Chemistry of Natural Compounds, Vol. 49, No. 6, January, 2014 [Russian original No. 6, November–December, 2013]

SYNTHESIS OF *bis*-TETRAHYDROISOQUINOLINES BASED ON HOMOVERATRYLAMINE AND DIBASIC ACIDS. 2.

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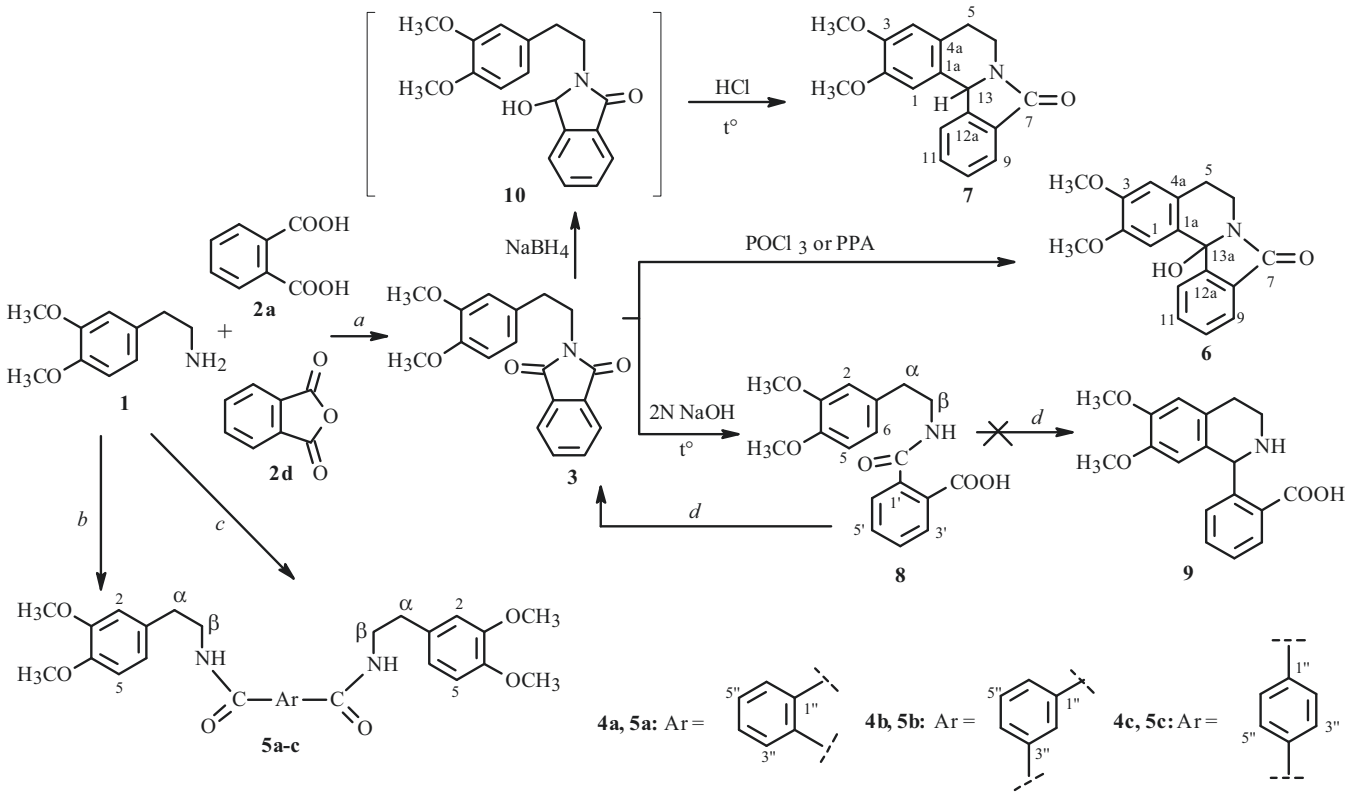
UDC 547.945

Bis-tetrahydroisoquinolines were prepared from homoveratrylamine and phthalic acids using a Bischler–Napieralski reaction. Their structures were confirmed by IR and NMR spectral data.

