Synthesis of stereoisomeric 4-(2-methylindolin-1-yl)- and 4-(2-methylindol-1-yl) derivatives of glutamic acid *

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The reaction of dimethyl (2*S*,4*RS*)-*N*-phthaloyl-4-bromoglutamate with 2-methylindoline afforded diastereomeric 4-(2-methylindolin-1-yl)-(*S*)-glutamic acid derivatives, whose oxidation gave rise to 4-(2-methylindol-1-yl)-(*S*)-glutamic acid derivatives.

Key words: glutamic acid, 2-methylindoline, 2-methylindole, nucleophilic substitution, stereoisomers.

Nucleophilic substitution of halogen in 4-halogeno derivatives of glutamic acid is widely used for the synthesis of its 4-amino derivatives,[1—4] which attract interest because of their biological activity.[5—8] Residues of 4-amino derivatives of glutamic acid were introduced into analogs of known antitumor pharmaceuticals instead of glutamic acid to change their spectrum of action.[9,10]

The aim of the present study was to synthesize glutamic acid derivatives containing 2-methylindoline and 2-methylindole residues at position 4.

Dimethyl (2*S*,4*RS*)-*N*-phthaloyl-4-bromoglutamate (**1**) was used as the starting compound. The reaction of **1** with racemic 2-methylindoline (**2**) afforded diastereomeric dimethyl (2*S*,4*RS*)-*N*-phthaloyl-4-[(2*RS*)-2-methylindolin-1-yl]glutamates (**3a—d**) (Scheme 1).

The presence of four isomeric products in the reaction mixture was confirmed by ^{1}H NMR spectroscopy and HPLC.

Diastereomer **3a** (*de* 92.1%) was isolated from the reaction mixture by crystallization. A mixture of diastereomers enriched in isomer **3b** (*de* 33%) was isolated by column chromatography. A mixture of isomers **3c** and **3d** in a ratio of 1.1 : 1.0 was not separated because of the similarity of their properties. Diastereomer **3c** (*de* 84%) was isolated by preparative HPLC from a mixture of diastereomers **3a** and **3c**, which was prepared by the reaction of bromide **1** with enantiomerically pure (*S*)-2-methylindoline (**2a**).

The assignment of the configuration of the diaminopentanedioic acid residue in compounds **3a—d** to either (2*S*,4*S*) (*threo*) or (2*S*,4*R*) (*erythro*) was made based on the ^{1}H NMR spectroscopic data taking into account that the difference in the chemical shifts of the protons of the CH_2 group ($\Delta\delta$) in the spectra of compounds possessing the (2*S*,4*S*) configuration is smaller than that in the spectra of the corresponding (2*S*,4*R*) diastereomers[1,2] (Table 1).

Table 1. Data from ^{1}H NMR spectroscopy of compounds **3a—d** and **4a,b**

Compound	Configuration of C(2), C(4), C(2′)	δ		
		$H_2C(3)$		$\Delta\delta = \delta_A - \delta_B$
		H_A	H_B	
3a	*S*, *S*, *S*	2.92 (m)		—
3b	*S*, *S*, *R*	3.20 (ddd)	3.02 (ddd)	0.18
3c	*S*, *R*, *S*	3.20 (ddd)	2.61 (ddd)	0.59
3d	*S*, *R*, *R*	3.11 (ddd)	2.51 (ddd)	0.60
4a	*S*, *S*	3.34 (ddd)	3.28 (ddd)	0.06
4b	*S*, *R*	3.32 (m)	3.16 (m)	0.16

To determine the configuration of the 2-methylindoline residue in compounds **3a—d**, we synthesized (*S*)-2-methylindoline (**2a**) (*ee* > 99%) according to a known procedure[11] and carried out its reaction with compound **1**. The reaction afforded isomers **3a** and **3c**, which is evidence for the (*S*) configuration of the chiral center in the 2-methylindoline fragment of these compounds. Besides, this fact indicates that the starting compound **1** and diamino derivatives **3a—d** do not undergo C(2)-epimerization in the course of the reaction. Otherwise, the reaction mixture would contain four diastereomeric products.

