and Lee 2008), displays bacteriostatic properties against actively growing TB bacilli. It impedes the formation of a cell wall, thus increasing its permeability.

Tense epidemic situation with tuberculosis and permanently increasing resistance of pathogens to drugs dictate an urgent need to find and develop new efficient means of combating the disease (Vergara et al. 2009). Therefore, the synthesis of new structural analogs of ethambutol and their

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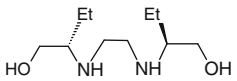


Fig. 1 Anti-TB drug ethambutol

preclinical testing in vitro can bring to life new modifications of compounds possessing antituberculous activity (Jia et al. 2005). Recently, it was demonstrated that nitrogen-containing compounds, such as diaminoalcohols and triamines, possess antituberculous (Nikonenko et al. 2007) and antiparasitic (Heby et al. 2007) activities. It should be emphasized that both natural and synthetic precursors should be considered in drug design since the list of the available natural compounds is limited. The idea of the so-called semisynthetic approach (Weisell et al. 2010) implies further modification of functional groups of natural compounds not affecting carbon skeletons (usually sugars), but in such cases it is difficult to obtain enantiomers that do not exist in nature. A number of methods for the synthesis of diamines (Robinson and Brown 1961; Stetter and Findeisen 1965; Aeberli and Houlihan 1969; Feuer and Brown 1970) have been reported. However, the general approach to the synthesis of chiral amino compounds with three or more functional groups has been still undeveloped. In the present paper, a relatively simple process for production of chiral polyamines is proposed. It combines the synthesis of functionally substituted pyrazolidines and pyrazolines with the follow-up step of N–N bond reductive cleavage in a heterocycle. The preliminary results have been published in (Sviridova et al. 2009).

Results and discussion

Various methods for reductive N–N and N–O bonds cleavage in organic compounds have been already developed. The reduction by active metals (Aeberli and Houlihan 1969) or boron compounds (Feuer and Brown 1970), hydrogenation on platinum group metals (Stetter and Findeisen 1965), and application of hydrazine hydrate on Raney nickel (Robinson and Brown 1961) should be mentioned as the most widely used methods. A number of chiral compounds, for example, γ-amino alcohols, or some other bifunctional compounds (Tufariello 1979; Kozikowski and Chen 1981; Kozikowski and Adamczyk 1983) have been obtained via N–O bond breaking in chiral isoxazolines and isoxazolidines. However, the reductive cleavage of chiral functionally substituted pyrazolidines and pyrazolines has not been studied yet.

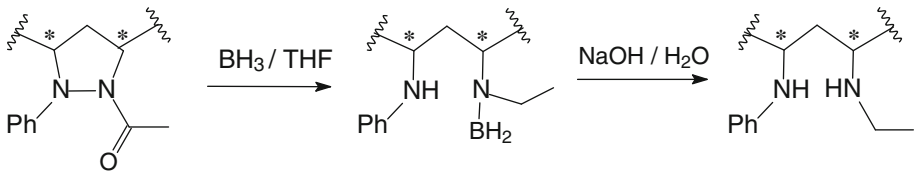
We chose diastereomerically pure 1-phenyl(acetyl)-2-acetyl(phenyl)-3,5-alkylsubstituted pyrazolidines and pyrazolines **1a**, **1b**, **2**, **8**, **9**, **12** for our study. The convenient way of synthesis of the starting compounds in diasteriomerically pure forms had been developed by us earlier (Sviridova et al. 2008; Tavtorkin et al. 2009). All aforementioned reductive methods were tested for the preparation of polyamines; however, the satisfactory results were obtained only for the borane-tetrahydrofuran complex (Feuer and Brown 1970; Enders et al. 1998, 1999). This reagent not only reduced N-acetyl group, but also splitted N–N bond in a heterocycle, giving rise to polyamines in the form of boron-containing complexes. The latter were decomposed by aqueous alkali to give amino compounds (Fig. 2).

It should be emphasized that the stereocenters of a starting heterocycle were not affected in this process, thus allowing the synthesis of chiral polyamines. N–N Bond breaking in pure diastereomers of γ-hydroxypyrazolidine derivatives **1a**, **1b**, **2** (produced using the previously described procedure (Sviridova et al. 2008) allowed to obtain diastereomerically pure 1,3,5-hydroxydiamines **3a**, **3b** and **4** (Fig. 3).

