A new approach to the synthesis of aliphatic triamines and diamino alcohols that are analogs of the anti-TB drug ethambutol

K. A. Kochetkov,[a] A. N. Tavtorkin,[a] N. I. Vorozhtsov,[b] L. A. Sviridova,[b] A. M. Moroz,[c] and I. R. Dorozhkova[c]*

[a]*A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 119991 Moscow, Russian Federation. Fax: +7 (499) 135 5085. E-mail: const@ineos.ac.ru*

[b]*Department of Chemistry, M. V. Lomonosov Moscow State University, 1 Leninskie Gory, 119899 Moscow, Russian Federation. Fax: +7 (495) 932 8846. E-mail: svirid@org.chem.msu.ru*

[c]*Moscow Scientific and Practical Center for Tuberculosis Control, Moscow Department of Health, 10 ul. Stromynka, 107014 Moscow, Russian Federation. E-mail: tub@mosgorzdrav.ru*

A method for the synthesis of diastereomerically pure diamino alcohols and triamines was developed. The products obtained are new asymmetric structural analogs of the anti-TB drug ethambutol. The method involves reductive cleavage of the N—N bond in appropriate functionalized pyrazolidines and 2-pyrazolines under the action of a diborane complex with THF. The cleavage occurs with retention of the configurations of the asymmetric centers of the starting compounds.

Key words: reductive cleavage of the N—N bond, pyrazolidines, 2-pyrazolines, diastereomerically pure diamino alcohols, diastereomerically pure triamines, ethambutol.

Being efficient ligands, polyamines have found wide application in catalysis; chiral polyamines are used in asymmetric synthesis.[1] In addition, linear polyamines and amino alcohols are not only employed in drug design[2] but also exhibit a broad spectrum of biological activity and find increasingly frequent medical use.[3] A tight tuberculosis epidemic situation and the enhanced resistance of its pathogen to antibiotics urge a search for, and development of, new efficient medicaments against this disease.[4] A number of drugs[5] are available for tuberculosis control. One of the most efficient first-line drugs is the dihydroxy diamine ethambutol ((+)-*N*,*N*′-bis[1-(hydroxymethyl)-propyl]ethylenediamine dihydrochloride).[5] This compound has a bacteriostatic effect on actively replicating drug-sensitive *Mycobacterium tuberculosis* and *M. bovis*, some nontuberculous mycobacteria (*M. kansasii*, *M. avium*, and *M. xenopi*), and mycobacteria resistant to streptomycin, kanamycin, isoniazid, and ethionamide. The mechanism of action of ethambutol is not fully understood. This drug is believed to penetrate promptly into the actively replicating mycobacterial cells and precludes the formation of their walls by disrupting the cell metabolism. According to biochemical data,[6] when penetrating into a mycobacterial cell, ethambutol inhibits the biosynthesis of not only arabinogalactan but also lipoarabinomannan, which are the main structural components of the mycobacterial cell wall. In addition, ethambutol disrupts the lipid metabolism in the cell, inhibits the synthesis of RNA and proteins, reacts with divalent metal ions (Cu and Mg), and breaks the ribosome structure.[4b,7] Data on the nature of the increasing resistance of *M. tuberculosis* to ethambutol have been published.[8]

The synthesis and preclinical *in vitro* tests of new structural analogs of ethambutol can reveal its new modifications with anti-TB activity.[9] Therefore, a search for new nitrogen-containing compounds (earlier unknown diamino alcohols and triamines with anti-TB activity) is a topic of current interest.[10] The natural sources providing suitable compounds for the solution of this problem are very limited, for which reason the main attention is given to synthetic and semisynthetic methods.[11] The latter involves modification of the functional groups in natural compounds possessing carbon frameworks (typically, sugars). However, other enantiomers and diastereomers are not easily accessible. A number of methods[12] have been developed for the synthesis of diamines; nevertheless, general routes to asymmetric chiral amino compounds containing three and more functions are lacking.

Results and Discussion

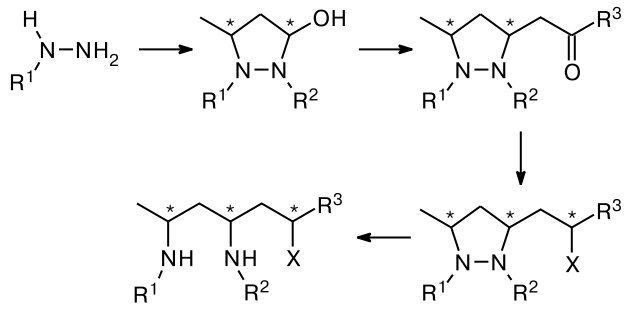
We developed a novel approach to the synthesis of stereochemically individual 1,3,5-triamines and 3,5-diamino 1-alcohols (Scheme 1). The general strategy con-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 4, pp. 688—692, April, 2011.