The absolute configuration of compound **3a** was also confirmed by X-ray diffraction analysis (Fig. 1) taking into account the known (2*S*) configuration of the C(2) atom of the diester fragment.

The above data allowed us to determine the ratio between diastereomers **3a—d** in mixtures of the reaction products based on the results of ^{1}H NMR spectroscopy and HPLC. The reaction of bromide **1** with 2-methyl-

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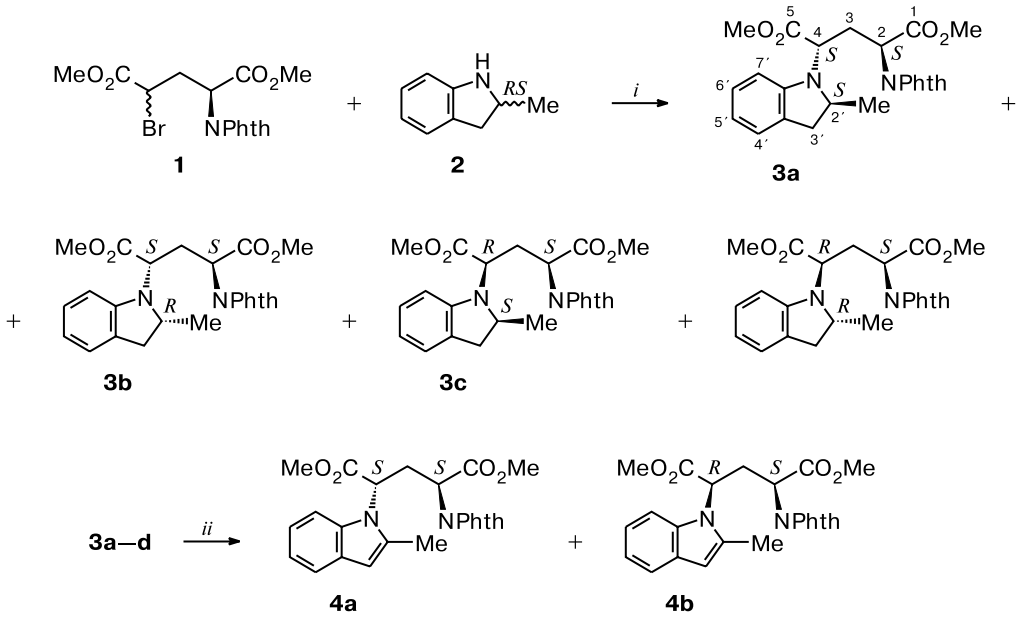
Scheme 1



Phth is phthaloyl

Reagents and conditions: *i*. MeCN or EtOH, Δ, 35 h; *ii*. DDQ, toluene, Δ, 30 min.

indoline was found to proceed diastereoselectively. Heating of compound **1** (the ratio of the diastereomers (2*S*,4*S*) : (2*S*,4*R*) ≈ 1 : 1) with racemic compound **2** in acetonitrile afforded a mixture of diastereomers **3a**, **3b**, **3c**, and **3d** in a ratio of 43 : 34 : 13 : 10 (^{1}H NMR spectroscopic data), *i.e.*, the products with the (2*S*,4*S*) configuration of the chain prevail, as in the case of the reactions of compound **1** with arylamines.[1,2]

The use of ethanol instead of acetonitrile led to but a small change in the ratio of products **3a—d**.

Oxidation of a mixture of diastereomers **3a—d** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded a mixture of diastereomeric dimethyl (2*S*,4*RS*)-*N*-phthaloyl-4-(2-methylindol-1-yl)glutamates (**4a**, **4b**) (see Scheme 1). Oxidation of a mixture of isomers **3a—d** with the diastereomer ratio **3a** : **3b** : **3c** : **3d** =