Diaminoalcohols **7** and **7′** are of special interest since they contain unsubstituted NH_2 group thus providing a possibility for further modification. To obtain compounds without N-ethyl group (**7**, **7′**), a reductive cleavage of N–N bond in NH-pyrazolidine **5** (in the form of a single diastereomer) and pyrazoline **6** was carried out. It should be noted that hydroxydiamine **7** obtained from pyrazolidine **5** had a configuration in which stereochemistry of 3-C center is retained, whereas for the mixture of diastereomeres **7′** (obtained from pyrazoline **6**) stereochemistry of 3-C was not preserved due to epimerization. However, the diastereomers derived from both pyrazoline and NH-pyrazolidine were almost spectrally identical. NMR ^{1}H spectra of **7** and **7′** differed only by the positions of low-informative signals for easily replaceable protons of NH, NH_2 and OH groups.

New triamines **10** and **11** were produced via the same method as hydroxydiamines (the splitting of aminopyrazolidines **8** and **9**). Dimethylamino derivative **8** obtained by reductive amination of the corresponding pyrazolidinyl substituted ketones (Tavtorkin et al. 2009) was used as a mixture of two diastereomers with the molar ratio of 3.5:1. Triamine **10** was isolated after reductive cleavage of **8** in the same diastereomeric ratio. The pyrazolidine **9** (isomeric to **8**) was used as an individual diastereomer, and the splitting of N–N bond yields only one diastereomer **11** (in a racemic form, Fig. 3). All of the synthesized polyamines, **3**, **4**, **7**, **10**, **11**, except **3b**, were uncrystallizable oils that absorb carbon dioxide while standing in air, thus impeding quantitative elemental analysis. Therefore, polyamines **3a**, **7** and **10** were converted to phenylisothiocarbamoyl derivatives and the latter were identified using elemental analysis. It should be mentioned that in all cases phenyl isothiocyanate interacts with the aliphatic amino group only, thus opening the possibility for regioselective synthesis of polyamine derivatives.