1066-5285/11/6004-702

sists in initial introduction of nitrogen- or oxygen-containing substituents into an accessible N_2-containing matrix (pyrazolidine ring).[13] Then the introduced functional groups are transformed into substituents containing the desired hydroxy or amino groups.[14a,b] The key step of the synthesis is final cleavage of the endocyclic N—N bond, which leads to the target linear triamines or diamino alcohols*.

Scheme 1



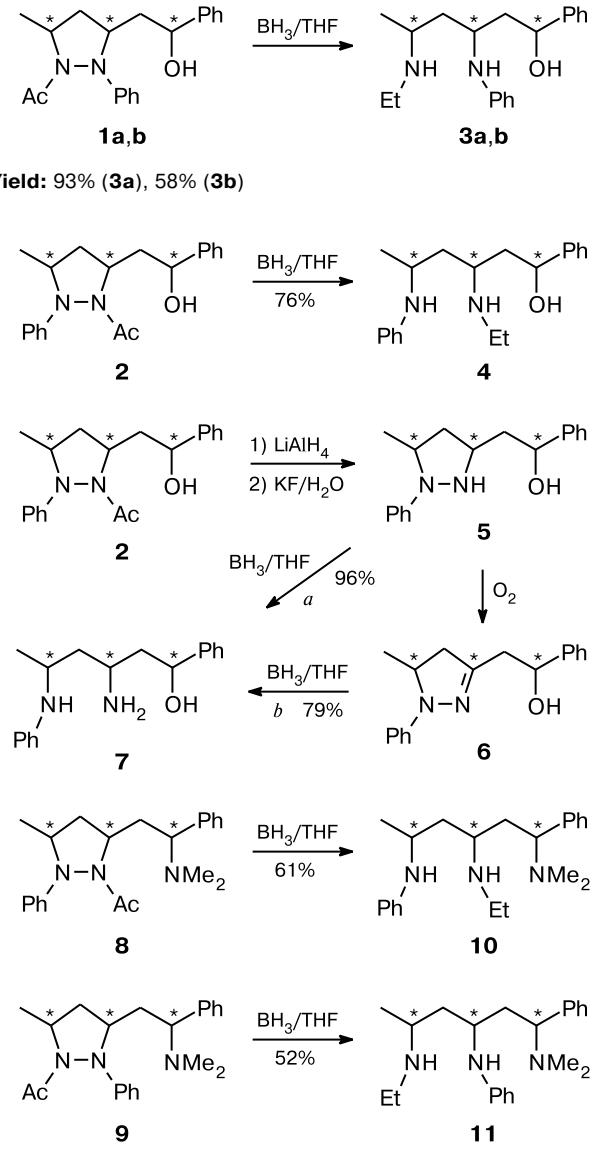
R^1, R^2 = Ph, Ac; R^3 = alkyl, aryl; X = OH, NH_2, NHAlk, $NAlk_2$

It is worth noting that cleavage of the N—O bond in chiral isoxazolines and isoxazolidines is used to obtain chiral γ-amino alcohols and other bifunctional compounds.[15] There are a number of methods for reductive cleavage of the N—N bond in heterocyclic compounds: the action of active metals,[12a] hydrogen at Group VIII metals,[12b] hydrazine hydrate at Raney nickel,[12c] and borane complexes.[12d] For our substrates, the best results were obtained with a diborane complex with THF, which reduces the carbonyl group and causes cleavage of the N—N bond borane to give diamines. This method is of particular value for ring opening in chiral compounds.[1] Ring opening in 5-substituted pyrazolidines in which the substituents in positions 3 and 5 are *trans* to each other occurs with retention of the configuration of the stereogenic centers.

We found that the cleavage of the N—N bond in the previously[14b] obtained racemates of hydroxy pyrazolidines **1a**,**b** (two diastereomers) and **2** (one diastereomer) yields racemates of diamino alcohols **3a**,**b** and **4**, the acetyl substituent being reduced to the ethyl group (Scheme 2). Compounds containing no N-ethyl group became accessible through cleavage of the N—N bond in NH-pyrazolidine **5** obtained as one diastereomer and in the corresponding pyrazoline **6**.

