Chemistry of Heterocyclic Compounds, Vol. 48, No. 5, August, 2012 (Russian Original Vol. 48, No. 5, May, 2012)

SYNTHESIS OF IMIDAZO[4,5-*b*]PYRIDINES WITH A CHIRAL SUBSTITUENT AT THE NITROGEN ATOM AND THEIR CONVERSION TO PIPERAZINE DERIVATIVES

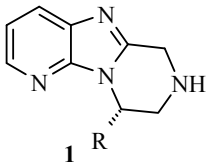
K. V. Bukhryakov[1], A. V. Kurkin[1]*, and M. A. Yurovskaya[1]

Imidazopyridine and benzimidazole derivatives have been prepared with chiral substituents at the nitrogen atom and have been converted to the corresponding condensed structures fused with a piperazine ring. A method has been developed for the synthesis of novel class of compounds – 6,7,8,9-tetrahydropyrido[3',2':4,5]imidazo[1,2-a]pyrazine derivatives.

Keywords: *tert*-butyl imidazo[4,5-*b*]pyridine-2-carboxylate, 2-chloro-3-nitropyridine, chiral substituent at a nitrogen atom, nucleophilic substitution, optically active amino acid esters.

Interest in imidazopyridines is due to their biological activity, the most important aspects of which have been summarized in a review [1]. Based on this data and with the current trend to use non-racemic medications in mind, we have developed a method for the synthesis of imidazo[4,5-*b*]pyridines with a chiral substituent on the nitrogen atom [2].

Benzimidazoles fused to a piperazine ring are also of special interest, since they possess antiviral [3] and analgesic [4] properties. It is known that in some cases the exchange of a benzene ring for pyridine markedly increases biological activity due to the high affinity of the latter towards the benzodiazepine receptor [5]. The aim of our work was to develop a method for the preparation of a novel class of compounds, namely the 9-substituted 6,7,8,9-tetrahydropyrido[3',2':4,5]imidazo[1,2-*a*]pyrazine derivatives **1**.



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A synthetic route based on the use of L-alanine was initially proposed by us for the preparation of the target compounds.

The imidazopyridines **6a-c** were synthesized using our previously developed procedure for optically active imidazo[4,5-*b*]pyridine-2-carboxylates using the enantiomerically pure L-phenylalanine *tert*-butyl

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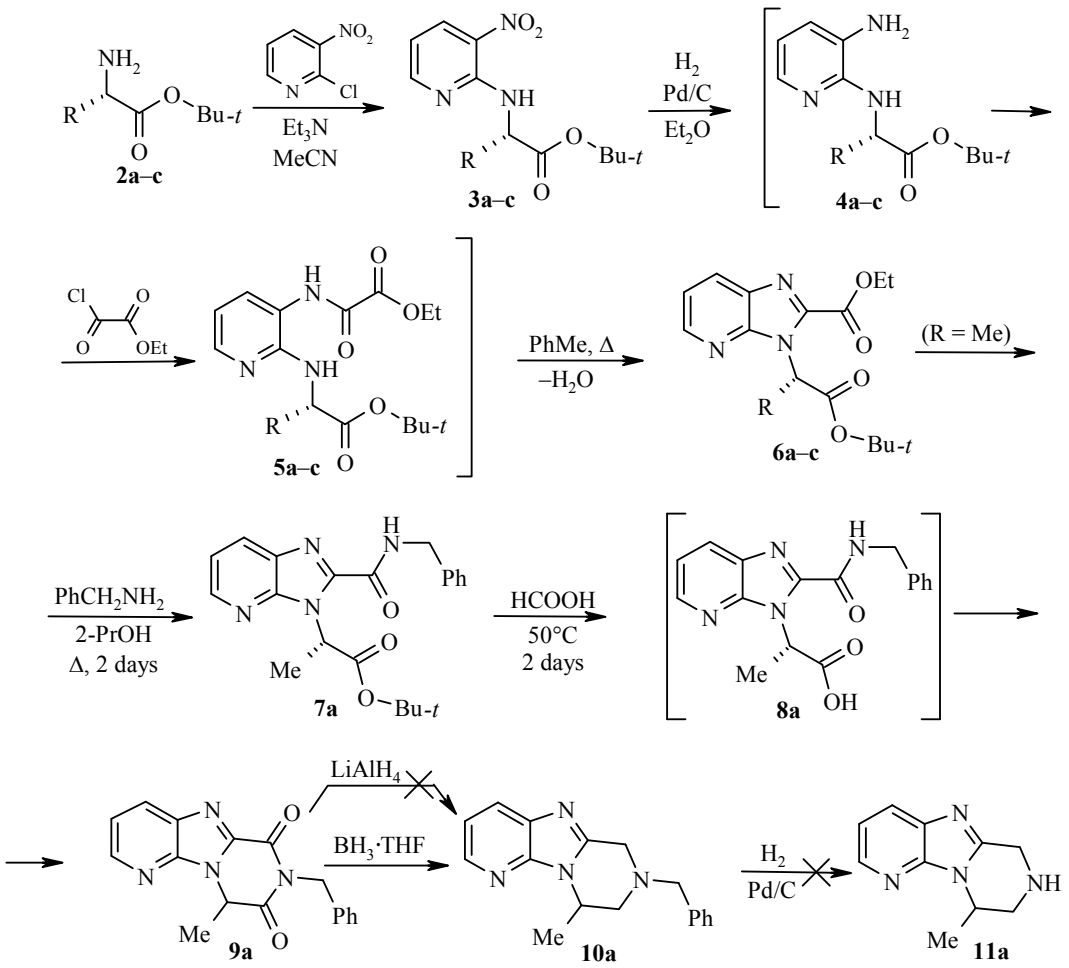
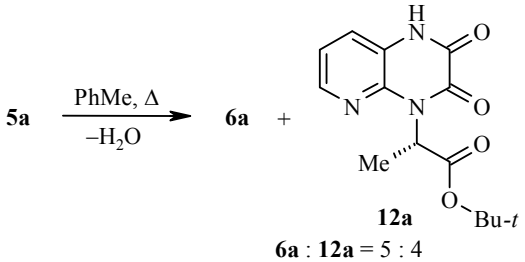
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 831-843, May, 2012. Original article submitted December 7, 2011.



a R = Me, **b** R = *i*-Bu, **c** R = Bn

ester [2] as the chirality source. It was shown that the selectivity of cyclization of compounds of type **5** with a phenylalanine residue (forming imidazopyridines or pyridopyrazines) was markedly governed by the solvent used in the reaction. None the less the cyclization of compound **5a** (with an alanine fragment) in toluene occurred non-selectively. In addition to the imidazopyridine **6a** target product, we also separated the minor pyridopyrazine **12a** in the ratio 5:4. Hence we can conclude that both the solvent and the substituent at the nitrogen atom affect the cyclization route.



6a : **12a** = 5 : 4

Ammonolysis of imidazopyridine **6a** was brought about with a 3-fold excess of benzylamine by refluxing in 2-propanol. An attempt to separate acid **8a** after hydrolysis of the *tert*-butyl ester **7a** proved unsuccessful since an intramolecular cyclization occurs under the reaction conditions to give the racemic compound **9a**. The reasons for the loss of chirality in the derivative **9a** are considered later. The structure of compound **9a** was confirmed by X-ray structural analysis data (Fig. 1).

Reduction of compound **9a** with $LiAlH_4$ gave a complex mixture of unidentified reaction products. When reduced with the $BH_3 \cdot THF$ complex, however, it was possible to detect an ion mass peak corresponding to the derivative **10a**, but all our attempts to prepare piperazine **10a** in a pure state were unsuccessful. We also attempted to remove the benzyl group from the unpurified compound **10a** by hydrogenolysis in the presence of palladium, but, to our surprise, the mixture contained neither the expected reaction product **11a** nor the starting piperazine **10a**.

The target piperazine **11a** could only be obtained after exchange of the benzyl group for 2,4-dimethoxybenzyl, the removal of which is generally achieved under milder conditions [6].