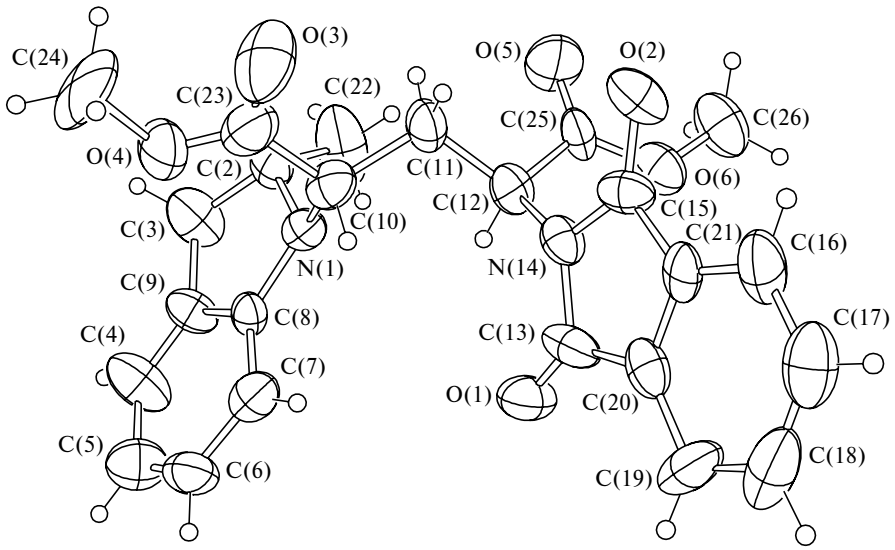


Fig. 1. Molecular view of **3a**.

41.9 : 39.0 : 10.9 : 8.2 gave rise to a mixture of diastereomers **4a** and **4b** in a ratio of 82 : 18 (HPLC and ^{1}H NMR spectroscopic data).

A mixture of diastereomers enriched in **4b** (*de* 32%), was isolated by chromatography.

The configurations of the reaction products were determined by ^{1}H NMR spectroscopy (see Table 1). The configuration of stereoisomer **4a** was also confirmed by the fact that it was formed by oxidation of compound **3a** having the (2*S*,4*S*) configuration.

To summarize, we synthesized for the first time stereoisomeric derivatives of 4-(2-methylindolin-1-yl)- and 4-(2-methylindol-1-yl)glutamic acid. The reaction of protected 4-bromoglutamic acid **1** with 2-methylindoline was demonstrated to proceed diastereoselectively to form predominantly *threo*-diastereomeric products.

Experimental

Dimethyl (2*S*,4*RS*)-*N*-phthaloyl-4-bromoglutamate (**1**) was prepared according to a known procedure.[12] Commercial (*RS*)-2-methylindoline (Aldrich) and DDQ (Lancaster) were used.

The ^{1}H NMR spectra (δ, *J*/Hz) were recorded on a Bruker DRX-400 instrument (400.13 MHz) in $CDCl_3$ with $SiMe_4$ as the internal standard. The IR spectra were measured on a Specord IR-75 instrument in Nujol mulls. Melting points were determined on a Boetius instrument. Elemental analysis was carried out on a CHNSO Carlo Erba EA 1102 analyzer.

Mixtures of diastereomers were analyzed by HPLC on a Merck—Hitachi chromatograph (L-4000A UV Detector, D-2500A Chromato-Integrator) equipped with a 250×4-mm Hibar Pre-packed RT250-4 column with LiChrosorb Si-60 (5 μm); an 80 : 1 hexane—propan-2-ol mixture was used as the mobile phase; the elution rate was 1.0 mL min^{-1}. The detection was carried out at a wavelength of 230 nm.

X-ray diffraction data were collected on a Bruker P4 diffractometer (Mo-Kα radiation, graphite monochromator, ω scanning technique in the region $2\theta < 45°$, the scan range was 3.5°).

The TLC analysis was performed on Sorbfil plates; visualization was carried out with UV light and iodine vapor. Preparative column chromatography was performed using L 40/100 μ silica gel (Chemapol).

Dimethyl (2*S*,4*RS*)-*N*-phthaloyl-4-[(2*RS*)-2-methylindolin-1-yl]glutamates (3a—d). ***A.*** A solution of bromide **1** (5.01 g, 13.04 mmol) and amine **2** (4.7 mL, 36.10 mmol) in dry MeCN (50 mL) was refluxed for 35 h. The precipitate was separated and the filtrate was concentrated under reduced pressure. A solution of the residue in ethyl acetate was washed successively with 1 *M* HCl, water, 5% $NaHCO_3$, and water. The solution was dried with Na_2SO_4, the solvent was removed *in vacuo*, and the residue was dried over P_2O_5 at 50 °C. An amorphous product was obtained in a yield of 5.50 g (96.7%). According to the ^{1}H NMR spectroscopic data, the diastereomer ratio **3a** : **3b** : **3c** : **3d** was 43 : 34 : 13 : 10. The retention times were 13.4 (**3a**), 12.8 (**3b**), and 11.7 min (**3c** and **3d**).