The ^{1}H NMR spectra of diamino alcohol **7** obtained from pyrazoline **6** and pyrazolidine **5** differ only in poorly informative signals of acidic protons (NH, NH_2, and OH), while the other signals are identical. Therefore, one can believe that the reduction of NH-pyrazolidine **5** and pyrazoline **6** under these conditions give identical products.

Scheme 2



Yield: 93% (**3a**), 58% (**3b**)

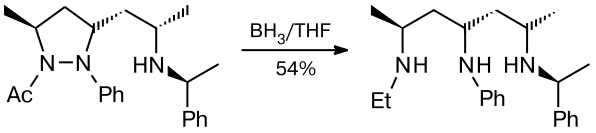
Triamines **10** and **11** were obtained by ring opening in aminopyrazolidines **8** and **9** using the same reagent as in the case of the above hydroxy pyrazolidines. The starting dimethylamino derivative **8** was used as a 3.5 : 1 mixture of two diastereomers, which had been prepared by reductive amination of an appropriate ketone.[14a] Two diastereomers of triamine **10** were isolated in the same ratio. Racemic pyrazolidine **9**, which is isomeric to compound **8**, was employed as an individual racemic diastereomer; cleavage of the N—N bond also gave one racemic diastereomer. The polyamines obtained, except for compound **3b**, are uncrystallizable oils that absorb carbon dioxide when stored in air; because of this, elemental analysis data

* See the preliminary brief communication.[14c]

fail to converge. For this reason, polyamines **3**, **4**, and **10** were identified as their phenylthiocarbamoyl derivatives. In all cases, phenyl isothiocyanate reacted only with the aliphatic amino group, which suggests the possibility of similar selective syntheses using other polyamines with different amine N atoms.

To verify that the reductive cleavage does not change the configuration of the stereogenic centers, we carried out this reaction with enantiomerically pure (1′*S*,2′*S*,3*S*,5*S*)-1-acetyl-5-methyl-2-phenyl-3-[2-(1-phenylethylamino)-propyl]pyrazolidine (**12**) obtained previously[14a] (Scheme 3). The product was enantiomerically pure (1′*S*,2*S*,4*R*,6*S*)-4-phenylamino-6-ethylamino-2-(1-phenylethylamino)-heptane (**13**). Since the ^{1}H NMR spectra show no doubled signals, one can believe that none of the four stereogenic centers undergoes racemization; therefore, we obtained enantiomerically pure triamine **13** with the specific rotation $[\alpha]_D$ + 10.2 (*c* 2.24 · 10^{-3}, $CHCl_3$).

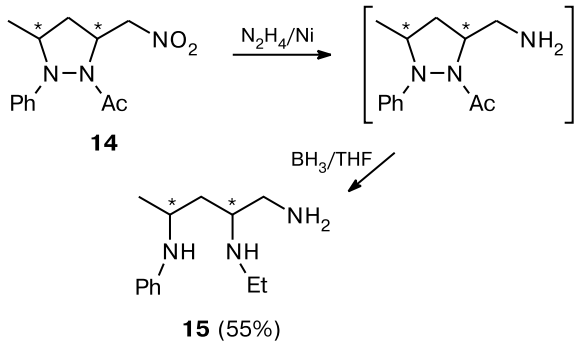
Scheme 3



12 **13**

Attempted synthesis of a triamine from the previously[16] obtained nitro compound **14** under the same conditions as for alcohols **1** and **2** gave an unidentified mixture of compounds, probably because of incomplete reduction of the nitro group. At the same time, attempted cleavage of the N—N bond with hydrazine hydrate at Raney nickel according to a known procedure[12c] resulted in reduction of the nitro group to an amine group without opening of the pyrazolidine ring. That is why we used these two methods in succession: first we reduced nitro compound **14** to an amine and then broke down the N—N bond with the borane complex (Scheme 4), thus producing the corresponding 1,2,4-triaminopentane **15**.

Scheme 4



14

15 (55%)

The ^{1}H NMR spectra of all the polyamines, compared to those of the starting compounds, contain no singlet for the acetyl group; instead, they show a triplet for the methyl group and two doublets of quadruplets for the methylene group of the resulting N-ethyl substituent. The signals for the *ortho*- and *para*-protons of the N-phenyl substituent are shifted from δ 6.9—7.2 to δ 6.5—6.7, which confirms the cleavage of the N—N bond. The absence of doubled signals (except for compound **10**, when two diastereomers of pyrazolidine **8** were used) suggests that the configurations of all stereogenic centers are retained. Therefore, polyamines **3**, **4**, **7**, **11**, and **15** were obtained as one diastereomer and product **13**, as one enantiomer.