Fig. 2 The general scheme of chiral polyamine synthesis



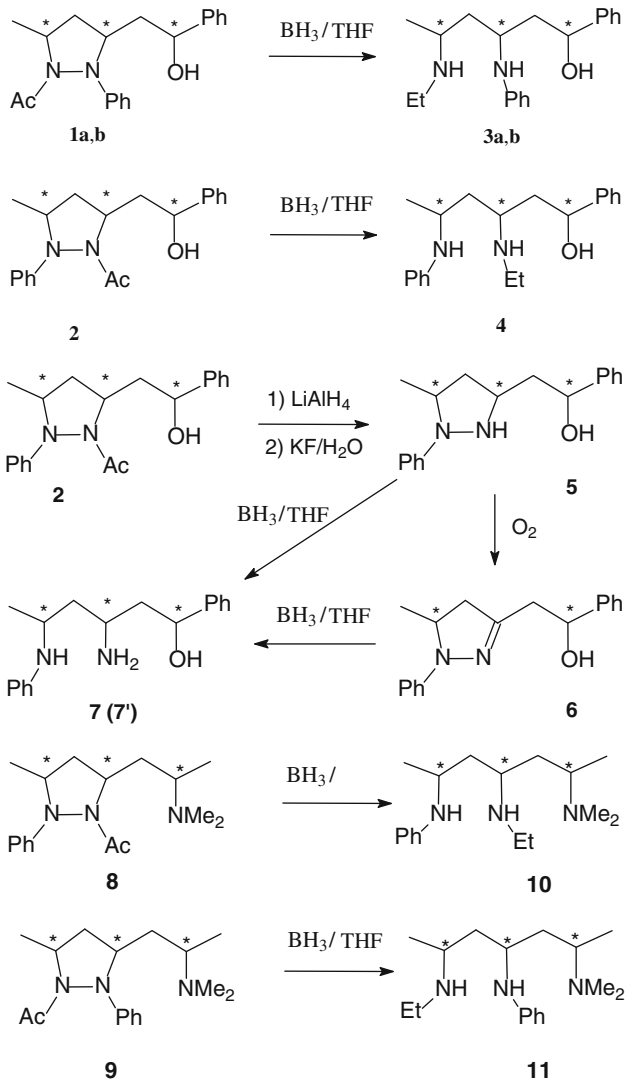


Fig. 3 Starting pyrazolines and pyrazolidines and final polyamines

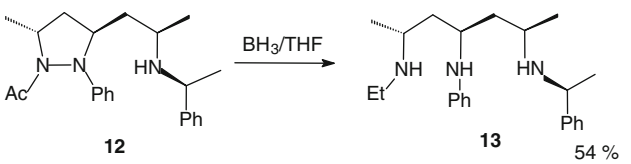


Fig. 4 Scheme for the synthesis of the enantiomerically pure triamine **13**

To confirm the fact that the reductive cleavage occurred without affecting the stereocenters, we introduced enantiomerically pure (1′*S*, 2′*S*, 3*S*, 5*S*)-1-acetyl-5-methyl-2-phenyl-3-[2-(1′-phenylethylamine)propyl]pyrazolidine **12** ($[\alpha]_D = +23.8$ ($c = 0.39$, $CHCl_3$) obtained as described in (Sviridova et al. 2008) into the reaction. As a result, the enantiomerically pure (*1′S, 2S, 4R, 6S*)-4-aniline-6-ethylamino-2-(1-phenylethylamino)heptane **13** was isolated (Fig. 4). Actually, the configurations of asymmetric atoms in compounds **12** and **13** were identical; the difference in *notations* was attributed only to the conversion of the substituent superiority. As there was no duplication of signals in the ^{1}H NMR spectra of **13**, we could assume that none of four stereocenters had been epimerized. Thus, we succeeded in obtaining the enantiomerically pure triamine **13** with four fixed stereocenters. Isolated yields of final products are given in Table 1.

The structure of polyamines was confirmed with ^{1}H NMR and mass spectrometry. The signal of acetyl group in the starting heterocycle in ^{1}H NMR spectra of polyamines disappeared; instead, characteristic signals of an ethyl group were observed. The signals of *o*- and *p*-protons of N-phenyl substituent were shifted from 6.9–7.2 to 6.5–6.7 ppm (in $CDCl_3$), thus confirming a cleavage of N–N bond. There was no doubling of signals in the spectra of diastereomeric polyamines **3**, **4**, **7**, and **11** indicating the retention of all stereocenters. The same situation was observed in case of enantiomerically pure triamine **13**. The only exception was compound **10**, since the starting heterocycle **8** was used as a mixture of two diastereomers.

Table 1 The isolated yields of polyamines

Initial compound	Linear product	Isolated yield of product, %
1a	**3a**	93
1b	**3b**	58
2	**4**	76
5	**7**	96
6	**7′**	79
8	**10**	61
9	**11**	52
12	**13**	54

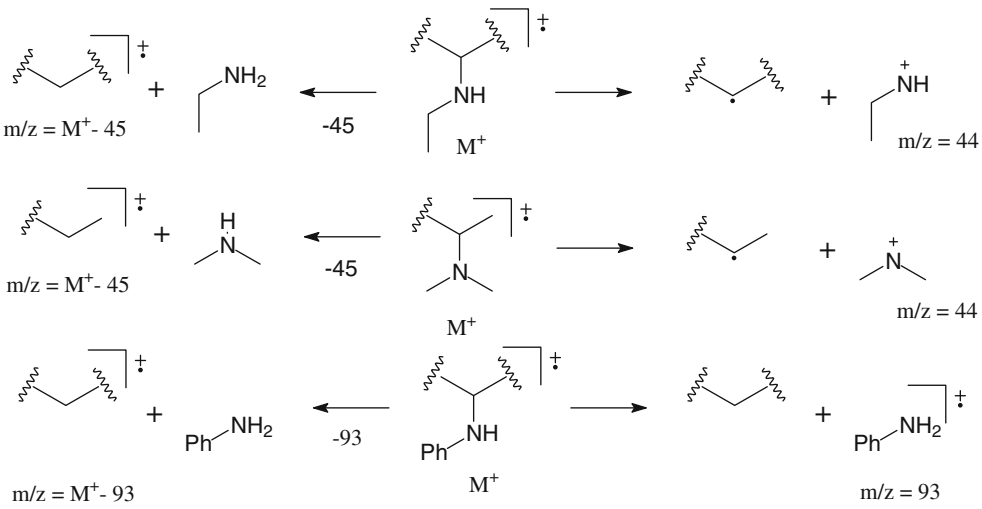


Fig. 5 The most important processes of mass spectral fragmentation for obtained polyamines

In the mass spectra of polyamines **3**, **4**, **10**, and **11**, the molecular ions were detected. In case of **7**, the MH^+ ion was observed instead, due to an increased vapor pressure of the sample in an ion source. The masses corresponding to molecular ions of the starting heterocycles were of two units less. This confirmed that the reductive cleavage of N–N bond did occur. The characteristic fragmentation included the removal of ethylamino, dimethylamino, and phenylamino groups (Lebedev 1991), and it was observed in the spectra (Fig. 5).