Keywords: Bischler–Napieralski reaction, phthalic anhydride, phthalic acids, homoveratrylamine.

We reported previously [1] on the preparation of simple *bis*-tetrahydroisoquinolines containing various C_1–$C_1{}^1$-alkyl groups. The good analgesic activity of 1-(4′-methoxyphenyl)-2*β*-hydroxyethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline [2] prompted us to study the possibility of preparing *bis*-tetrahydroisoquinolines based on phthalic acids using a Bischler–Napieralski reaction.

The amides of the first step were difficult to prepare directly from phthalic acids and homoveratrylamine (**1**) by using method A [1]. Thus, use of *o*-phthalic acid (**2a**) produced imide **3**, the formation of which was confirmed by convergent synthesis of **1** with phthalic anhydride (**2d**). Isophthalic acid (**2b**) gave amide **5b** in 29% yield whereas terephthalic acid (**2c**) did not react with **1** by heating (180°C) the mixture of starting materials or by dissolution in DMF and subsequent heating.



a. CH_3OH, t°, *b*. $Ar(COCl)_2$ **4a-c**; *c*. $C_6H_4(COOH)_2$ **2b,c**; *d*. 1. $POCl_3$, 2. $NaBH_4$

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0009-3130/14/4906-1099

The reaction of **1** with phthalic acid chlorides **4a**–**c** (method B) turned out to be more productive [3, 4] and enabled amides **5a**–**c** to be isolated in 82% yield. The reaction of *o*-phthalic acid chloride with amide **5a** formed imide **3** in about 10% yield.

Formation of amides **5a**–**c** was confirmed by the presence in the IR spectra of strong absorption bands for amide carbonyl at 1711 and 1636 cm^{-1} for **5a**; 1671 and 1634, **5b**; and 1629, **5c** and the presence in the PMR spectra of resonances for protons of both the 1,3,4-substituted aromatic ring of β-phenylethylamine [e.g., for **5b**, 6.68 ppm (2H, d, J = 2, H-2,2′), 6.69 (2H, dd, J = 2, 8, H-6,6′), 6.76 (2H, d, J = 8, H-5,5′)] and the corresponding substituted phthalamide ring [for **5b**, 7.40 (1H, t, J = 7.7, H-5″), 7.75 (2H, dd, J = 2, 8, H-6″,4″), 8.01 (1H, t, J = 2, H-2″)].

Cyclization of compounds containing a phthalimide group has been reported, e.g. 2-(3-hydroxy-4-phenylmercaptobutyl)-1,3-isoindolinyldiones [5] to the corresponding isoquinolines.

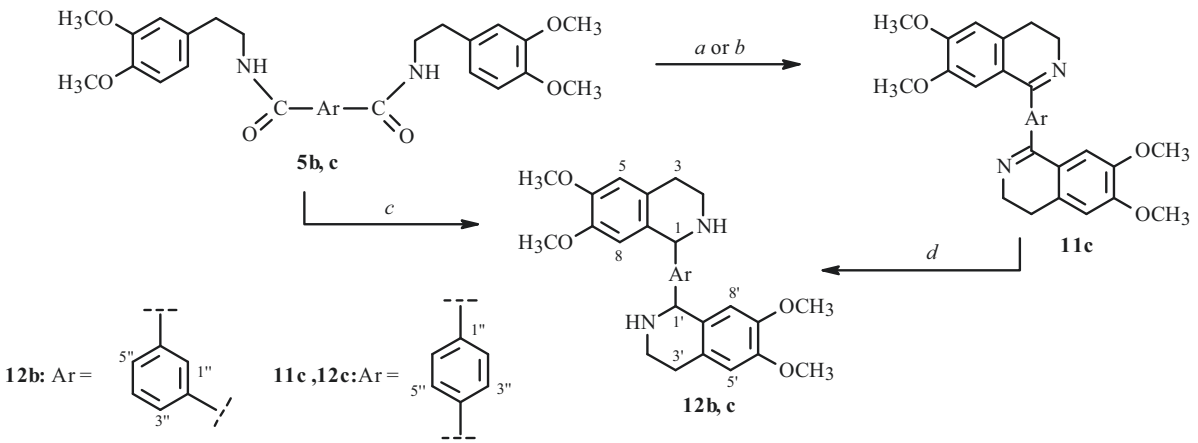
All attempts to cyclize imide **3** in benzene with $POCl_3$ were unsuccessful whereas the cyclization of **3** with $POCl_3$ used as a reagent and solvent and in polyphosphoric acid (PPA) by the literature method [5] produced **6** (2,3-dimethoxy-13-hydroxyisoindoloisoquinoline) instead of the expected 2,3-dimethoxy-5,6-dihydro-8-isoindolo[1,2-*a*]isoquinoline (dehydro-**7** with a C_{13}=N double bond).