The mass spectra of the polyamines provide further evidence for the cleavage of the N—N bond: they contain molecular ion peaks with the corresponding masses (the ions M^+ for **3**, **4**, **10**, and **11**). If the N—N bond were retained in the reduced products, the masses of their molecular ions would be less by two units (the ions with the corresponding masses are absent from the mass spectra). Among the fragmentation processes in the polyamines obtained, elimination of the ethylamino, dimethylamino, and phenylamino groups are most important. It is known that compounds containing the ethylamino or dimethylamino group can eliminate either the ion with the corresponding mass (*m*/*z* 44) or a dimethylamine or ethylamine molecule (*m* = 45).[17] Indeed, we observed such a fragmentation pattern in our case. The ions with *m*/*z* $M^+ - 45$ are very specific because the fragments with a mass of 45 prove the presence of the ethylamino and dimethylamino groups in the compounds under discussion. The mass spectrum of polyamine **7** shows an ion peak with *m*/*z* 267 due to elimination of an ammonia molecule. In addition, almost all the compounds obtained eliminate an aniline molecule in the MS experiments.

To sum up, we developed a novel method for the synthesis of stereochemically individual diamino alcohols and triamines from functionalized pyrazolidines and pyrazolines *via* cleavage of the endocyclic N—N bond under the action of a diborane complex with THF. Calculations with the PASS software[18] designed at the V. N. Orekhovich Research Institute of Biomedicinal Chemistry for prediction of the biological activity of compounds showed that such polyamines can exhibit anti-TB and antiparasitic properties.

Experimental

IR spectra were recorded on a UR-20 instrument (Nujol or thin films). ^{1}H NMR spectra were recorded on Bruker Avance 300, Bruker Avance 400, and Bruker Avance 600 instruments (300, 400, and 600 MHz, respectively) in $CDCl_3$ at 30 °C. The coupling constants are given to within ±0.1 Hz. Mass spectra (EI, 70 eV, direct inlet probe) were measured on a Finnigan SSQ-7000 instrument. Elemental analysis was carried out on

a EA1108 CHNS-O automatic microanalyzer (Carlo Erba). Optical rotation was determined on a Perkin—Elmer 341 polarimeter in 0.5-dm cells at 25 °C. Melting points were measured in sealed capillaries on an Electrothermal IA 9000 melting point apparatus. The course of the reactions was monitored and the purity of the products was checked by TLC on Silufol UV-254 plates with light petroleum—ethyl acetate (3 : 1 → 1 : 1) as an eluent. The complex $BH_3 \cdot THF$ was purchased from Aldrich.

Reductive cleavage of the N—N bond (general procedure). A flask fitted with a reflux condenser was charged with pyrazoline or pyrazolidine (0.5 mmol) and 1 *M* borane in THF (2.5 mL). The solution was refluxed under argon for 8 h. Then methanol (250 μL) was added, the solvent was removed, and a saturated solution of NaOH (1 mL) was added. The reaction mixture was stirred for 2 h and the product was extracted with diethyl ether (4×2 mL). The combined extracts were concentrated and separated by column chromatography on SiO_2 in chloroform—methanol (100 : 1 → 1 : 1).

5-Ethylamino-1-phenyl-3-phenylaminohexanol (3a). Yield 93%, oil. IR, ν/cm^{-1}: 3150—3450 (NH, OH). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.01 (d, 3 H, C(6)H, J = 6.2 Hz); 1.05 (t, 3 H, MeCH$_2$N, J = 7.1 Hz); 1.47, 1.65, 1.80, 1.97 (all m, 1 H each, C(2)H$_2$, C(4)H$_2$); 2.42 (dq, 1 H, MeCH$_2$N, J = 11.2 Hz, J = 7.1 Hz); 2.69 (dq, 1 H, MeCH´$_2$N, J = 11.2 Hz, J = 7.1 Hz); 2.78 (m, 1 H, C(5)H); 3.76 (m, 1 H, C(3)H); 4.89 (dd, 1 H, C(1)H, J = 9.1 Hz, J = 3.0 Hz); 6.68 (d, 2 H, *o*-H, N—Ph, J = 7.5 Hz); 6.73 (t, 1 H, *p*-H, N—Ph, J = 7.3 Hz); 7.15 (t, 2 H, *m*-H, N—Ph, J = 7.5 Hz); 7.22—7.38 (m, 5 H, CHPh). MS, M^+ = 312.

Phenylthiocarbamoyl 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.