B. A solution of bromide **1** (192 mg, 0.50 mmol) and amine **2** (185 mg, 1.39 mmol) in anhydrous EtOH (2 mL) was refluxed for 35 h. The reaction mixture was worked up as described above to obtain an amorphous product in a yield of 195 mg (89%). According to the ^{1}H NMR spectroscopic data, the diastereomer ratio **3a** : **3b** : **3c** : **3d** was 41 : 35 : 14 : 10.

Dimethyl (2*S*,4*S*)-*N*-phthaloyl-4-[(2*S*)-2-methylindolin-1-yl]glutamate (3a). A mixture of diastereomers **3a—d** (6.61 g) was recrystallized seven times from methanol. Compound **3a** was obtained as yellow needle-like crystals (*de* 92.1%) in a yield of 0.96 g (14.5%), m.p. 129—133 °C. Found (%): C, 66.36; H, 5.58; N, 6.28. $C_{24}H_{24}N_2O_6$. Calculated (%): C, 66.05; H, 5.54; N, 6.42. IR, ν/cm^{-1}: 1740 (C=O of the phthaloyl group), 1715 (C=O of ester groups). ^{1}H NMR, δ: 1.31 (d, 3 H, C(2′)Me, *J* = 6.3 Hz); 2.60 (dd, 1 H, H_B(3′), *J* = 15.5 and 6.3 Hz); 2.92 (m, 2 H, H_AH_B(3)); 3.31 (dd, 1 H, H_A(3′), *J* = 15.5 and 9.1 Hz); 3.61 and 3.72 (both s, 3 H each, C(5)O_2Me, C(1)O_2Me); 3.81 (ddq, 1 H, H(2′), *J* = 9.1, 6.3, and 6.3 Hz); 4.08 (dd, 1 H, H(4), *J* = 8.0 and 7.6 Hz); 5.17 (dd, 1 H, H(2), *J* = 8.2 and 6.8 Hz); 6.28, 6.62, 6.89, and 7.03 (all m, 1 H each, H(7′), H(5′), H(6′),H(4′), Ar-Ind); 7.76 and 7.88 (both m, 2 H each, Ar-Phth).

Single crystals of compound **3a** with dimensions 1.4×0.1×0.1 mm were grown by crystallization from a 5 : 1 hexane—ethyl acetate mixture. The crystallographic data: $C_{24}H_{24}N_2O_6$, M = 436.45, orthorhombic system, space group $P2_12_12_1$. The unit cell parameters: *a* = 9.152(3) Å, *b* = 14.857(5) Å, *c* = 16.159(12) Å, *V* = 2197.0(19) Å^3, *Z* = 4, d_{calc} = 1.320 g cm^{-3}, μ = 0.096 mm^{-1}. A total of 1654 independent reflections were measured. Absorption was ignored. The structure was solved by direct methods using the SHELXS-97 program package and refined by the full-matrix least-squares method using the SHELXL-97 program package with anisotropic and isotropic thermal parameters for nonhydrogen and H atoms, respectively. The positions of the hydrogen atoms were calculated geometrically. The final refinement of the structure with the use of all reflections converged to $wR_2 = 0.02415$, $S = 1.019$, 290 parameters ($R = 0.0801$ for 722 reflections with $F > 4\sigma$). The bond lengths have standard values to within experimental error.[13] The atomic coordinates and equivalent thermal parameters were deposited with the Cambridge Structural Database (CSD).