Formation of **6** was proved by NMR spectroscopy. Resonances in PMR and ^{13}C NMR spectra of **6** were completely assigned using two-dimensional homo- (^1H–^1H COSY, NOESY) and heteronuclear (^1H–^{13}C HMBC) experiments. The presence of weak-field singlets for aromatic protons H-4 and H-1 at 6.50 and 7.35 ppm in the PMR spectrum of **6** indicated that **3** had cyclized. An analysis of ^{13}C NMR and DEPT data allowed the presence of one carbonyl (C=O), two methoxyl (OCH_3), two methylene (CH_2), six methine (aromatic), and seven quaternary (six aromatic and one saturated C-13) C atoms to be found in **6**. The lack in the PMR spectrum of a resonance for an H-13 proton and the presence of a resonance for saturated quaternary C-13 at δ 86.51 in addition to the presence in the IR spectrum of bands for amide carbonyl (1670 cm^{-1}) and hydroxyl (3332) indicated unambiguously that the OH was situated on C-13.

According to the literature, 2-[*N*-(2[3,4-dimethoxyphenyl]ethyl)carboxamido]phenylacetic acid, obtained from *N*-2(3,4-dimethoxyphenyl)ethylhomophthalimide, cyclized to the isoquinoline [6]. Amidoacid **8** was cyclized under the experimental conditions [6] with subsequent reduction by $NaBH_4$. However, the principal reaction product was imide **3**. The presence of a small quantity of expected isoquinoline **9** in a mixture with **3** could be confirmed only by PMR data (presence of singlets for 5 and 8 protons). Although the formation of **3** in this reaction was not confirmed by an X-ray crystal structure analysis, we proposed that hydroxyphthalimide **10** was formed as an intermediate that transformed reversibly into imide **3** upon work up and isolation.

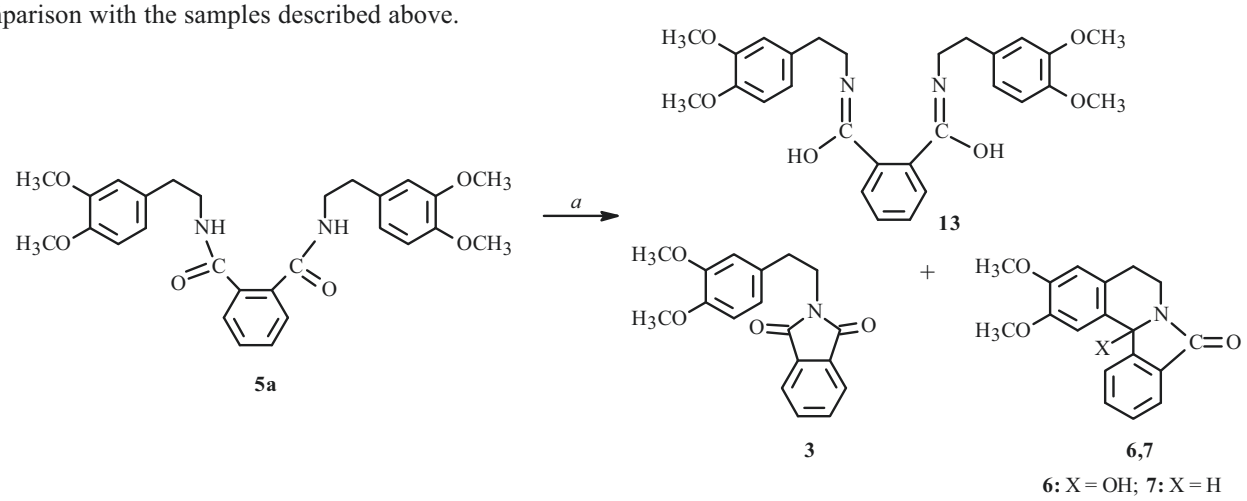
The existence of intermediate **10** was also proposed in the reduction of **3** by $NaBH_4$ under the reaction conditions [7] because subsequent acidification and heating of the reaction mixture without isolating **10** gave isoquinoline **7** in quantitative yield. A characteristic feature of this structure was the presence in the PMR spectrum of a resonance for the H-13 proton at 5.56 ppm (1H, s) that was missing in the spectrum of **6**.