5-Ethylamino-1-phenyl-3-phenylaminohexanol (3b). Yield 58%, m.p. 88—90 °C. IR, ν/cm^{-1}: 3150—3500 (NH, OH). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.04 (d, 3 H, C(6)H, J = 6.4 Hz); 1.09 (t, 3 H, MeCH$_2$N, J = 7.1 Hz); 1.64 (m, 2 H, H(2), H(4)); 1.88, 2.00 (both ddd, 1 H each, C(2)H$_2$, J_2 = 14.15 Hz, J_2 = 7.95 Hz, J_2 = 3.18 Hz, J_4 = 14.14 Hz, J_4 = 8.59 Hz, J_4 = 3.82 Hz); 2.50 (dq, 1 H, MeC(H$_a$)N, J = 11.29 Hz, J = 7.15 Hz); 2.72 (dq, 1 H, MeC(H$_b$)N, J = 11.29 Hz, J = 6.99 Hz); 2.90 (m, 1 H, C(5)H); 3.77 (m, 1 H, C(3)H); 4.99 (dd, 1 H, C(1)H, J = 8.42 Hz, J = 3.17 Hz); 6.63 (d, 2 H, *o*-H, N—Ph, J = 7.79 Hz); 6.70 (t, 1 H, *p*-H, N—Ph, J = 7.31 Hz); 7.14 (t, 2 H, *m*-H, N—Ph, J = 7.47 Hz); 7.22—7.35 (m, 5 H, CHPh).

Phenylthiocarbamoyl derivative. Found (%): C, 72.04; H, 7.32; N, 9.22; S, 7.53. $C_{27}H_{33}N_3OS$. Calculated (%): C, 72.45; H, 7.43; N, 9.39; S, 7.16.

3-Ethylamino-1-phenyl-5-phenylaminohexanol (4). Yield 76%, oil. IR, ν/cm^{-1}: 3100—3450 (NH, OH). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.12 (t, 3 H, MeCH$_2$N, J = 7.1 Hz); 1.19 (d, 3 H, C(6)H, J = 6.7 Hz); 1.48, 1.64, 1.77 (all m, 1 H each, C(2)H$_2$, C(4)H$_2$); 2.60 (dq, 1 H, MeC(H$_a$)N, J = 11.2 Hz, J = 7.2 Hz); 2.85 (dq, 1 H, MeC(H$_b$)N, J = 11.2 Hz, J = 7.2 Hz); 3.08 (m, 1 H, H(3)); 3.56 (m, 1 H, H(5)); 4.89 (dd, 1 H, H(1), J = 10.6 Hz, J = 1.8 Hz); 6.56 (d, 2 H, *o*-H, N—Ph, J = 7.9 Hz); 6.70 (t, 1 H, *p*-H, N—Ph, J = 7.5 Hz); 7.15 (t, 2 H, *m*-H, N—Ph, J = 7.9 Hz); 7.25 (m, 1 H, *p*-H, CHPh); 7.33 (t, 2 H, *m*-H, CHPh, J = 7.9 Hz); 7.37 (t, 2 H, *o*-H, CHPh, J = 7.5 Hz). MS, M^+ = 312.

Phenylthiocarbamoyl 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-1-phenyl-5-phenylaminohexanol (7). Yield 96%, oil. IR, ν/cm^{-1}: 3100—3450 (NH, OH). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.18 (d, 3 H, C(6)H, J = 6.3 Hz); 1.49, 1.59, 1.64, 1.74 (all m, 1 H each, C(2)H$_2$, C(4)H$_2$); 3.28 (m, 1 H, C(3)H); 3.64 (m, 1 H, C(5)H); 4.88 (dd, 1 H, C(1)H, J = 11.6 Hz, J = 2.2 Hz); 6.59 (d, 2 H, *o*-H, N—Ph, J = 7.6 Hz); 6.69 (t, 1 H, *p*-H, N—Ph, J = 7.3 Hz); 7.15 (t, 2 H, *m*-H, N—Ph, J = 7.4 Hz); 7.22—7.38 (m, 5 H, C(1)Ph). MS, MH^+ = 285.

Hydrochloride. Found (%): C, 67.16; H, 8.14; N, 6.45; Cl, 10.54. $C_{18}H_{24}N_2O \cdot HCl$. Calculated (%): C, 67.38; H, 7.85; N, 8.73; Cl, 11.05.