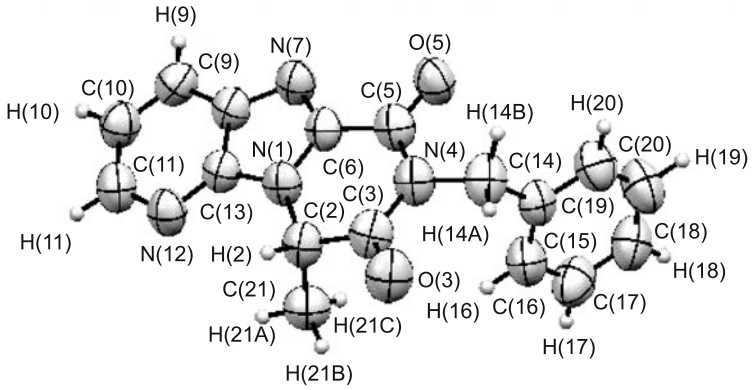
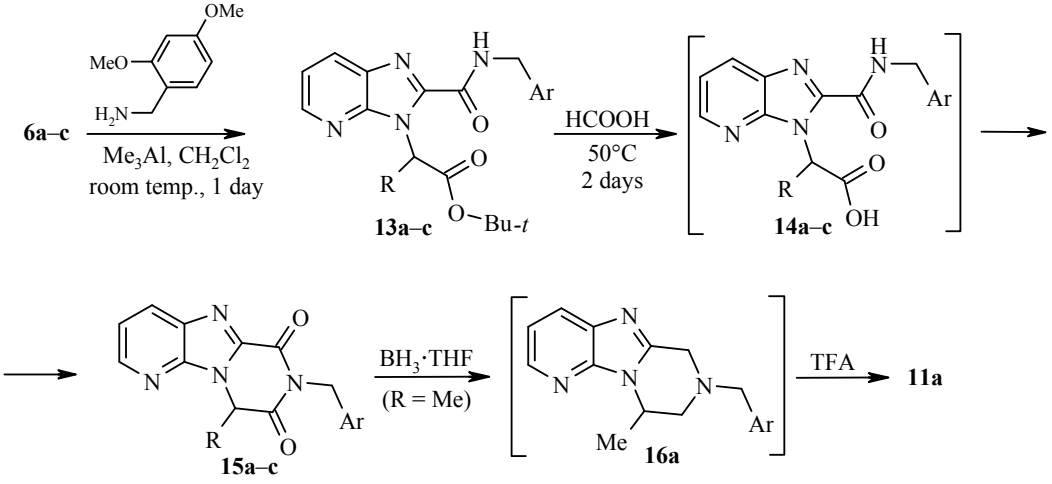


Fig. 1. Molecular structure of compound **9a** with 50% probability atomic thermal vibration ellipsoids.

The imides **15a-c** were prepared from the imidazopyridines **6a-c** by the same scheme we used for the synthesis of compound **9a**. Reduction of compound **15a** with the $BH_3 \cdot THF$ complex and treatment with trifluoroacetic acid without separation of piperazine **16a** gave the target 6,7,8,9-tetrahydropyrido[3',2':4,5]-imidazo[1,2-*a*]pyrazine **11a**, which was isolated as the dihydrobromide after treatment with 20% HBr.

Analysis of the enantiomeric purity of compound **11a** by HPLC with a chiral stationary phase showed total loss of the enantiomeric purity. It has been found that racemization is observed in two stages, *viz*. the preparation of amide **13a** and its cyclization to the derivative **15a**.



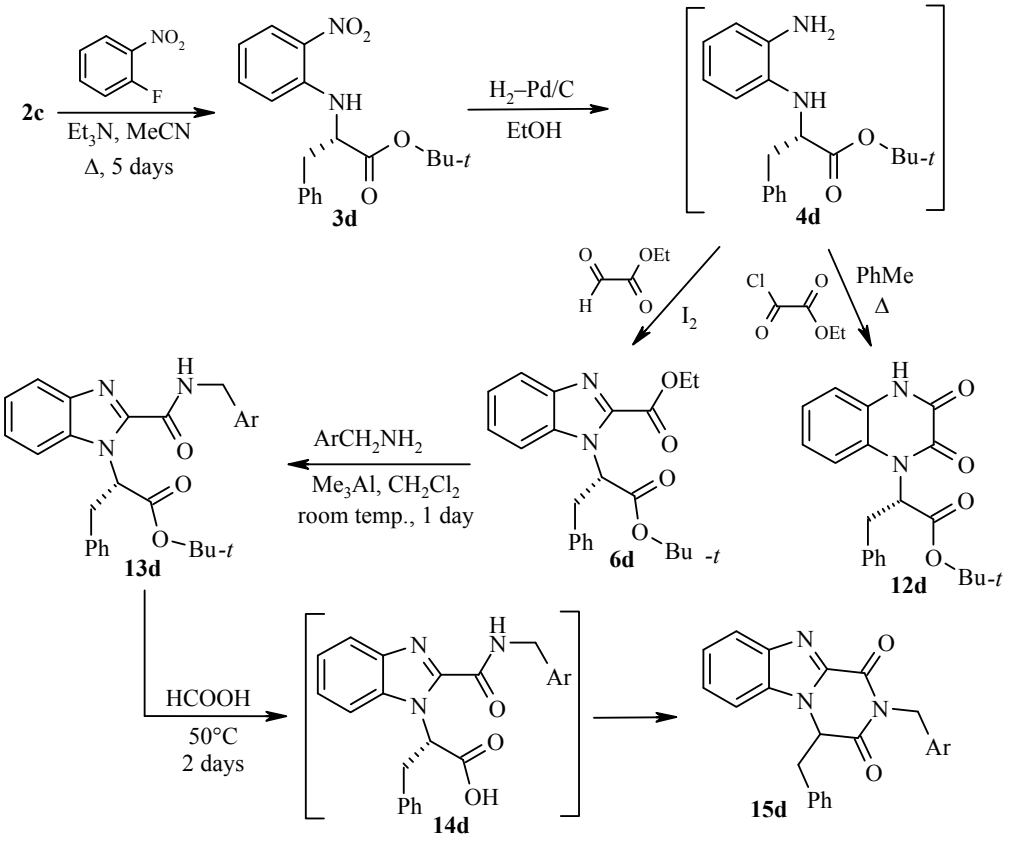
a–c Ar = 2,4-$(MeO)_2C_6H_3$; **a** R = Me, **b** R = *i*-Bu, **c** R = Bn

We have attempted to preserve the optical activity in the course of synthetic transformations in order to obtain final imidazo[4,5-*b*]pyridines with high enantiomeric purity. With this aim, we tried to carry out a first

stage preparation of the pure acid **14a** which can be transformed to the amide **15a** using mild reagents, which are employed in peptide synthesis and do not lead to racemization [6]. We have used all of the known methods for the removal of *tert*-butyl protection in the ester **13a**, but, unfortunately, none of those gave a positive result. Moreover, the acid **14a** proved to be extremely unstable to protonic media. All of the reactions led to its decarboxylation.

We succeeded in preparing the amide **13a** in high enantiomeric purity (*ee* 98%) by treating compound **6a** with 2,4-dimethoxybenzylamine hydrochloride in CH_2Cl_2 at room temperature in the presence of trimethyl aluminum [7]. Although the maximum conversion was as low as 40%, racemization was not observed (according to HPLC with a chiral stationary phase).

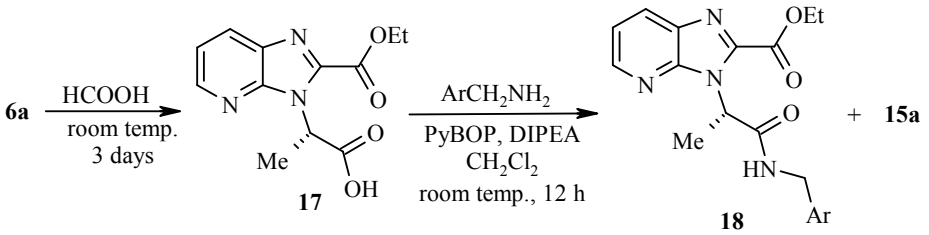
The following step in the work was an attempt to exclude racemization in the stage of cyclizing compounds **13a-c** to the amides **15a-c**. We have proposed that the presence of the basic pyridine nitrogen atom can promote racemization due to speeding up of the enolization process in the piperazine fragment. In order to prove this hypothesis, we have synthesized the benzene analog **13d** from the *tert*-butyl phenylalanine ester **2c** and *o*-fluoronitrobenzene.



It should be noted that use of chloroethyl oxalate in the third stage of the synthesis and subsequent refluxing of the acylation product in toluene does not lead to formation of the benzimidazole **6d** (as occurs in the synthesis of an imidazopyridine) but forms exclusively the quinoxalinedione **12d**. In order to prepare compound **6d**, we have used the alternative procedure of treating amine **4d** with ethyl glyoxalate in the presence of iodine (which is needed as oxidant).

Unfortunately, the cyclic amide **15d** also failed to show optical activity, and analysis of its enantiomeric purity allowed us to establish that a racemic compound had been obtained in the course of the synthetic reaction.