Dimethyl (2*S*,4*S*)-*N*-phthaloyl-4-[(2*R*)-2-methylindolin-1-yl]glutamate (3b). Column chromatography of a mixture of diastereomers **3a—d** (0.15 g) (70×1.7-cm column, a 5 : 4 : 1 hexane—toluene—acetone mixture as the eluent) afforded a fraction (11.0 mg, 7.3%) containing a mixture of diastereomers enriched in isomer **3b** (*de* 33%). ^{1}H NMR, δ, **3b:** 1.16 (d, 3 H, C(2′)Me, *J* = 6.2 Hz); 2.62 (dd, 1 H, H_B(3′), *J* = 15.3 and 9.6 Hz); 3.02 (ddd, 1 H, H_B(3), *J* = 15.0, 10.0, and 4.7 Hz); 3.12 (dd, 1 H, H_A(3′), *J* = 15.3 and 8.6 Hz); 3.20 (ddd, 1 H, H_A(3), *J* = 15.0, 10.7, and 5.7 Hz); 3.56 and 3.72 (both s, 3 H each, C(5)O_2Me, C(1)O_2Me); 3.95 (dd, 1 H, H(4), *J* = 10.0 and 5.7 Hz); 3.96 (m, 1 H, H(2′)); 5.10 (dd, 1 H, H(2), *J* = 10.7 and 4.7 Hz); 6.44, 6.64, 6.93, and 7.02 (all m, 1 H each, H(7′), H(5′), H(6′), H(4′), Ar-Ind); 7.74 and 7.86 (both m, 2 H each, Ar-Phth).

Dimethyl (2*S*,4*R*)-*N*-phthaloyl-4-[(2*S*)-2-methylindolin-1-yl]glutamate (3c). Compound **3c** was isolated by HPLC of a mixture of diastereomers **3a** and **3c** (10.0 mg) (100×0.9-cm column; Silasorb 600, SPH 10 μm, as the sorbent; an 80 : 1 hexane—propan-2-ol mixture as the mobile phase; the elution rate was 1.25 mL min^{-1}) in a yield of 1.2 mg (12%) as a yellow

amorphous product (*de* 84%). ^{1}H NMR, δ: 1.24 (d, 3 H, C(2′)Me, J = 6.2 Hz); 2.57 (dd, 1 H, H_B(3′), J = 15.4 and 9.3 Hz); 2.61 (ddd, 1 H, H_B(3), J = 14.8, 9.2, and 7.3 Hz); 3.07 (dd, 1 H, H_A(3′), J = 15.4 and 8.9 Hz); 3.20 (ddd, 1 H, H_A(3), J = 14.8, 6.6, and 6.6 Hz); 3.63 and 3.74 (both s, 3 H each, C(5)O_2Me, C(1)O_2Me); 3.98 (ddq, 1 H, H(2′), J = 9.3, 8.9, and 6.2 Hz); 4.22 (dd, 1 H, H(4), J = 9.2 and 6.6 Hz); 5.09 (dd, 1 H, H(2), J = 7.3 and 6.6 Hz); 6.27, 6.48, 6.82, and 6.88 (all m, 1 H each, H(7′), H(5′), H(6′), H(4′), Ar-Ind); 7.68 and 7.78 (both m, 2 H each, Ar-Phth).

Dimethyl (2*S*,4*R*)-*N*-phthaloyl-4-[(2*R*)-2-methylindolin-1-yl]glutamate (3d). A mixture of compounds **3c** and **3d** (in a ratio of 1.1 : 1.0) was isolated by column chromatography (70×1.7-cm column, a 5 : 4 : 1 hexane—toluene—acetone mixture as the eluent). ^{1}H NMR, δ, **3d:** 1.235 (d, 3 H, C(2′)Me, J = 6.2 Hz); 2.51 (ddd, 1 H, H_B(3), J = 14.5, 8.4, and 7.6 Hz); 2.56 (m, 1 H, H_B(3′)); 3.11 (ddd, 1 H, H_A(3), J = 14.5, 7.2, and 7.2 Hz); 3.15 (dd, 1 H, H_A(3′), J = 15.3 and 8.5 Hz); 3.69 and 3.73 (both s, 3 H each, C(5)O_2Me, C(1)O_2Me); 3.97 (m, 1 H, H(2′)); 4.38 (dd, 1 H, H(4), J = 8.4 and 7.2 Hz); 5.19 (dd, 1 H, H(2), J = 7.6 and 7.2 Hz); 6.40, 6.56, 6.91, and 6.94 (all m, 1 H each, H(7′), H(5′), H(4′), H(6′), Ar-Ind); 7.72 and 7.82 (both m, 2 H each, Ar-Phth).