We used amides **5a**–**c** as starting materials in attempted cyclization by a Bischler–Napieralski reaction. As expected, amides **5b** and **5c** cyclized readily into 3,4-dihydroisoquinolines (e.g., **11c**, 71%), subsequent reduction of which produced the target *bis*-tetrahydroisoquinolines **12b** and **12c**. Use of PCl_5 as the dehydrating agent instead of $POCl_3$ gave a higher yield of **12c** (85 and 38%, respectively).



a. $POCl_3$, C_6H_6; *b*. PCl_5, $CHCl_3$; *c*. 1. $POCl_3$, 2. $NaBH_4$; *d*. $NaBH_4$, CH_3OH

The reaction of amide **5a** proceeded differently. The desired *bis*-1,2,3,4-tetrahydroisoquinoline (**12a**) was not detected in the reaction mixture obtained from **5a** and $POCl_3$ in benzene. In contrast with **5b** and **5c**, cyclization of **5a** occurred variously and produced four main products, i.e., imide **3**, imine **13**, and oxo-compounds (2,3-dimethoxyisoindoloisoquinolines) **6** and **7**, which were observed previously upon cyclization of **3** under different conditions. Isoindoloisoquinoline **7**, which was an analog of the alkaloid neuvamine, was prepared earlier by the reaction of 3-chlorophthalide with **1** [8]. Cyclization of **5a** in $POCl_3$, which was used as a reagent and solvent, gave mainly **6**. Formation of **6** and **7** was confirmed by spectral data and comparison with the samples described above.



5a

6: X = OH; **7:** X = H

a. 1. $POCl_3$, 2. $NaBH_4$

Thus, *bis*-tetrahydroisoquinolines were prepared by a Bischler–Napieralski reaction only from *m*- and *p*-phthalic acids. Cyclization of **3** and **5a** was variable and depended on the nature of the reagents and the experimental conditions.

EXPERIMENTAL

IR spectra were recorded in KBr pellets on an FTIR system 2000 (PerkinElmer). PMR spectra were taken in $CDCl_3$ with HMDS internal standard on a Unity-400+ instrument (400 MHz, Varian). R_f values were determined on silica gel LS 5/40 plates (Czechoslovakia) using $CHCl_3$–MeOH (15:1, 1; 10:1, 2; 8:1, 3; 4:1, 4). Melting points of all synthesized compounds were determined on a Boetius microstage. *o*-Phthalic acid chloride was prepared as before [9]; isophthalic and terephthalic acid chlorides, by the literature method [10].

Preparation of Amides. *Method A*. A mixture of homoveratrylamine (0.02 mol) and dicarboxylic acid (0.011 mol) dissolved in MeOH (5 mL) was heated on an oil bath at 170–180°C for 2–5 h, dissolved in $CHCl_3$ (100 mL), and washed with HCl solution (3%), NaOH solution (2%), and H_2O until neutral. The $CHCl_3$ was distilled off. The residue was crystallized from Me_2CO.

Method B. A mixture of homoveratrylamine (0.02 mol), $CHCl_3$ (30 mL), and NaOH solution (30 mL, 10%) was treated dropwise over 1 h with a solution of dicarboxylic acid anhydride (0.013 mol) in C_6H_6 (10 mL) at 5°C. The resulting precipitate (**5a** or **5b**) was separated and crystallized from Me_2CO. The resulting crystals were filtered off.