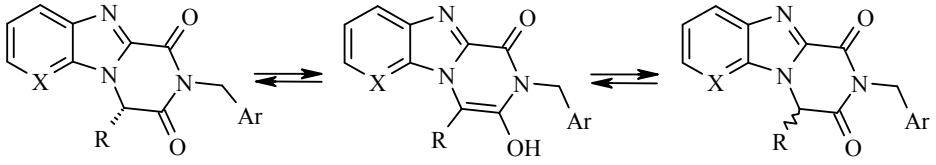
We then attempted to change the route to a synthesis of the cyclic amide **15a**. The acid **17**, which was obtained through hydrolysis of the *tert*-butyl ester **6a**, was dissolved in CH_2Cl_2 and condensed with 2,4-dimethoxybenzylamine. The process was activated by benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP) in the presence of diisopropylethylamine (DIPEA), and the reaction mixture was then stirred at room temperature for 12 h.



Ar = 2,4-$(MeO)_2C_6H_3$

The mixture obtained contained uncyclized amide **18** and cyclic amide **15a**, and these were separated in the pure state and characterized. It was found that the amide **18** was optically active (+17.3º, *ee* 31%) but the cyclic diamide **15a** was found to be optically inactive (*ee* 5%).

It is likely that the loss in optical activity is a result of the keto-enol tautomerism in the substrates **15a-d**.



X = CH, N; R = Me, *i*-Bu, Bn; Ar = Ph, 2,4-$(MeO)_2C_6H_3$

Hence we have obtained imidazopyridine and benzimidazole derivatives with chiral substituent at the nitrogen atom and carried out their transformations to the corresponding derivatives fused with a piperazine ring. Unfortunately, it was not possible to prepare final products with a high enantiomeric purity, but a method has been developed for synthesis of a previously unknown class of substituted 6,7,8,9-tetrahydro-pyrido[3',2':4,5]imidazo[1,2-*a*]pyrazines.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker DPX instrument (400 MHz) using TMS as internal standard and the solvents D_2O (compound **11a**), DMSO-d_6 (compound **12d**), or $CDCl_3$ (remaining compounds). ^{13}C NMR spectra were recorded on a Bruker AMX-400 instrument (100 MHz) with DMSO-d_6 (compounds **11a, 12d**) or $CDCl_3$ (remaining compounds) as solvent. Chromato-mass spectrometric studies of the reaction mixture and separated compounds were performed using a Shimadzu Analytical SCL10Avp liquid chromatograph and PE SCIEX API 150 mass spectrometer (electrospray, positive ionization). The enantiomeric purity was measured by HPLC on a Waters Breeze 2 HPLC chromatograph using a Chiralpak AD-H chiral sorbent (5 micron, column 4.6×250 mm, hexane–2-propanol (85:15) as eluent, 1.0 ml/min flow, 20ºC, and with UV detection at 360 nm). Monitoring of the reaction course and the purity of the compounds obtained was carried out by using TLC on Sorbfil plates (silica gel CTX-1VE grade) in the system hexane–ethyl acetate (10:1;

compound **7a** – in CH_2Cl_2) or by liquid chromatography with the mass spectrometric detector (compounds **9a**, **15a-c**). Commercial 2-chloro-3-nitropyridine was used from the Aldrich company, and the *tert*-butyl amino acid esters were obtained by method [8].

***N*-(3-Nitropyridin-2-yl)-L-amino Acid Esters 3a-c (General Method)**. 2-Chloro-3-nitropyridine (11.10 g, 0.07 mol) was added to a solution of the corresponding amino acid ester (0.07 mol) in MeCN (100 ml), followed by Et_3N (14.85 g, 0.147 mol). The product was refluxed for 2 h (TLC monitoring). The solvent was evaporated, and the residue was treated with water (100 ml) and extracted with EtOAc (3×50 ml). The extract was dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column using the system hexane–EtOAc (10:1).

***N*-(3-Nitropyridin-2-yl)-L-alanine *tert*-Butyl Ester (3a)**. Yield 90%. Yellow crystals, mp 63-65ºC; $[\alpha]_D^{20}$ +80.2º (*c* 1.00, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49 (9H, s, $C(CH_3)_3$); 1.56 (3H, d, *J* = 7.3, $CHC\underline{H}_3$); 4.76-4.79 (1H, m, $C\underline{H}CH_3$); 6.69 (1H, dd, *J* = 8.4, *J* = 4.6, H-5); 8.38 (1H, dd, *J* = 4.4, *J* = 1.8, H-6); 8.43 (1H, dd, *J* = 8.2, *J* = 1.8, H-4); 8.49 (1H, d, *J* = 5.3, NH). ^{13}C NMR spectrum, δ, ppm: 18.3 (CH_3); 27.9 ($C(\underline{C}H_3)_3$); 50.6 ($\underline{C}HCH_3$); 81.8 ($\underline{C}(CH_3)_3$); 112.3 (C-5); 135.1 (C-3); 144.6 (C-4); 151.5 (C-2); 155.2 (C-6); 172.2 (C=O). Found, %: C 54.04; H 6.32; N 15.89. $C_{12}H_{17}N_3O_4$. Calculated, %: C 53.92; H 6.41; N 15.72.

***N*-(3-Nitropyridin-2-yl)-L-leucine *tert*-Butyl Ester (3b).** Yield 80%. Yellow crystals; mp 55-57ºC; $[\alpha]_D^{20}$ +23.8º (*c* 1.01, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.98 (3H, d, *J* = 6.2) and 1.03 (3H, d, *J* = 6.2, $CH(C\underline{H}_3)_2$); 1.47 (9H, s, $C(CH_3)_3$); 1.76-1.78 (3H, m, $C\underline{H}_2C\underline{H}Me_2$); 4.76-4.82 (1H, m, $C\underline{H}CH_2$); 6.69 (1H, dd, *J* = 8.2, *J* = 4.4, H-5); 8.34 (1H, d, *J* = 6.4, NH); 8.38 (1H, dd, *J* = 4.9, *J* = 1.8, H-6); 8.43 (1H, dd, *J* = 8.4, *J* = 1.8, H-4). ^{13}C NMR spectrum, δ, ppm: 22.1 ($CH(\underline{C}H_3)_2$); 22.9 ($CH(\underline{C}H_3)_2$); 25.1 ($\underline{C}H(CH_3)_2$); 28.0 ($C(\underline{C}H_3)_3$); 41.3 (CH_2); 53.4 ($\underline{C}HCH_2$); 81.5 ($\underline{C}(CH_3)_3$); 112.3 (C-5); 128.3 (C-3); 135.1 (C-4); 151.9 (C-2); 155.2 (C-6); 172.2 (C=O). Found, %: C 58.39; H 7.45; N 13.55. $C_{15}H_{23}N_3O_4$. Calculated, %: C 58.24; H 7.49; N 13.58.

***N*-(3-Nitropyridin-2-yl)-L-phenylalanine *tert*-Butyl Ester (3c)**. Yield 70%. Yellow crystals; mp 137-139ºC; $[\alpha]_D^{20}$ -112.6º (*c* 0.76, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.41 (9H, s, $C(CH_3)_3$); 3.22-3.25 (2H, m, CH_2Ph); 5.02-5.04 (1H, m, $C\underline{H}CH_2$); 6.71-6.75 (1H, m, NH); 7.26-7.29 (5H, m, H Ph); 8.37 (1H, d, *J* = 4.5, H-5); 8.41 (1H, d, *J* = 8.3, H-6); 8.46-8.49 (1H, m, H-4). ^{13}C NMR spectrum, δ, ppm: 27.9 ($C(\underline{C}H_3)_3$); 38.1 (CH_2); 56.0 ($\underline{C}HCH_2$); 82.0 ($\underline{C}(CH_3)_3$); 108.7 (C-6); 112.4 (C-4'); 127.0 (C-3); 128.5 (C-3',5'); 129.4 (C-2',6'); 135.4 (C-1'); 137.1 (C-4); 155.1 (C-6); 158.0 (C-2); 175.7 (C=O). Found, %: C 63.11; H 6.12; N 12.21. $C_{18}H_{21}N_3O_4$. Calculated, %: C 62.96; H 6.16; N 12.24

***N*-(2-Nitrophenyl)-L-phenylalanine *tert*-Butyl Ester (3d).** L-Phenylalanine *t*-butyl ester hydrochloride (5.2 g, 0.020 mol) was added to a solution of 2-fluoronitrobenzene (2.6 g, 0.018 mol) in MeCN (30 ml), followed by Et_3N (3.9 g, 0.038 mol). The product was refluxed for 5 days (TLC monitoring), evaporated, EtOAc (50 ml) and water (50 ml) added, and the organic layer was separated and dried over Na_2SO_4. The product was evaporated, and the residue was chromatographed on a silica gel column using the system hexane–EtOAc (10:1). Yield 4.7 g (74%). Yellow crystals; mp 101-103ºC; $[\alpha]_D^{20}$ -117.6º (*c* 1.00, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.40 (9H, s, $C(CH_3)_3$); 3.16-3.29 (2H, m, CH_2Ph); 4.35-4.41 (1H, m, $C\underline{H}CH_2$); 6.67-6.73 (2H, m, H Ar); 7.24-7.43 (6H, m, H Ph, H Ar); 8.18 (1H, d, *J* = 8.9, H Ar); 8.19 (1H, d, *J* = 7.5, NH). ^{13}C NMR spectrum, δ, ppm: 27.9 ($C(\underline{C}H_3)_3$); 38.6 (CH_2); 57.9 ($\underline{C}HCH_2$); 82.6 ($\underline{C}(CH_3)_3$); 113.9 (C-4); 116.1 (C-6); 127.0 (C-4'); 127.3 (C-3); 128.7 (C-3',5'); 129.4 (C-2',6'); 135.8 (C-2); 136.0 (C-5); 144.0 (C-1'); 149.8 (C-1); 170.4 (C=O). Found, %: C 66.61; H 6.41; N 8.19. $C_{19}H_{22}N_2O_4$. Calculated, %: C 66.65; H 6.48; N 8.18.