The peak with $m/z = 44$ observed for all obtained polyamines was not specific, unfortunately. However, the ions with $m/z = M^+$-45 were quite specific, the elimination of 45 mass units proved the presence of dimethylamino or ethylamino groups in the initial compounds. In the mass spectrum of polyamine **7**, an ion with $m/z = 267$ (M^+-17) was detected, evidencing for the removal of ammonia. Fragmentation with the removal of aniline molecule was observed for all of the compounds; ion-radical of aniline was detected in all cases, except **7**.

Conclusions

Aliphatic polyamines, being a versatile class of organic compounds, are widely used in many fields of medicine and organic chemistry. However, the general approach to the synthesis of chiral aliphatic polyamines has been still undeveloped. The present paper demonstrates a new method for the synthesis of chiral trifunctional amino compounds (hydroxydiamines and triamines). It was shown that the key step was N–N bond cleavage in substituted hydroxy or amino pyrazolidines and pyrazolines by the diborane-THF complex, other known methods for N–N bond cleavage turned out to be ineffective. The main advantage of the proposed method is the retention of configuration of stereocenters in the course of reaction, as well as availability of the initial compounds, namely substituted hydroxy- or aminopyrazolidines and pyrazolines, which can be easily obtained using convenient stereoselective methods developed by us earlier. The approach allows synthesizing chiral diaminoalcohols and triamines. In future, using this new synthetic route a lot of side chain modifications can be studied in detail, in particular amino acid derivatives of pyrazolidines. Now, six new chiral diasteomerically pure substituted hydroxydiamines and triamines and enantiomerically pure triamine with four chiral centers were synthesized. These new compounds are the analogs of the well-known anti-TB drug, that is, ethambutol, and they cannot be obtained by other known methods. Now, the compounds obtained are being tested for antituberculous activity in vitro and preliminary results seem promising. Thus, polyamine studies remain a robust research area of drug development, with great potential for the identification of new anti-TB agents.

Materials and methods

The IR spectra were recorded with a UR-20 instrument in Nujol mulls. The ^{1}H NMR spectra were measured with Bruker Avance 600, 400 and 300 instruments in $CDCl_3$ at 30°C. Resonances were characterized as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m). The spin–spin coupling constants are given with an accuracy of ±0.1 Hz. Mass spectra (EI, 70 eV, direct injection) were recorded with a Finnigan SSQ-7000 instrument. The elemental analysis was carried out on an automated Carlo Erba EA1108 CHNS-OCHN microanalyzer. Optical rotations were measured with a Perkin-Elmer (model 341) polarimeter in 0.5 dm cells at 25°C. Melting points were measured on an Electrothermal IA 9000 series device in sealed

capillaries. Thin-layer chromatography was performed on Silufol-254 plates using a 50% petroleum ether–ethyl acetate or 20% methanol–chloroform mixtures as the eluent. Spots were visualized by spraying an ethanolic solution of ferric chloride ($FeCl_3$). Chromatographic purification of the obtained compounds was carried out by flash chromatography on a dry column of silica gel (type L 5/40) in the chloroform–methanol system in a gradient range from 100:1 to 1:1.

General procedure for reductive N–N bond cleavage

A volume of 2.5 ml of 1 M solution of borane-tetrahydrofuran complex was added to 0.5 mmol of pyrazolidine in a flask with a reflux condenser and was refluxed under argon for 8 h. Then, 250 ml of methanol was added, the solvents were evaporated, 1 ml of saturated solution of NaOH was added, and the mixture was agitated for 2 h and extracted with 4 × 2 ml of diethyl ether. The extract was evaporated, and the resulting compound was isolated chromatographically.