2-(3,4-Dimethoxy-β-phenylethyl)isoindolyldione-1,3 (3), $C_{18}H_{17}NO_4$. ***Method A*.** Prepared from homoveratrylamine (2.89 g, 0.016 mol) and *o*-phthalic acid (1.41 g, 0.0085 mol). Yield 62% (1.63 g), mp 171–174°C (Me_2CO), R_f 0.9 (system 3).

Method A. Prepared from homoveratrylamine (3.6 g, 0.02 mol) and phthalic anhydride (1.7 g, 0.011 mol). Yield 90% (3.23 g), mp 172–174°C (Me_2CO).

IR spectrum (KBr, ν, cm^{-1}): 3457 (NH), 2943 (Ar-C), 1764 (C=O), 1710 (C=O), 1593, 1518 (Ar-H). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.87 (2H, t, J = 7.7, Hα), 3.75 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.84 (2H, t, J = 7.7, Hβ), 6.68 (1H, d, J = 1.5, H-2), 6.71 (1H, d, J = 7.5, H-5), 6.74 (1H, dd, J = 1.5, 7.5, H-6), 7.64 and 7.76 (each 2H, m, system AA′BB′, H-2′, 3′, 4′, 5′).

***N,N-bis*-(3,4-Dimethoxy-β-phenylethyl)-*o*-phthalamide (5a),** $C_{28}H_{32}N_2O_6$. ***Method B*.** Prepared from homoveratrylamine (3.17 g, 0.017 mol) and phthalic acid chloride (2 g, 9.8 mmol). Yield 82% (3.53 g), mp 150–152°C, R_f 0.7, Me_2CO (system 2).

IR spectrum (KBr, ν, cm^{-1}): 3279 (NH), 2922 (Ar-C), 1711 (N-C=O), 1636 (N-C=O), 1590, 1518 (Ar-H). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.78 (4H, t, J = 7.2, Hα), 3.57 (4H, q, J = 7.2, Hβ), 3.78 (6H, s, OCH_3), 3.79 (6H, s, OCH_3), 6.56 (2H, br.t, J = 7.2, NH), 6.70 (2H, dd, J = 2, 8.5, H-6), 6.72 (2H, d, J = 2, H-2), 6.74 (2H, d, J = 8.5, H-5), 7.37 and 7.44 (each 2H, m, system AA′BB′, H-2′, 3′, 4′, 5′).

***N,N-bis*-(3,4-Dimethoxy-β-phenylethyl)isophthalamide (5b),** $C_{28}H_{32}N_2O_6$. ***Method A*.** Prepared from homoveratrylamine (3.06 g, 0.017 mol) and isophthalic acid (1.5 g, 0.009 mol). Yield 29% (1.2 g), mp 132–134°C (Me_2CO), R_f 0.47 (system 3).

***Method B*.** Prepared from homoveratrylamine (2.1 g, 0.011 mol) and isophthalic acid chloride (1.2 g, 0.006 mol). Yield 82% (2.33 g).

IR spectrum (KBr, ν, cm^{-1}): 3316 (NH), 2938 (Ar-C), 1671, 1634 (N-C=O), 1542, 1516 (Ar-H). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.82 (4H, t, J = 7, Hα, α′), 3.64 (4H, q, J = 7, Hβ, β′), 3.78 (6H, s, OCH_3-3, 3′), 3.80 (6H, s, OCH_3-4, 4′), 6.18 (2H, m, NH), 6.68 (2H, d, J = 2, H-2, 2′), 6.69 (2H, dd, J = 2, 8, H-6, 6′), 6.76 (2H, d, J = 8, H-5, 5′), 7.40 (1H, t, J = 7.7, H-5″), 7.75 (2H, dd, J = 2, 8, H-6″, 4″), 8.01 (1H, t, J = 2, H-2″).