Synthesis of Compounds 6a-c and 12a (General Method). Pd/C (10%) was added to a solution of compound **3a-c** (17.2 mmol) in ether (50 ml) and argon was passed through, followed by hydrogen. Hydrogenation was carried out in the hydrogen atmosphere at room temperature (TLC monitoring), and the reaction mixture was then filtered. Et_3N (3.2 ml, 22.4 mmol) was added to the filtrate containing the diamino compound **4a-c**. The product was cooled to 0ºC, and ethyl oxalyl chloride (2.3 ml, 20.6 mmol) was added dropwise. A white precipitate of triethylamine hydrochloride was formed. The mixture was stirred for 1 h at

room temperature. The precipitate was filtered off, the filtrate washed with water (2×50 ml), and the organic layer was dried over Na_2SO_4 and evaporated. Compound **5a-c** was obtained as a yellow, oily liquid which without further purification was refluxed for 10 h in toluene (100 ml) and evaporated. The residue containing the products **6a-c** and **12a** was chromatographed in the corresponding system (see further).

Ethyl 3-[(*S*)-2-*tert*-Butoxy-1-methyl-2-oxoethyl]-3*H*-imidazo[4,5-*b*]pyridine-2-carboxylate (6a). The material was chromatographed on a silica gel column using CH_2Cl_2 to give compound **6a** as a light-yellow oil. Yield 52%. $[\alpha]_D^{20}$ +16.3º (*c* 1.00, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.34 (9H, s, $C(CH_3)_3$); 1.46 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 1.86 (3H, d, *J* = 7.3, $CHC\underline{H}_3$); 4.48-4.50 (2H, m, $C\underline{H}_2CH_3$); 6.06 (1H, q, *J* = 7.3, $C\underline{H}CH_3$); 7.29 (1H, dd, *J* = 8.2, *J* = 4.4, H-6); 8.16 (1H, dd, *J* = 8.2, *J* = 1.1, H-5); 8.48 (1H, dd, *J* = 4.4, *J* = 1.1, H-7). ^{13}C NMR spectrum, δ, ppm: 14.0 ($CH_2\underline{C}H_3$); 17.0 ($CH\underline{C}H_3$); 27.9 ($C(\underline{C}H_3)_3$); 53.6 ($C\underline{H}CH_3$); 62.6 ($\underline{C}H_2CH_3$); 82.4 ($\underline{C}(CH_3)_3$); 120.0 (C-6); 129.8 (C-7); 133.7 (C-7a); 141.5 (C-3a); 146.9 (C-5); 147.4 (COOEt); 159.7 (C-2); 168.6 (COOBu-*t*). Found, %: C 60.05; H 6.52; N 13.03. $C_{16}H_{21}N_3O_4$. Calculated, %: C 60.18; H 6.63; N 13.16.

***tert*-Butyl (*S*)-2-(2,3-Dioxo-1,4-dihydropyrido[2,3-*b*]pyrazin-4-yl)propionate (12a)**. After separation of compound **6a**, chromatography was continued with ethyl acetate to give compound **12a** as gray crystals. Yield 40%; mp 97-99ºC. $[\alpha]_D^{20}$ -7.3º (*c* 1.09, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.40 (9H, s, $C(CH_3)_3$); 1.70 (3H, d, *J* = 7.3, $CHC\underline{H}_3$); 5.97 (1H, q, *J* = 7.1, $C\underline{H}CH_3$); 7.19 (1H, dd, *J* = 7.8, *J* = 4.7, H-7); 7.76 (1H, d, *J* = 7.9, H-8); 8.24 (1H, d, *J* = 4.6, H-6). ^{13}C NMR spectrum, δ, ppm: 14.4 ($CH\underline{C}H_3$); 27.8 ($C(\underline{C}H_3)_3$); 51.7; 81.9 ($\underline{C}(CH_3)_3$; 119.9 (C-8); 120.9 (C-8a); 124.5 (C-7); 137.8 (C-4a); 142.9 (C-6); 155.3 (C-3); 160.4 (C-2); 168.6 (COOBu-*t*). Found, %: C 57.68; H 5.82; N 14.48. $C_{14}H_{17}N_3O_4$. Calculated, %: C 57.72; H 5.88; N 14.42.

Ethyl 3-[(*S*)-1-(*tert*-Butoxycarbonyl)-3-methylbutyl]-3*H*-imidazo[4,5-*b*]pyridine-2-carboxylate (6b). The compound was chromatographed on a silica gel column using CH_2Cl_2 to give compound **6b** as a light-yellow oil. Yield 50%. $[\alpha]_D^{20}$ +9.5º (c 1.00, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.78 (3H, d, *J* = 6.6, $CHC\underline{H}_3$); 0.95 (3H, d, *J* = 6.6, $CHC\underline{H}_3$); 1.25-1.28 (1H, m, $C\underline{H}(CH_3)_2$); 1.33 (9H, s, $C(CH_3)_3$); 1.45 (3H, t, *J* = 7.3, $CH_2C\underline{H}_3$); 2.25-2.28 (1H, m, $CHC\underline{H}_2$); 2.43-2.45 (1H, m, $CHC\underline{H}_2$); 4.47-4.49 (2H, m, $C\underline{H}_2CH_3$); 6.06 (1H, dd, *J* = 10.2, *J* = 4.4, $C\underline{H}CH_2$); 7.29 (1H, dd, *J* = 8.2, *J* = 4.7, H-6); 8.17 (1H, dd, *J* = 8.2, *J* = 1.3, H-5); 8.49 (1H, dd, *J* = 4.6, *J* = 1.3, H-7). ^{13}C NMR spectrum, δ, ppm: 13.8 ($CH_2\underline{C}H_3$); 21.3 ($CH(\underline{C}H_3)_2$); 22.6 $CH(\underline{C}H_3)_2$); 24.9 ($\underline{C}H(CH_3)_2$); 27.4 ($C(\underline{C}H_3)_3$); 39.4 ($CH\underline{C}H_2$); 56.3 ($\underline{C}HCH_2$); 62.2 ($\underline{C}H_2CH_3$); 81.9 ($\underline{C}(CH_3)_3$); 119.5 (C-6); 129.3 (C-7); 133.2 (C-7a); 141.4 (C-3a); 146.5 (C-5); 147.6 (COOEt); 159.3 (C-2); 168.3 (COOBu-*t*). Found, %: C 63.08; H 7.45; N 11.54. $C_{19}H_{27}N_3O_4$. Calculated, %: C 63.14; H 7.53; N 11.63.

Ethyl 3-[(*S*)-1-Benzyl-2-*tert*-butoxy-2-oxoethyl]-3*H*-imidazo[4,5-*b*]pyridine-2-carboxylate (6c). The substance was chromatographed on a silica gel column using CH_2Cl_2 to give compound **6c** as a light-yellow oil. Yield 55%. $[\alpha]_D^{20}$ -44.3º (*c* 1.00, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.39-1.43 (12H, m, $C(CH_3)_3$, $CH_2C\underline{H}_3$); 3.71-3.74 (2H, m, CH_2Ph); 4.39-4.42 (2H, m, $C\underline{H}_2CH_3$); 6.36 (1H, dd, *J* = 10.4, *J* = 5.5, NCHCO); 6.85 (2H, dd, *J* = 6.6, *J* = 2.7, H Ar); 7.00-7.05 (3H, m, H Ar); 7.25 (1H, dd, *J* = 8.2, *J* = 4.6, H-6); 8.10 (1H, dd, *J* = 8.2, *J* = 1.5, H-5); 8.43 (1H, dd, *J* = 4.6, *J* = 1.3, H-7). ^{13}C NMR spectrum, δ, ppm: 14.2 ($CH_2\underline{C}H_3$); 27.9 ($C(\underline{C}H_3)_3$); 36.7 ($\underline{C}H_2Ph$); 59.3 ($\underline{C}HCH_2$); 62.6 ($\underline{C}H_2CH_3$); 82.8 ($\underline{C}(CH_3)_3$); 119.9 (C-6); 126.6 (C-7); 128.2 (C-4'); 128.9 (C-3',5'); 129.6 (C-2',6'); 133.4 (C-7a); 136.9 (C-1'); 141.5 (C-5); 146.8 (C-3a); 147.6 (COOEt); 159.7 (C-2); 167.9 (COOBu-*t*). Found, %: C 66.86; H 6.40; N 10.67. $C_{22}H_{25}N_3O_4$. Calculated, %: C 66.82; H 6.37; N 10.63.