1-Dimethylamino-3-ethylamino-1-phenyl-5-phenylaminohexane (10). Yield 61%, oil. IR, ν/cm^{-1}: 3100—3450 (NHPh, NHEt). ^{1}H NMR (600 MHz, $CDCl_3$), δ (major isomer): 1.08 (t, 3 H, MeCH$_2$N, J = 7.2 Hz); 1.20 (d, 3 H, C(1)H, J = 6.1 Hz); 1.26 (d, 3 H, C(7)H, J = 6.6 Hz); 1.50, 1.55 (both m, 1 H each, C(3)H$_2$); 1.60 (ddd, 1 H, C(5)H$_a$, J = 14.3 Hz, J = 8.3 Hz, J = 2.8 Hz); 2.08 (m, 1 H, C(5)H$_b$), 2.47 (s, 3 H, MeN); 2.50 (dq, 1 H, MeC(H$_a$)N, J = 11.0 Hz, J = 7.2 Hz); 2.54 (s, 3 H, MeN); 2.66 (m, 1 H, H(2)); 2.70 (dq, 1 H, MeC(H$_b$)N, J = 11.0 Hz, J = 7.2 Hz); 2.79 (m, 1 H, H(4)); 3.75 (m, 1 H, H(6)); 6.60 (d, 2 H, *o*-H, N—Ph, J = 8.3 Hz); 6.65 (t, 1 H, *p*-H, N—Ph, J = 7.2 Hz); 7.14 (m, 2 H, *m*-H, N—Ph). MS, M^+ = 277.

Phenylthiocarbamoyl 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.

1-Dimethylamino-5-ethylamino-1-phenyl-3-phenylaminohexane (11). Yield 52%, oil. IR, ν/cm^{-1}: 3100—3550 (NHPh, NHEt). ^{1}H NMR (600 MHz, $CDCl_3$), δ: 0.90 (d, 3 H, C(1)H, J = 6.6 Hz); 1.06 (t, 3 H, MeCH$_2$N, J = 7.2 Hz); 1.07 (d, 3 H, C(7)H, J = 6.6 Hz); 1.32 (ddd, 1 H, C(3)H$_a$, J = 14.0 Hz, J = 6.1 Hz, J = 6.1 Hz); 1.47 (ddd, 1 H, C(5)H$_a$, J = 14.0 Hz, J = 7.0 Hz, J = 5.0 Hz); 1.60 (ddd, 1 H, C(3)H$_b$, J = 14.0 Hz, J = 8.1 Hz, J = 5.0 Hz); 1.71 (ddd, 1 H, C(5)H$_b$, J = 14.0 Hz, J = 7.2 Hz, J = 7.2 Hz); 2.22 (s, 6 H, Me$_2$N); 2.46 (dq, 1 H, MeC(H$_a$)N, J = 11.2 Hz, J = 7.2 Hz); 2.70 (dq, 1 H, MeC(H$_b$)N, J = 11.2 Hz, J = 7.2 Hz); 2.72 (m, 1 H, C(2)H); 2.81 (m, 1 H, C(6)H); 3.60 (m, 1 H, C(4)H); 6.56 (d, 2 H, *o*-H, N—Ph, J = 7.9 Hz); 6.59 (t, 1 H, *p*-H, N—Ph, J = 7.2 Hz); 7.11 (m, 2 H, *m*-H, N—Ph). MS, M^+ = 277.

6-Ethylamino-4-phenylamino-2-(1-phenylethylamino)heptane (13). Yield 54%, oil, $[\alpha]_D$ +10.2 (c 2.24 · 10^{-3}, $CHCl_3$). IR, ν/cm^{-1}: 3100—3550 (NHPh, NHEt, NHCHPh). ^{1}H NMR (600 MHz, $CDCl_3$), δ: 1.00 (d, 3 H, C(1)H, J = 6.16 Hz); 1.07 (t, 3 H, MeCH$_2$N, J = 7.18 Hz); 1.10 (d, 3 H, C(7)H, J = 6.67 Hz); 1.29 (d, 3 H, MeCHPh, J = 6.63 Hz); 1.44 (ddd, 1 H, C(3)H$_a$, J = 14.01 Hz, J = 6.49 Hz, J = 5.00 Hz); 1.54 (ddd, 1 H, C(5)H$_a$, J = 14.01 Hz, J = 6.19 Hz, J = 6.19 Hz); 1.61 (ddd, 1 H, C(5)H$_b$, J = 14.01 Hz, J = 6.27 Hz, J = 7.09 Hz); 1.67 (ddd, 1 H, C(3)H$_b$, J = 14.01 Hz, J = 8.28 Hz, J = 6.49 Hz); 2.50 (dq, 1 H, MeC(H$_a$)N, J = 11.07 Hz, J = 7.15 Hz); 2.69 (dq, 1 H, MeC(H$_b$)N, J = 11.04 Hz, J = 7.13 Hz); 2.76 (m, 1 H, H(2)); 2.83 (m, 1 H, H(6)); 3.60 (m, 1 H, H(4)); 3.89 (q, 1 H, MeCHPh, J = 6.57 Hz); 6.54 (d, 2 H, *o*-H, N—Ph, J = 7.96 Hz); 6.62 (t, 1 H, *p*-H, N—Ph, J = 7.12 Hz); 7.11 (t, 2 H, *m*-H, N—Ph, J = 7.83 Hz); 7.24 (t, 2 H, *m*-H, CHPh, J = 7.83 Hz); 7.31 (m, 3 H, *o*-H, *p*-H, CHPh). MS, M^+ = 353.