*3-Aniline-5-ethylamino-1-phenylhexanol (**3a**)*

Yield 93%, oil. R_f 0.11 (20% CH_3OH–$CHCl_3$), IR spectrum (ν, cm^{-1}): 3,150–3,450 (NH, OH). ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm, J (Hz): 1.01 (3H, d, $J = 6.2$, 6-Me); 1.05, (3H, t, $J = 7.1$, $MeCH_2N$); 1.47, 1.65, 1.80, 1.97 (4H, m, H-2, H′-2, H-4, H′-4); 2.42 (1H, d.q, $J = 11.2$, 7.1, $MeCH_2N$); 2.69 (1H, d. q, $J = 11.2$, 7.1, $MeCH_2'N$); 2.78 (1H, m, H-5); 3.76 (1H, m, H-3); 4.89 (1H, dd, $J = 9.1$, 3.0, H-1); 6.68 (2H, d, $J = 7.5$, Ho, N-Ph); 6.73 (1H, t, $J = 7.3$, Hp, N-Ph); 7.15 (2H, t, $J = 7.5$, Hm, N-Ph); 7.22–7.38 (5H, m, CHPh). Phenylisothiocarbamoyl derivative: Found,%: C, 71.99; H, 7.43; N, 9.31; S, 7.46. $C_{27}H_{33}N_3OS$. Calculated,%: C, 72.45; H, 7.43; N, 9.39; S, 7.16.

*3-Aniline-5-ethylamino-1-phenylhexanol (**3b**)*

Yield 58%, mp = 88–90°C. R_f 0.10 (20% CH_3OH–$CHCl_3$), IR spectrum (ν, cm^{-1}): 3,150–3,500 (NH, OH). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J (Hz): 1.04 (3H, d, $J = 6.4$, 6-Me); 1.09, (3H, t, $J = 7.1$, $MeCH_2N$); 1.64 (2H, m, H-2, H-4); 1.88, 2.00 (2H, d.d.d, $J = 14.15$, 7.95, 3.18, d.d.d, $J = 14.14$, 8.59, 3.82, H′-2, H′-4); 2.50 (1H, d.q, $J = 11.29$, 7.15, $MeCH_2N$); 2.72 (1H, d.q, $J = 11.29$, 6.99, $MeCH_2'N$); 2.90 (1H, m, H-5); 3.77 (1H, m, H-3); 4.99 (1H, dd, $J = 8.42$, 3.17, H-1); 6.63 (2H, d, $J = 7.79$, Ho, N-Ph); 6.70 (1H, t, $J = 7.31$, Hp, N-Ph); 7.14 (2H, t, $J = 7.47$, Hm, N-Ph); 7.22–7.35 (5H, m, CHPh).

*5-Aniline-3-ethylamino-1-phenylhexanol (**4**)*

Yield 76%, oil. R_f 0.12 (20% CH_3OH–$CHCl_3$), IR spectrum (ν, cm^{-1}): 3,100–3,450 (NH, OH), ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm, J (Hz): 1.12, (3H, t, $J = 7.1$, $MeCH_2N$); 1.19 (3H, d, $J = 6.7$, 6-Me); 1.48, 1.64, 1.77 (4H, m, H-2, H′-2, H-4, H′-4); 2.60 (1H, d.q, $J = 11.2$, 7.2, $MeCH_2N$); 2.85 (1H, d.q, $J = 11.2$, 7.2, $MeCH_2'N$); 3.08 (1H, m, H-3); 3.56 (1H, m, H-5); 4.89 (1H, dd, $J = 10.6$, 1.8, H-1); 6.56 (2H, d, $J = 7.9$, Ho, N-Ph); 6.70 (1H, t, $J = 7.5$, Hp, N-Ph); 7.15 (2H, t, $J = 7.9$, Hm, N-Ph); 7.25 (1H, m, H-p, CHPh); 7.33 (2H, t, $J = 7.9$, Hm, CHPh); 7.37 (2H, t, $J = 7.5$, Ho, CHPh). Found, $M^+ = 312$, 248[M-$C_2H_5NH_2$], 219[M-PhNH], 191[M-$PhNHC_2H_5$], 176 [M-PhNHPr-i], 120 [PhCHOHCH]. $C_{20}H_{28}N_2O$. Calculated, M = 312. Phenylisothiocarbamoyl derivative: Found,%: C, 72.51; H, 7.49; N, 9.34. $C_{27}H_{33}N_3OS$. Calculated,%: C, 72.45; H, 7.43; N, 9.39.