Ethyl 1-[(*S*)-1-Benzyl-2-*tert*-butoxy-2-oxoethyl]-1*H*-benzimidazole-2-carboxylate (6d). Pd/C (10%) was added to a solution of compound **3d** (5.0 g, 0.015 mol) in ethanol (50 ml), and argon was passed through, followed by hydrogen. Hydrogenation was carried out in the hydrogen atmosphere at room temperature. After reduction of the nitro group, the product was filtered and the mother liquor was treated with a solution of glyoxalic aldehyde ester (3.0 g, 0.015 mol) (50% solution in toluene) and iodine (3.7 g, 0.015 mol). The solution obtained was stirred at room temperature for 12 h. The solution was evaporated, and the residue was chromatographed on a silica gel column using the system hexane–EtOAc (10:1), to give compound **6d** (4.7 g, 82%) as a light-yellow oil. $[\alpha]_D^{20}$ -42.7º (*c* 1.00, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.36 (3H, t,

J = 7.3, $CH_2C\underline{H}_3$); 1.40 (9H, s, $C(CH_3)_3$); 3.45 (2H, q, *J* = 7.3, $C\underline{H}_2CH_3$); 3.67-3.72 (2H, m, CH_2Ph); 6.31-6.34 (1H, m, $C\underline{H}CH_2$); 6.75-6.82 (2H, m, H Ar); 7.03-7.11 (3H, m, H Ar); 7.29-7.41 (3H, m, H Ar); 7.85-7.91 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 14.3 ($CH_2\underline{C}H_3$); 27.8 ($C(\underline{C}H_3)_3$); 36.8 ($CH\underline{C}H_2$); 60.7 ($\underline{C}HCH_2$); 62.3 ($\underline{C}H_2CH_3$); 83.1 ($\underline{C}(CH_3)_3$); 111.8 (C-7); 122.2 (C-4); 123.6 (C-6); 125.3 (C-5); 126.9 (C-4'); 128.5 (C-3',5'); 128.8 (C-2',6'); 136.5 (C-1'); 140.7 (C-7a); 141.6 (C-3a); 160.0 (COOEt); 161.1 (C-2); 167.8 (COOBu-*t*). Found, %: C 69.95; H 6.59; N 7.04. $C_{23}H_{26}N_2O_4$. Calculated, %: C 70.03; H 6.64; N 7.10.

***tert*-Butyl (*S*)-(2,3-dioxo-3,4-dihydro-2*H*-quinoxalin-1-yl)-3-phenylpropionate (12d)**. The residue, after evaporation of toluene, was chromatographed on a silica gel column using EtOAc. Yield 82%. White crystals; mp 180-182ºC. $[\alpha]_D^{20}$ -41.3º (*c* 1.00, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.35 (9H, s, $C(CH_3)_3$); 3.30-3.51 (2H, m, CH_2Ph); 5.70-5.73 (1H, m, $C\underline{H}CH_2$); 7.04-7.17 (9H, m, H Ar); 12.09 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 27.5 ($C(\underline{C}H_3)_3$); 33.3 ($CH\underline{C}H_2$); 58.1 ($\underline{C}HCH_2$); 81.5 ($\underline{C}(CH_3)_3$); 114.9 (C-5); 115.8 (C-7); 123.0 (C-8); 123.7 (C-6); 125.1 (C-4'); 126.4 (C-4a); 128.0 (C-3',5'); 129.0 (C-2',6'); 136.8 (C-8a); 136.9 (C-1'); 153.0 (C-2); 154.8 (C-3); 167.5 ($\underline{C}$OOBu-*t*). Found, %: C 68.75; H 5.97; N 7.57. $C_{21}H_{22}N_2O_4$. Calculated, %: C 68.84; H 6.05; N 7.65.

***tert*-Butyl (*S*)-2-[2-(Benzylamino)carbonyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl]propionate (7a)**. Benzylamine (0.9 g, 8.4 mmol) was added to a solution of compound **6a** (0.9 g, 2.8 mmol) in 2-PrOH (10 ml) and refluxed for 48 h. The solvent was evaporated, and the residue was chromatographed using CH_2Cl_2. Yield 84%. White crystals; mp 107-109ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.38 (9H, s, $C(CH_3)_3$); 1.96 (3H, d, *J* = 7.1, $CHC\underline{H}_3$); 4.47-4.50 (2H, m, CH_2); 6.30 (1H, q, *J* = 7.1, $C\underline{H}CH_3$); 7.29-7.42 (6H, m, H Ph, H-6); 8.04-8.07 (2H, m, H-7, NH); 8.49 (1H, d, *J* = 4.6, H-5). ^{13}C NMR spectrum, δ, ppm: 17.0 ($CH\underline{C}H_3$); 27.7 ($C(\underline{C}H_3)_3$); 43.5 ($NH\underline{C}H_2$); 53.8 ($\underline{C}HCH_3$); 82.1 ($\underline{C}(CH_3)_3$); 119.7 (C-6); 127.7 (C-7); 127.9 (C-4'); 128.5 (C-3',5'); 128.8 (C-2',6'); 128.9 (C-7a); 133.3 (C-1'); 137.5 (C-5); 144.1 (C-3a); 146.1 (CONH); 159.0 (C-2); 168.8 (COOBu-*t*). Found, %: C 66.12; H 6.21; N 14.65. $C_{21}H_{24}N_4O_3$. Calculated, %: C 66.30; H 6.36; N 14.73.

Synthesis of Compounds 13a-d (General Method). Argon was passed through a suspension of 2,4-dimethoxybenzylamine hydrochloride (1.28 g, 6.3 mmol) in CH_2Cl_2 (30 ml) and cooled to 0ºC. The reaction was carried out in an argon atmosphere. A solution of trimethyl aluminum (9.5 ml, 18.9 mmol) (a 2 mol/l solution in hexane) was added dropwise. The solution formed was stirred for 30 min at room temperature and the corresponding ester **6a-d** (6.3 mmol) in CH_2Cl_2 (10 ml) was added dropwise. The obtained orange solution was stirred at room temperature for 1 day. The reaction mixture was poured into a weakly acid aqueos solution (5% HCl), and the organic layer was separated, washed with water, and dried over Na_2SO_4. Solvent was evaporated, and the residue was chromatographed on a silica gel column using the system hexane–EtOAc (10:1).

***tert*-Butyl (*S*)-2-[2-(2,4-Dimethoxybenzylaminocarbonyl)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]propionate (13a)**. Yield 41%. Light-yellow oil. $[\alpha]_D^{20}$ +8.8º (*c* 1.10, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.34 (9H, s, $C(CH_3)_3$); 1.93 (3H, d, *J* = 7.2, $CHC\underline{H}_3$); 3.81 (3H, s, 2'-OCH_3); 3.88 (3H, s, 4'-OCH_3); 4.55-4.58 (2H, m, CH_2); 6.30 (1H, q, *J* = 7.2, $C\underline{H}CH_3$); 6.47-6.49 (2H, m, H Ar); 7.28-7.30 (2H, m, H Ar, H-6); 8.07-8.09 (2H, m, H-7, NH); 8.46 (1H, dd, *J* = 4.6, *J* = 1.5, H-5). ^{13}C NMR spectrum, δ, ppm: 17.0 ($CH\underline{C}H_3$); 27.8 ($C(\underline{C}H_3)_3$); 38.8 (CH_2); 53.7 ($\underline{C}HCH_3$); 55.4 (2-CH_3O, 4-CH_3O); 82.0 ($\underline{C}(CH_3)_3$); 98.6 (C-3'); 100.0 (C-5'); 103.9 (C-1'); 118.1 (C-6); 119.5 (C-7); 123.0 (C-7a); 128.4 (C-6'); 130.6 (C-5); 133.3 (C-3a); 145.8 (CONH); 158.7 (C-4'); 160.4 (C-2); 160.7 (C-2'); 168.8 (COOBu-*t*). Found, %: C 62.62; H 6.35; N 12.66. $C_{23}H_{28}N_4O_5$. Calculated, %: C 62.71; H 6.41; N 12.72.