Hydrochloride. Found (%): C, 70.68; H, 9.49; N, 10.59; Cl, 8.99. $C_{23}H_{35}N_3 \cdot HCl$. Calculated (%): C, 70.83; H, 9.30; N, 10.77; Cl, 9.09.

1-Amino-2-ethylamino-4-phenylaminopentane (15). Nitro compound **14** (see Ref. 16; 27 mg, 0.1 mmol) was dissolved in ethanol (0.27 mL) and Raney nickel (1 g) was added. Then hydrazine hydrate (100 μL) was added dropwise with stirring for 2 h. After 3 h, K_2CO_3 (100 mg) and benzene (0.2 mL) were added. The organic layer was separated and the product from the aqueous layer was extracted with ether (3×2 mL). The combined organic phases were concentrated *in vacuo*. The residue was used in the reaction according to the general procedure for the synthesis of polyamines. The yield of compound **15** was 55%, oil. IR, ν/cm^{-1}: 3100—3500 (NHPh, NHEt, NH_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.10 (t, 3 H, $\underline{Me}CH_2N$, J = 7.1 Hz); 1.19 (d, 3 H, C(5)H, J = 6.4 Hz); 1.58 (m, 1 H, C(3)H_a); 1.64 (m, 1 H, C(3)H_b); 2.57, 2.67 (both m, 1 H each, $Me\underline{CH_2}N$); 2.93 (m, 2 H, $\underline{CH_2}NH_2$), 3.16 (m, 1 H, C(2)H); 3.61 (m, 1 H, C(5)H); 6.54 (d, 2 H, *o*-H, N—Ph, J = 7.8 Hz); 6.62 (m, 1 H, *p*-H, N—Ph, J = 7.3 Hz); 7.12 (m, 2 H, *m*-H, N—Ph).

Phenylthiocarbamoyl derivative. Found (%): C, 67.03; H, 8.02; N, 15.32; S, 8.67. $C_{20}H_{29}N_4S$. Calculated (%): C, 67.38; H, 7.92; N, 15.71; S, 8.99.

This work was financially supported by the Presidium of the Russian Academy of Sciences (Program P5 "Basic Sciences to Medicine"), the Division of Chemistry and Materials Science of the Russian Academy of Sciences (Program No. 09 "Biomolecular and Medicinal Chemistry"), and the Russian Foundation for Basic Research (Project No. 11-04-01245).