*3-Amino-5-anilino-1-phenylhexanol (**7**)*

Yield 96%, oil. R_f 0.10 (20% CH_3OH–$CHCl_3$), ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J (Hz)): 1.18 (3H, d, $J = 6.3$, 6-Me); 1.49, 1.59, 1.64, 1.74 (4H, m, H-2, H′-2, H-4, H′-4); 3.28 (1H, m, H-3); 3.64 (1H, m, H-5); 4.88 (1H, dd, $J = 11.6$; 2.2, H-1); 6.59 (2H, d, $J = 7.6$, Ho, N-Ph); 6.69 (1H, t, $J = 7.3$, m, Hp, N-Ph); 7.15 (2H, m, $J = 7.4$, Hm, N-Ph); 7.22–7.38 (5H, m, CHPh). Found, $MH^+ = 285$; 267[M-NH_3]; 250 [M-NH_3-OH]; 191 [M-$PhNH_3$]; 176 [M-$PhCH_2OH$]; 164 [M-$PhCHOHCH_2$]; 161 [M-$PhCH_2OHCH_3$]; 149 [M-PhNHPr-i-2H]; 133 [164-CH_3NH_2]; 121 [149-$C_2H_2NH_2$]; 102 [PhCCH]; 79 [C_5H_4NH]. $C_{18}H_{25}N_2O$. Calculated, $M^+ = 284$.

*6-Aniline-2-dimethylamino-4-ethylaminoheptane (**10**)*

Yield 61%, oil. R_f 0.13 (20% CH_3OH–$CHCl_3$), IR spectrum (ν, cm^{-1}): 3,100–3,450 (NHPh, NHEt). ^1H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm, J (Hz), the predominant isomer): 1.08 (3H, t, $J = 7.2$, $MeCH_2N$); 1.20 (3H, d, $J = 6.1$, 1-Me); 1.26 (3H, d, $J = 6.6$, 7-Me); 1.50 (1H, m, H); 1.55 (1H, m, H); 1.60 (1H, d.d.d, $J = 14.3$, 8.3, 2.8, H); 2.08 (1H, m, H); 2.47 (3H, a, Me_2N); 2.50 (1H, d.q, $J = 11.0$, 7.2, H); 2.54 (3H, a, $Me_2'N$); 2.70 (1H, d.q, $J = 11.0$, 7.2, H′); 2.66 (1H, m, H); 2.79 (1H, m, H); 3.75 (1H, m, H-6) 6.60 (2H, d, $J = 8.3$, Ho, N-Ph); 6.65 (1H, t, $J = 7.2$, Hp, N-Ph); 7.14 (2H, m, Hm, N-Ph). Found, $M^+ = 277$. $C_{17}H_{31}N_3$. Calculated, M = 277. Phenylisothiocarbamoyl derivative: Found,%: C, 69.73; H, 8.69; N, 13.37; S, 8.13. $C_{24}H_{36}N_4S$. Calculated,%: C, 69.86; H, 8.79; N, 13.58; S, 7.77.

*4-Aniline-2-dimethylamino-6-ethylaminoheptane (**11**)*

Yield 52%, oil. R_f 0.12 (20% CH_3OH–$CHCl_3$), IR spectrum (ν, cm^{-1}): 3,100–3,550 (NHPh, NHEt). ^1H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm, J (Hz): 0.90 (3H, d, $J = 6.6$, 1-Me); 1.06 (3H, t, $J = 7.2$, $MeCH_2N$); 1.07 (3H, d, $J = 6.6$, 7-Me); 1.32 (1H, d.d.d, $J = 14.0$, 6.1, 6.1, H); 1.47 (1H, d.d.d, $J = 14.0$, 7.0, 5.0, H); 1.60 (1H, d.d.d, $J = 14.0$, 8.1, 5.0, H); 1.71 (1H, d.d.d, $J = 14.0$, 7.2, 7.2, H); 2.22 (6H, a, Me_2N); 2.46 (1H, d.q, $J = 11.2$, 7.2, H); 2.70 (1H, d.q, $J = 11.2$, 7.2, H); 2.72 (1H, m, H); 2.81 (1H, m, H); 3.60 (1H, m, H); 6.56 (2H, d, $J = 7.9$, Ho, N-Ph); 6.59 (1H, t, $J = 7.2$, Hp, N-Ph); 7.11 (2H, m, Hm, N-Ph); Found, $M^+ = 277$; 232[M-N$(CH_3)_2$]; 192 [M-C_2H_5NPr-i]; 161 [232-$C_2H_5NHC_2H_3$]; 146 [192-NH$(CH_3)_2$]; 132 [PhNHC_3H_5]; 93 [PhNH_2]; 86 [$(CH_3)_2$NPr-i]. $C_{17}H_{31}N_3$. Calculated, M = 277.