***tert*-Butyl (*S*)-2-[2-(2,4-Dimethoxybenzylaminocarbonyl)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]-4-methylpentanoate (13b)**. Yield 43%. Light-yellow oil. $[\alpha]_D^{20}$ +5.5º (*c* 1.03, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.82 (3H, d, *J* = 6.4, $CHC\underline{H}_3$); 1.01 (3H, d, *J* = 6.4, $CHC\underline{H}_3$); 1.00-1.04 (10H, m, $C(CH_3)_3$, $C\underline{H}(CH_3)_2$); 2.28-2.35 (1H, m) and 2.55-2.63 (1H, m, $C\underline{H}_2CH$); 3.81 (3H, s, 2'-OCH_3); 3.88 (3H, s, 4'-OCH_3); 4.57-4.59 (2H, m, CH_2); 6.27-6.30 (1H, m, $C\underline{H}CH_2$); 6.42-6.50 (2H, m, H Ar); 7.23-7.31 (2H, m, H Ar, H-6); 8.02-8.11 (2H, m, H-5,7); 8.45-8.48 (1H, m, NH). ^{13}C NMR spectrum, δ, ppm: 21.4 ($CH(\underline{C}H_3)_2$); 22.7 ($CH(\underline{C}H_3)_2$); 25.0 ($\underline{C}H(CH_3)_2$); 27.4 ($C(\underline{C}H_3)_3$); 38.3 (CH_2Ph); 39.3 ($CH\underline{C}H_2$); 55.0 (2',4'-OCH_3); 56.4 ($\underline{C}HCH_2$); 81.5 ($\underline{C}(CH_3)_3$); 98.2 (C-3'); 103.6 (C-5'); 117.8 (C-1'); 118.9 (C-6); 127.9 (C-7); 130.1 (C-7a); 132.7 (C-6'); 144.35 (C-4); 145.3

(C-3a); 148.1 (CONH); 158.2 (C-4'); 158.3 (C-2); 160.3 (C-4'); 168.6 (COOBu-*t*). Found, %: C 64.61; H 7.04; N 11.56. $C_{26}H_{34}N_4O_5$. Calculated, %: C 64.71; H 7.10; N 11.61.

***tert*-Butyl (*S*)-2-[2-(2,4-Dimethoxybenzylaminocarbonyl)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]-3-phenylpropionate (13c)**. Yield 39%. Light-yellow oil. $[\alpha]_D^{20}$ -40.7º (*c* 1.10, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.38 (9H, s, $C(CH_3)_3$); 3.75-3.84 (5H, m, $C\underline{H}_2Ar$, 2'-OCH_3); 3.86 (3H, s, 4'-OCH_3); 4.51-4.52 (2H, m, CH_2Ar); 6.44-6.50 (2H, m, $C\underline{H}CH_2$, H Ar); 6.57-6.69 (1H, m, H Ar); 6.87-7.01 (5H, m, H Ph); 7.18-7.25 (2H, m, H Ar, H-6); 7.84-7.91 (1H, m, H-7); 7.95 (1H, d, *J* = 8.1, H-5); 8.39 (1H, d, *J* = 4.6, NH). ^{13}C NMR spectrum, δ, ppm: 27.4 ($C(\underline{C}H_3)_3$); 36.2 ($CH\underline{C}H_2$); 38.1 (CH_2Ph); 54.9 (2',4'-OCH_3); 58.4 ($\underline{C}HCH_2$); 81.8 ($\underline{C}(CH_3)_3$); 98.1 (C-3'); 103.5 (C-5'); 117.6 (C-1'); 118.8 (C-6); 125.8 (C-7); 127.5 (C-3",5"); 127.7 (C-4"); 128.5 (C-2",6"); 130.0 (C-5'); 132.4 (C-7a); 136.8 (C-5); 143.9 (C-1"); 145.1 (C-7a); 147.6 (CONH); 158.1 (C-4'); 158.2 (C-2); 160.2 (C-2'); 167.6 (COOBu-*t*). Found, %: C 67.33; H 6.18; N 10.77. $C_{29}H_{32}N_4O_5$. Calculated, %: C 67.43; H 6.24; N 10.85.

***tert*-Butyl (*S*)-2-[2-(2,4-Dimethoxybenzylaminocarbonyl)-1*H*-benzimidazol-1-yl]-3-phenylpropionate (13d)**. Yield 23%. Light-yellow oil. $[\alpha]_D^{20}$ -30.1º (c 0.99, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.40 (9H, s, $C(CH_3)_3$); 3.46-3.56 (1H, m) and 3.67-3.74 (1H, m, CH_2Ar); 3.81 (3H, s, 2'-OCH_3); 3.85 (3H, s, 4'-OCH_3); 4.45-4.50 (2H, m, CH_2Ar); 6.43-6.50 (2H, m, H Ar, $C\underline{H}CH_2$); 6.79-6.84 (3H, m, H Ar); 6.94-7.05 (3H, m, H Ar); 7.15-7.21 (1H, m, H Ar); 7.28-7.32 (3H, m, H Ar); 7.68-7.85 (1H, m, H Ar); 7.86-7.93 (1H, m, NH). ^{13}C NMR spectrum, δ, ppm: 27.4 ($C(\underline{C}H_3)_3$); 36.5 ($CH\underline{C}H_2$); 38.1 (CH_2Ar); 55.0 (2',4'-OCH_3); 59.9 (NCH); 82.3 ($\underline{C}(CH_3)_3$); 98.1 (C-3'); 103.6 (C-5'); 111.7 (C-7); 117.9 (C-1'); 120.3 (C-4); 122.9 (C-6); 123.9 (C-5); 126.2 (C-4"); 127.8 (C-3",5"); 128.5 (C-2",6"); 130.0 (C-6'); 134.9 (C-7a); 136.3 (C-1"); 140.6 (C-3a); 143.1 (CONH); 158.2 (C-4'); 158.7 (C-2); 160.3 (C-2'); 167.7 (COOBu-*t*). Found, %: C 69.79; H 6.39; N 8.07. $C_{30}H_{33}N_3O_5$. Calculated, %: C 69.88; H 6.45; N 8.15.

Synthesis of Compounds 9a, 15a-d (General Method). The corresponding amide **7a** or **13a-d** (1.8 mmol) was dissolved in formic acid (10 ml) and stirred for 48 h at 50ºC. Solvent was evaporated, and the residue was chromatographed using CH_2Cl_2.

7-Benzyl-9-methyl-7*H*,9*H*-pyrido[3',2':4,5]imidazo[1,2-*a*]pyrazine-6,8-dione (9a). Yield 47%; mp 179-181ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.04 (3H, d, *J* = 6.9, CH_3); 5.24-5.28 (2H, m, CH_2); 5.55 (1H, q, *J* = 7.0, $C\underline{H}CH_3$); 7.31-7.34 (3H, m, H Ph); 7.43 (1H, dd, *J* = 8.3, *J* = 4.6, H-3); 7.50-7.54 (2H, m, H Ph); 8.30 (1H, d, *J* = 8.3, H-4); 8.60 (1H, d, *J* = 4.5, H-2). ^{13}C NMR spectrum, δ, ppm: 20.7 ($CH\underline{C}H_3$); 43.8 (CH_2); 54.2 ($\underline{C}HCH_3$); 120.8 (C-3); 128.1 (C-4); 128.7 (C-4'); 129.3 (C-3',5'); 130.7 (C-2',6'); 133.0 (C-4a); 136.1 (C-1'); 137.8 (C-2); 148.0 (C-10a); 152.5 (C-6); 169.2 (C-5a); 173.0 (C-8). Found, %: C 66.41; H 4.61; N 18.29. $C_{17}H_{14}N_4O_2$. Calculated, %: C 66.66; H 4.61; N 18.29.

7-(2,4-Dimethoxybenzyl-9-methyl-7*H*,9*H*-pyrido[3',2':4,5]imidazo[1,2-*a*]pyrazine-6,8-dione (15a). Yield 53%. White crystals; mp 174-176ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.02 (3H, d, *J* = 7.1, CH_3); 3.78 (3H, s, 2-OCH_3); 3.81 (3H, s, 4-OCH_3); 5.10-5.13 (1H, m) and 5.31-5.33 (1H, m, CH_2Ar); 5.52 (1H, q, *J* = 7.0, $C\underline{H}CH_3$); 6.41-6.43 (2H, m, H Ar); 7.20 (1H, d, *J* = 8.8, H Ar); 7.42 (1H, dd, *J* = 8.2, *J* = 4.6, H-3); 8.28 (1H, dd, *J* = 8.2, *J* = 1.2, H-4); 8.59 (1H, dd, *J* = 4.6, *J* = 1.2, H-2). ^{13}C NMR spectrum, δ, ppm: 20.7 ($CH\underline{C}H_3$); 39.6 (CH_2Ar); 54.2 ($\underline{C}HCH_3$); 55.4 (2'-OCH_3); 55.5 (4'-OCH_3); 98.6 (C-3'); 104.1 (C-5'); 115.9 (C-3); 118.6 (C-1'); 120.7 (C-4); 130.5 (C-4a); 130.6 (C-6'); 136.1 (C-2); 145.8 (C-10a); 147.8 (C-6); 155.3 (C-5a); 158.5 (C-4'); 160.6 (C-2'); 169.0 (C-8). Found, %: C 62.10; H 5.02; N 15.31. $C_{19}H_{18}N_4O_4$. Calculated, %: C 62.29; H 4.95; N 15.29.