References

1. J.-C. Kizirian, *Chem. Rev.*, 2008, **108**, 140.
2. (a) E. Agostinelli, G. Tempera, A. Molinari, M. Salvi, V. Battaglia, A. Toninello, G. Arancia, *Amino Acids*, 2007, **33**, 175; (b) A. Minarini, A. Milelli, V. Tumiatti, M. Rosini, M. L. Bolognesi, C. Melchiorre, *Amino Acids*, 2010, **38**, 383; (c) G. J. S. Cooper, A. A. Young, G. D. Gamble, C. J. Occleshaw, A. M. Dissanayake, B. R. Cowan, D. H. Brunton, J. R. Baker, A. R. J. Phillips, C. M. Frampton, S. D. Poppitt, R. N. Doughty, *Diabetologia*, 2009, **52**, 715.
3. (a) R. J. Bergeron, R. Muller, G. Huang, J. S. McManis, S. E. Algee, H. Yao, W. R. Weimar, J. Wiegand, *J. Med. Chem.*, 2001, **44**, 2451; (b) H. M. Wallace, K. Niiranen, *Amino Acids*, 2007, **33**, 261; (c) R. A. Casero, Jr., L. J. Marton, *Nature*, 2007, **6**, 373; (d) R. A. Casero, Jr., P. M. Woster, *J. Med. Chem.*, 2009, **52**, 4551.
4. (a) F. M. F. Vergara, M. G. M. O. Henriques, A. L. P. Candea, J. L. Wardell, M. V. N. De Souza, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 4937; (b) D. B. Yung, *Strategiya razrabotki novykh preparatov* [*Strategy of Development of Novel Drugs*], in *Tuberkulez. Patogenez, zashchita, kontrol´* [*Tuberculosis. Pathogenesis, Protection, Control*], Ed. B. R. Blum, Moscow, Meditsina, 2002, pp. 610—615 (in Russian).
5. M. D. Mashkovskii, *Lekarstvennye sredstva* [*Drugs*], 14th ed., Moscow, Novaya Volna, 2000, **2**, p. 310 (in Russian).
6. (a) K. Mikusova, R. A. Slayden, G. S. Besra, *Antimicrob. Agents Chemother.*, 1995, **39**, 2484; (b) R. E. Lee, K. Mikusova, P. J. Brennan, *J. Am. Chem. Soc.*, 1995, **117**, 11829.
7. B. A. Wolucka, M. R. McNeil, E. de Hoffmann, *J. Biol. Chem.*, 1994, **269**, 23328.
8. Y. G. Stepanshin, V. N. Stepanshina, I. G. Shemjakin, *Antibiotiki i khimioterapiya* [*Antibiotics and Chemotherapy*], 1999, 39 (in Russian).
9. L. Jia, J. E. Tomaszewski, B. Nikonenko, M. Protopopova, *Br. J. Pharm.*, 2005, **144**, 80.
10. (a). B. Nikonenko, M. Protopopova, R. Samala, *Antimicrob. Agents Chemother.*, 2007, **51**, 1563; (b) O. Heby, L. Persson, M. Rentala, *Amino Acids*, 2007, **33**, 359.
11. (a) J. Weisell, M. T. Hyvonen, J. Vepsalainen, L. Alhonen, T. A. Keinanen, A. R. Khomutov, P. Soininen, *Amino Acids*, **38**, 501; (b) R. Yendapally, R. E. Lee, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 1607.
12. (a) P. Aeberli, W. J. Houlihan, *J. Org. Chem.*, 1969, **34**, 2720; (b) H. Stetter, K. Findeisen, *Ber.*, 1965, **98**, 3228; (c) F. P. Robinson, R. K. Brown, *Can. J. Chem.*, 1961, **39**, 1171; (d) H. Feuer, F. Brown, *J. Org. Chem.*, 1970, **35**, 1468.
13. L. A. Sviridova, A. N. Tavtorkin, P. B. Terent´ev, I. F. Leshcheva, N. G. Kolotyrkina, K. A. Kochetkov, *Khim. Geterotsikl. Soedin.*, 2005, 1566 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 2005, **42**, 1314].
14. (a) L. A. Sviridova, G. A. Golubeva, A. N. Tavtorkin, Yu. V. Nelyubina, K. A. Kochetkov, *Khim. Geterotsikl. Soedin.*, 2008, 608 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 2008, **44**, 542]; (b) A. N. Tavtorkin, L. A. Sviridova, G. A. Golubeva, Yu. V. Nelyubina, K. A. Lyssenko, K. A. Kochetkov, *Izv. Akad. Nauk, Ser. Khim.*, 2009, 608 [*Russ. Chem. Bull., Int. Ed.*, 2009, **58**, 624]; (c) L. A. Sviridova, A. N. Tavtorkin, K. A. Kochetkov, *Amino Acids*, 2009, **37** (Suppl. 1), 125.
15. (a) P. Kozikowski, Y.-Y. Chen, *J. Org. Chem.*, 1981, **46**, 5248; (b) J. J. Tufariello, *Acc. Chem. Res.*, 1979, **12**, 396; (c) A. P. Kozikowski, M. Adamczyk, *J. Org. Chem.*, 1983, **48**, 366.
16. L. A. Sviridova, G. A. Golubeva, S. V. Shorunov, *Khim. Geterotsikl. Soedin.*, 2006, 1365 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 2006, **42**, 1185].
17. A. T. Lebedev, *Mass-spektrometriya v organicheskoi khimii* [*Mass Spectrometry in Organic Chemistry*], BINOM. Laboratoriya Znanii, Moscow, 2003, 493 (in Russian).
18. V. V. Poroikov, D. A. Filimonov, *J. Comput. Aided Mol. Des.*, 2002, **16**, 819.

Received March 28, 2011;
in revised form April 8, 2011