Dimethyl (2*S*,4*RS*)-*N*-phthaloyl-4-(2-methylindol-1-yl)glutamates (4a, 4b). A solution of a mixture of isomers **3a—d** (0.5 g, 1.146 mmol) and DDQ (0.286 g, 1.260 mmol) in dry toluene (4 mL) was refluxed for 30 min. The reaction mixture was kept in a refrigerator for 16 h. The precipitate was filtered off, the filtrate was concentrated under reduced pressure, and the product was isolated by column chromatography (3×3-cm column, a 5 : 1 hexane—2-methylpropan-1-ol mixture as the eluent) in a yield of 426 mg (85.6%). After recrystallization from EtOH, a yellow crystalline product was obtained in a yield of 236 mg (47.4%), m.p. 59—64 °C. Found (%): C, 66.23; H, 5.14; N, 6.18. $C_{24}H_{22}N_2O_6$. Calculated (%): C, 66.35; H, 5.10; N, 6.45. IR, ν/cm^{-1}: 1740 (C=O of the phthaloyl group), 1720, 1710 (C=O of ester groups). According to the HPLC and ^{1}H NMR spectroscopic data, the isomer ratio **4a** : **4b** was 82 : 18. The retention times were 15.3 (**4a**) and 16.9 min (**4b**).

Dimethyl (2*S*,4*S*)-*N*-phthaloyl-4-(2-methylindol-1-yl)glutamate (4a). A solution of **3a** (*de* 92.1%) (0.417 g, 0.955 mmol) and DDQ (0.238 g, 1.05 mmol) in dry toluene (4 mL) was refluxed for 30 min. The reaction mixture was worked up as described above. After chromatographic purification, the yield of the product was 0.379 g (91.3%). After recrystallization from EtOH, yellow crystalline product **4a** (*de* 95.2%) was obtained in a yield of 0.236 g (56.9%), m.p. 64—69 °C. Found (%): C, 66.25; H, 5.21; N, 6.70. $C_{24}H_{22}N_2O_6$. Calculated (%): C, 66.35; H, 5.10; N, 6.45. ^{1}H NMR, δ: 2.34 (s, 3 H, C(2′)Me); 3.28 (ddd, 1 H, H_B(3), J = 14.9, 9.0, and 5.9 Hz); 3.34 (ddd, 1 H, H_A(3), J = 14.9, 9.4, and 7.0 Hz); 3.64 and 3.69 (both s, 3 H each, OMe); 4.75 (dd, 1 H, H(4), J = 9.4 and 5.9 Hz); 5.14 (dd, 1 H, H(2), J = 8.8 and 7.3 Hz); 6.30 (s, 1H, H(3′)); 7.01 (m, 2 H, Ar-Ind); 7.18 and 7.50 (both m, 1 H each, Ar-Ind); 7.76 and 7.86 (both m, 2 H each, Ar-Phth).

Dimethyl (2*S*,4*R*)-*N*-phthaloyl-4-(2-methylindol-1-yl)glutamate (4b). Column chromatography (80×2.0-cm column, a 10 : 1 hexane—isobutyl alcohol mixture as the eluent) of a mixture of **4a** and **4b** (520 mg) afforded a fraction (30 mg, 5.8%) enriched in isomer **4b** (*de* 32%). ^{1}H NMR, δ, **4b:** 2.36 (s, 3 H, C(2′)Me); 3.16 (m, 1 H, H_B(3)); 3.32 (m, 1 H, H_A(3)); 3.68 and 3.71 (both s, 3 H each, OMe); 4.85 (dd, 1 H, H(4), J = 9.1 and 4.9 Hz); 5.23 (dd, 1 H, H(2), J = 9.5 and 6.1 Hz); 6.06 (s, 1 H, H(3′)); 6.84 and 7.01 (both m, 1 H each, Ar-Ind); 7.12 (m, 2 H, Ar-Ind); 7.76 and 7.86 (both m, 2 H each, Ar-Phth).

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