7-(2,4-Dimethoxybenzyl)-9-isobutyl-7*H*,9*H*-pyrido[3',2':4,5]imidazo[1,2-*a*]pyrazine-6,8-dione (15b). Yield 73%. White crystals; mp 147-149ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.70 (3H, d, *J* = 6.4) and 0.91 (3H, d, *J* = 6.4, $CH(C\underline{H}_3)_2$); 0.80-0.90 (1H, m, $C\underline{H}(CH_3)_2$); 2.15-2.24 (1H, m) and 2.29-2.37 (1H, m, $CHC\underline{H}_2$); 3.78 (3H, s, 2'-OCH_3); 3.79 (3H, s, 4'-OCH_3); 5.21 (2H, dd, *J* = 21.2, *J* = 12.2, CH_2Ar); 5.52 (1H, dd, *J* = 7.4, *J* = 4.8, $C\underline{H}CH_2$); 6.40-6.44 (2H, m, H Ar); 7.20-7.23 (1H, m, H Ar); 7.41 (1H, dd, *J* = 8.1, *J* = 4.8, H-3); 8.28 (1H, dd, *J* = 8.1, *J* = 1.3, H-4); 8.58 (1H, dd, *J* = 4.8, *J* = 1.3, H-2). ^{13}C NMR spectrum, δ, ppm: 22.3 ($CH(\underline{C}H_3)_2$); 22.7 ($CH(\underline{C}H_3)_2$); 24.3 ($\underline{C}H(CH_3)_2$); 39.5 ($CH\underline{C}H_2$); 43.0 (CH_2Ar); 55.4 (2'-OCH_3); 55.5

(4'-OCH_3); 57.2 ($\underline{C}HCH_2$); 98.4 (C-3'); 103.9 (C-5'); 115.9 (C-3); 120.6 (C-1'); 130.5 (C-4); 130.8 (C-4a); 135.9 (C-6'); 138.7 (C-2); 145.8 (C-10a); 147.8 (C-6); 155.5 (C-5a); 158.5 (C-4'); 160.6 (C-2'); 168.4 (C-8). Found, %: C 64.61; H 5.87; N 13.64. $C_{22}H_{24}N_4O_4$. Calculated, %: C 64.69; H 5.92; N 13.72.

9-Benzyl-7-(2,4-dimethoxybenzyl)-7*H*,9*H*-pyrido[3',2':4,5]imidazo[1,2-*a*]pyrazine-6,8-dione (15c). Yield 59%. White crystals; mp 164-165ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.62-3.69 (1H, m) and 4.02-4.08 (1H, m, CH$\underline{C}H_2$); 3.77 (3H, s, 2'-OCH_3); 3.79 (3H, s, 4'-OCH_3); 5.01 (2H, s, CH_2Ar); 5.82 (1H, dd, *J* = 4.8, *J* = 3.2, C$\underline{H}CH_2$); 6.31-6.42 (4H, m, H Ar); 6.89-7.00 (3H, m, H Ar); 7.09-7.15 (1H, m, H Ar); 7.48 (1H, dd, *J* = 8.3, *J* = 4.3, H-3); 8.31 (1H, d, *J* = 8.3, H-4); 8.68 (1H, d, *J* = 4.3, H-2). ^{13}C NMR spectrum, δ, ppm: 38.6 (CH$\underline{C}H_2$); 39.1 (CH_2Ar); 55.4 (2'-OCH_3); 55.5 (4'-OCH_3); 58.9 ($\underline{C}HCH_2$); 98.4 (C-3'); 104.0 (C-5'); 115.7 (C-3); 120.8 (C-1'); 127.9 (C-4); 128.8 (C-4"); 128.9 (C-3",5"); 130.3 (C-4a); 130.8 (C-2",6"); 132.9 (C-6'); 135.9 (C-1"); 139.0 (C-2); 145.8 (C-10a); 147.9 (C-6); 154.8 (C-5a); 158.4 (C-4'); 160.5 (C-2'); 168.0 (C-8). Found, %: C 67.79; H 5.09; N 12.58. $C_{25}H_{22}N_4O_4$. Calculated, %: 67.86; H 5.01; N 12.66.

4-Benzyl-2-(2,4-dimethoxybenzyl)-2*H*,4*H*-pyrazino[1,2-*a*]benzimidazole-1,3-dione (15d). Yield 68%. White crystals; mp 213-215ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.54-3.67 (2H, m, CHC$\underline{H_2}$); 3.77 (3H, s, 2'-OCH_3); 3.79 (3H, s, 4'-OCH_3); 4.92-5.04 (2H, m, CH_2Ar); 5.61-5.65 (1H, м, C$\underline{H}CH_2$); 6.33–6.43 (4H, m, H Ar); 6.89-6.93 (1H, m, H Ar); 6.99-7.05 (2H, m, H Ar); 7.13-7.21 (1H, m, H Ar); 7.46-7.56 (3H, m, H Ar); 8.01-8.06 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 38.9 (CH$\underline{C}H_2$); 39.6 (CH_2Ar); 55.4 (2'-OCH_3); 55.5 (4'-OCH_3); 59.5 ($\underline{C}HCH_2$); 98.4 (C-3'); 104.0 (C-5'); 111.0 (C-6); 123.0 (C-9); 124.8 (C-1'); 126.4 (C-7); 128.2 (C-8); 128.7 (C-4"); 128.8 (C-3",5"); 128.9 (C-2",6"); 130.1 (C-5a); 132.4 (C-6'); 132.9 (C-1"); 138.6 (C-9a); 140.3 (C-1); 143.7 (C-10a); 158.3 (C-4'); 160.4 (C-2'); 168.0 (C-3). Found, %: C 70.71; H 5.20; N 9.43. $C_{26}H_{23}N_3O_4$. Calculated, %: C 70.74; H 5.25; N 9.52.

9-Methyl-6,7,8,9-tetrahydropyrido[3',2':4,5]imidazo[1,2-*a*]pyrazine Dihydrobromide (11a). The BH_3·THF complex (1 mol/l in THF, 5 ml) was added dropwise to a suspension of compound **15a** (0.10 g, 0.3 mmol) in THF (10 ml) cooled in an ice bath under a stream of argon. Cooling was removed and the product was stirred for 10 h at room temperature. The solution obtained was treated with MeOH (5 ml) and evaporated. The residue was treated with trifluoroacetic acid (10 ml) and stirred for 10 h. The violet solution was evaporated, 20% aqueous HBr solution (20 ml) was added, and it was washed with ethyl acetate (2×20 ml). The aqueous layer was separated and evaporated to dryness, and the residue was washed with acetonitrile. The precipitate was filtered off, washed with ether, and dried over Na_2SO_4 to give compound **11a** (0.06 g, 57%) as a cream colored powder. Mp 235ºC (sublimes). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.77 (3H, d, *J* = 6.6, CH_3); 3.81-3.83 (1H, m) and 3.96-3.98 (1H, m, CHC$\underline{H_2}$); 4.96-4.99 (2H, m, $\underline{C}H_2NH$); 5.18-5.20 (1H, m, C$\underline{H}CH_3$); 7.59 (1H, dd, *J* = 8.2, *J* = 4.9, H-3); 8.24 (1H, d, *J* = 8.2, H-4); 8.52 (1H, d, *J* = 4.8, H-2). ^{13}C NMR spectrum, δ, ppm: 17.9 (CH_3); 41.9 (CH_2NH); 45.9 ($\underline{C}HCH_2$); 47.2 (CH$\underline{C}H_2$); 119.8 (C-3); 127.0 (C-4); 133.2 (C-4a); 144.5 (C-2); 146.2 (C-10a); 146.7 (C-5a). Found, %: C 34.11; H 4.12; N 15.90. $C_{10}H_{14}N_4Br_2$. Calculated, %: C 34.31; H 4.03; N 16.01.