*(1′S, 2S, 4R, 6S)-4-Aniline-6-ethylamino-2-(1-phenylethylamino)heptane (**13**)*

Yield 54%, oil. $[\alpha]_D = +10.2$ ($c = 0.79$, $CHCl_3$). R_f 0.09 (20% CH_3OH–$CHCl_3$), ^1H NMR spectrum (600 MHz, $CDCl_3$), δ, ppm, J (Hz): 1.00 (3H, d, $J = 6.16$, 1-Me); 1.07 (3H, t, $J = 7.18$, $MeCH_2N$); 1.10 (3H, d, $J = 6.67$, 7-Me); 1.29 (3H, d, $J = 6.63$, MeCHPh); 1.44 (1H, d.d.d, $J = 14.01$, 6.49, 5.00, H); 1.54 (1H, d.d.d, $J = 14.01$, 6.19, 6.19, H); 1.61 (1H, d.d.d, $J = 14.01$, 6.27, 7.09, H); 1.67 (1H, d.d.d, $J = 14.01$, 8.28, 6.49, H); 2.50 (1H, d.q, $J = 11.07$, 7.15, H); 2.69 (1H, d.q, $J = 11.04$, 7.13, H); (1H, m, H); (1H, m, H); 3.60 (1H, m, H); 3.89 (1H, square, $J = 6.57$, H); 6.54 (2H, d, $J = 7.96$, Ho, N-Ph); 6.62 (1H, t, $J = 7.12$, Hp, N-Ph); 7.11 (2H, t, $J = 7.83$, Hm, N-Ph); 7.24 (2H, t, $J = 7.83$, Hm, CHPh); 7.31 (3H, m, Ho, p, CHPh). Found, $M^+ = 353$; 260 [M-PhNH_2]; 258 [260-2H]; 233 [M-PhCH$(CH_3)NH_2$]; 231[M-PhC$H_2(CH_3)NH_3$]; 203 [231-C_2H_4]; 201 [231-C_2H_6]; 146 [PhCH(CH_3) NHC_2H_2]; 120 [PhCH(CH_3)NH]; 112 [203-C_6H_5N]; 105 (100%) [PhCH(CH_3)]; 91 [C_6H_5N]. $C_{23}H_{35}N_3$. Calculated, M = 353.

*Preparation of 3-(2-hydroxy-2-phehylethyl)-5-methyl-1-phenylpyrazoline-2 (**6**)*

To a solution of 0.20 g (0.6 mmol) of 1-acetyl-5-(2-hydroxy-2-phehylethyl)-3-methyl-2-phenylpyrazolidine **2** in diethyl ether, 1 ml of saturated solution of lithium aluminum hydride in diethyl ether was added at −15°C. Then, benzene (2 ml) and saturated solution of sodium fluoride in water (1 ml) were added. The reaction mixture was agitated at 20°C during an hour, and the products were extracted with diethyl ether (2 ml × 5 ml). Ether extract was left for a few days in an open air at −15°C to oxidize unstable pyrazolidine **5** in pyrazoline **6**. The resulting mixture was chromatographed in the system benzene-ethyl acetate with gradient from 10:1 to the 1:1. 0.07 g (41%) of pyrazoline **6** (oil) was obtained. R_f 0.65 (50% petroleum ether–ethyl acetate). IR spectrum (ν, cm^{-1}): 1,620 (C=N), 3,250–3,400 (OH). ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 1.28(3H, d, 5-Me); 2.50(1H, dd, α-H); 2.76(1H, dd, α-H′); 2.77(1H, m, 4-H); 3.07 (1H, m, 4-H′); 3.69 (1H, d, OH); 4.27 (1H, m, 5-H); 5.19 (1H, m, β-H); 6.96–7.26 (5H, m, Ph). Found, $M^+ = 280$; 160 (100%) [M-PhCH(OH)CH]; 159 [M-PhCH(OH)CH_2]; 133 [160-CN]; 121 [PhCH(OH) CH_2]; 118 [160-C_3H_6]; 105 [PhN_2]. $C_{18}H_{20}N_2O$. Calculated, M = 280.

Acknowledgments This research was supported partly by the Russian Academy of Sciences, grant P5 "Fundamental Sciences to Medicine," grant no.10 "Biomolecular and Medical Chemistry" and the Russian Foundation for Basic Research (grant nos. 09-03-01097 and 11-04-01245).

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