Ethyl 3-(*S*)-2-[(2,4-Dimethoxybenzylamino)-1-methyl-2-oxoethyl]-3*H*-imidazo[4,5-*b*]pyridine-2-carboxylate (18). A solution of compound **6a** (0.50 g, 1.6 mmol) in formic acid (10 ml) was stirred for 3 days at room temperature. The solution obtained was evaporated and dissolved in CH_2Cl_2 (10 ml). Diisopropylethylamine (1.03 g, 8.0 mmol), 2,4-dimethoxybenzylamine (0.34 g, 1.7 mmol), and PyBOP (0.99 g, 1.9 mmol) were added. The obtained suspension was stirred for 12 h, water (20 ml) was added, and the organic layer was separated and dried over Na_2SO_4. Solvent was evaporated and the residue was chromatographed on a silica gel column using the system hexane–EtOAc (1:1). Initially, compound **15a** (0.29 g, 50%) was eluted followed by compound **18** (0.04 g, 6%). White crystals; mp 61-63ºC. $[\alpha]_D^{20}$ +17.3º (c 1.00, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.43 (3H, t, *J* = 7.4, $CH_2C\underline{H_3}$); 1.90 (3H, d, *J* = 7.3, CHC$\underline{H_3}$); 3.57 (3H, s, 2'-OCH_3); 3.77 (3H, s, 4'-OCH_3); 4.22-4.29 (1H, m, CH_2Ar); 4.35-4.44 (3H, m, C$\underline{H_2}CH_3$, C$\underline{H_2}$Ar); 6.15 (1H, dd, *J* = 14.5, *J* = 7.5, C$\underline{H}CH_3$); 6.31-6.42 (3H, m, H Ar); 7.33 (1H, dd, *J* = 8.3, *J* = 4.8, H-6); 8.18 (1H, dd, *J* = 8.3, *J* = 1.3,

TABLE 1. Basic Bond Lengths (*l*) in the Compound **9a** Structure

Bond	*l*, Å	Bond	*l*, Å	Bond	*l*, Å
N(1)–C(2)	1.447(3)	C(5)–C(6)	1.466(3)	C(14)–C(15)	1.510(3)
N(1)–C(6)	1.360(2)	C(6)–N(7)	1.320(3)	C(15)–C(16)	1.365(3)
N(1)–C(13)	1.385(3)	N(7)–C(8)	1.376(3)	C(15)–C(20)	1.355(3)
C(2)–H(2)	0.980(2)	C(8)–C(9)	1.404(3)	C(16–H(16)	0.930(2)
C(2)–C(21)	1.518(3)	C(8)–C(13)	1.392(3)	C(16)–C(17)	1.397(3)
C(2)–C(3)	1.515(3)	C(9)–H(9)	0.929(2)	C(17)–H(17)	0.930(2)
C(21)–H(21A)	0.960(2)	C(9)–C(10)	1.352(3)	C(17)–C(18)	1.358(3)
C(21)–H(21A)	0.961(2)	C(10)–H(10)	0.929(2)	C(18)–H(18)	0.929(3)
C(21)–H(21C)	0.960(2)	C(10)–C(11)	1.396(3)	C(18)–C(19)	1.342(3)
C(3)–O(3)	1.217(3)	C(11)–H(11)	0.929(2)	C(19)–H(19)	0.929(2)
C(3)–N(4)	1.381(3)	C(11)–N(12)	1.335(3)	C(19)–C(20)	1.385(4)
N(4)–C(5)	1.397(3)	N(12)–C(13)	1.322(2)	C(20)–H(20)	0.931(2)
N(4)–C(14)	1.472(3)	C(14)–H(14A)	0.970(2)		
C(5)–O(5)	1.218(2)	C(14)–H(14B)	0.970(2)		

TABLE 2. Valence Angles (ω) in the Compound **9a** Structure

Angle	ω,deg.	Angle	ω, deg.
C(2)–N(1)–C(6)	125.7(2)	N(1)–C(6)–N(7)	114.8(2)
C(2)–N(1)–C(13)	128.7(2)	C(5)–C(6)–N(7)	125.0(2)
C(6)–N(1)–C(13)	105.3(1)	C(6)–N(7)–C(8)	103.3(2)
N(1)–C(2)–H(2)	108.4(2)	N(7)–C(8)–C(9)	131.5(2)
N(1)–C(2)–C(21)	111.8(2)	N(7)–C(8)–C(13)	111.2(2)
N(1)–C(2)–C(3)	111.4(2)	C(9)–C(8)–C(13)	117.3(2)
H(2)–C(2)–C(21)	108.3(2)	C(8)–C(9)–H(9)	122.1(2)
H(2)–C(2)–C(3)	108.3(2)	C(8)–C(9)–C(10)	115.9(2)
C(21)–C(2)–C(3)	108.5(2)	H(9)–C(9)–C(10)	122.0(2)
C(2)–C(21)–H(21A)	109.5(2)	C(9)–C(10)–H(10)	119.2(2)
C(2)–C(21)–H(21B)	109.5(2)	C(9)–C(10)–C(11)	121.6(2)
C(2)–C(21)–H(21C)	109.6(2)	H(10)–C(10)–C(11)	119.2(2)
H(21A)–C(21)–H(21B)	109.5(2)	C(10)–C(11)–H(11)	117.7(2)
H(21A)–C(21)–H(21C)	109.4(2)	C(10)–C(11)–N(12)	124.4(2)
H(21B)–C(21)–H(21C)	109.3(2)	H(11)–C(11)–N(12)	117.9(2)
C(2)–C(3)–O(3)	118.6(2)	C(11)–N(12)–C(13)	112.6(2)
C(2)–C(3)–N(4)	120.7(2)	N(1)–C(13)–C(8)	105.4(2)
O(3)–C(3)–N(4)	120.6(2)	N(1)–C(13)–N(12)	126.4(2)
C(3)–N(4)–C(5)	123.8(2)	C(8)–C(13)–N(12)	128.1(2)
C(3)–N(4)–C(14)	119.4(2)	N(4)–C(14)–H(14A)	109.1(2)
C(5)–N(4)–C(14)	116.8(2)	N(4)–C(14)–H(14B)	109.1(2)
N(4)–C(5)–O(5)	121.5(2)	N(4)–C(14)–C(15)	112.6(2)
N(4)–C(5)–C(6)	116.4(2)	H(14A)–C(14)–H(14B)	107.8(2)
O(5)–C(5)–C(6)	122.0(2)	H(14A)–C(14)–C(15)	109.1(2)
N(1)–C(6)–C(5)	120.2(2)		

H-7); 8.47 (1H, dd, J = 4.8, J = 1.3, H-5). ^{13}C NMR spectrum, δ, ppm: 13.7 ($CH_2\underline{C}H_3$); 16.2 ($CH\underline{C}H_3$); 39.2 (CH_2Ar); 54.5 (2'-OCH_3); 54.6 (4'-OCH_3); 55.0 ($\underline{C}HCH_3$); 62.4 ($\underline{C}H_2CH_3$); 98.1 (C-3'); 103.5 (C-5'); 118.0 (C-1'); 119.7 (C-6); 129.5 (C-7); 130.0 (C-6'); 133.5 (C-7a); 141.4 (C-5); 146.7 (C-3a); 147.0 (COOEt); 158.0 (C-4'); 159.0 (C-2); 160.0 (C-2'); 168.2 (CONH). Found, %: C 61.08; H 5.79; N 13.53. $C_{21}H_{24}N_4O_5$. Calculated, %: C 61.16; H 5.87; N 13.58.

X-ray Structural Analysis of Compound 9a. Monoclinic crystals of 7-benzyl-9-methyl-7*H*,9*H*-pyrido[3',2':4,5]imidazo[1,2-*a*]pyrazine-6,8-dione (**9a**) were obtained by crystallization from EtOAc. Parameters were: a = 30.4142(15), b = 4.9443(3), c = 19.8461(12) Å, α = 90.00, β = 102.848(10), γ = 90.00º, V = 2909.68 Å^3, M = 306.33, Z = 8, space group C 2/c, R factor 3.27%. The X-ray structural data is given in Tables 1 and 2 and has been placed in the Cambridge Crystallographic Data Center as deposit CCDC 853690.

REFERENCES

1. P. K. Dubey, R. V. Kumar, A. Naidu, and S. M. Kulkarni, *Asian J. Chem.*, **14**, 1129 (2002).
2. A. V. Kurkin, K. V. Bukhryakov, and M. A. Yurovskaya, *Khim. Geterotsikl. Soedin.*, 237 (2009). [*Chem. Heterocycl. Compd.*, **45**, 190 (2009)].
3. O. Cherkaoui, E. M. Essassi, and R. Zniber, *Bull. Soc. Chim. Fr.*, **128**, 255 (1991).
4. H. Matrick and A. R. Day, *J. Org. Chem.*, **26**, 1511 (1961).
5. H. C. Hansen and F. Watjen, US Pat. Appl. 4968682.
6. T. W. Greene and P. G. Wuts in: *Protective Groups in Organic Synthesis*, Second Edition, John Wiley & Sons, New York (1991).
7. F. A. Carey and R. J. Sundberg in: *Advanced Organic Chemistry. Part B. Reactions and Synthesis*, 4th Edition, Kluwer Academic/Plenum Publishers, New York (2000), p. 177.
8. R. W. Roeske, *Chem. Ind.* (London), 1121 (1959).