***N,N-bis*-(3,4-Dimethoxy-β-phenylethyl)terephthalamide (5c),** $C_{28}H_{32}N_2O_6$. ***Method B*.** Prepared from homoveratrylamine (2.5 g, 0.013 mol) and terephthalic acid chloride (1.4 g, 0.007 mol). When the reaction was finished, the amide was extracted by $CHCl_3$. The solvent was removed. The residue was crystallized from Me_2CO. Yield 81.67% (2.77 g), mp 219–222°C (Me_2CO), R_f 0.44 (system 3).

IR spectrum (KBr, ν, cm^{-1}): 3302 (NH), 2938 (Ar-C), 1629 (N-C=O), 1546, 1519 (Ar-H). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.82 (4H, t, J = 6.8, Hα, α′), 3.64 (4H, q, J = 6.8, Hβ, β′), 3.78 (6H, s, OCH_3), 3.80 (6H, s, OCH_3), 6.13 (2H, t, J = 5.6, NH). 6.68 (2H, d, J = 2, H-2, 2′), 6.69 (2H, dd, J = 2, 8, H-6, 6′), 6.76 (2H, d, J = 8, H-5, 5′), 7.65 (4H, s, H-2″, 3″, 5″, 6″).

2,3-Dimethoxy-13-hydroxyisoindoloisoquinoline (6), $C_{18}H_{17}NO_4$. ***Method 1*.** Polyphosphoric acid (3 g) was treated with phthalimide **3** (0.3 g), stirred for 4 h at 100°C [5], poured warm into H_2O (50 mL), and stirred for 2 h. The precipitate was filtered off, washed with warm H_2O, and crystallized from CH_3CN. Yield 50% (0.15 g), mp of phosphate 227–230°C, R_f 0.44 (system 2).

***Method 2*.** A mixture of **3** (0.5 g) and $POCl_3$ (0.016 mol) was refluxed on a water bath for 5–6 h. The course of the reaction was monitored by TLC. The reaction mixture was poured onto ice, made basic with NH_4OH solution (25%), and extracted with $CHCl_3$. The solvent was removed. The residue was dissolved in MeOH (40 mL), cooled to 0–5°C, and treated in portions with $NaBH_4$ (0.04 mol). The MeOH was distilled off. The residue was dissolved in H_2O and extracted with $CHCl_3$. The $CHCl_3$ was removed. The residue was crystallized from Me_2CO. Yield 42% (0.21 g), mp 185–188°C, R_f 0.44 (system 2).

IR spectrum (KBr, ν, cm^{-1}): 3332 (OH), 2926 (Ar-C), 1670 (C=O), 1516, 1469, 1453, 1438 (Ar-H). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.62 (1H, ddd, J = 1.6, 4.3, 16.2, H-5e), 2.83 (1H, ddd, J = 16.2, 12.0, 5.9, H-5a), 3.30 (1H, ddd, J = 13.1, 12.0, 4.3, H-6a), 3.77 (3H, s, OCH_3-2), 3.89 (3H, s, OCH_3-3), 4.03 (1H, ddd, J = 13.1, 5.9, 1.6, H-6e), 4.2 (1H, s, OH-13), 6.50 (1H, s, H-4), 7.35 (1H, s, H-1), 7.42 (2H, dt, J =7.5, 1.2, H-10), 7.58 (1H, td, J = 7.8, 1.2, H-11), 7.64 (1H, d, J = 7.5, H-9). 7.93 (1H, d, J = 7.8, H-12).

^{13}C NMR spectrum (100 MHz, $CDCl_3$, 20°C, δ, ppm): 29.25 (C-5), 34.98 (C-6), 56.07 (C-3), 56.31 (C-2), 86.51 (C-13), 110.38 (C-4), 111.51 (C-1), 123.14 (C-12), 123.76 (C-9), 127.67 (C-4a), 127.78 (C-1a), 129.66 (C-10), 130.64 (C-8), 132.79 (C-11), 148.06 (C-2), 148.25 (C-12a), 149.42 (C-3), 167.55 (C-7).

2,3-Dimethoxy-5,6-dihydroisoindolyl[1,2-*a*]isoquinolin-8(12bH)-one (7), $C_{18}H_{17}NO_3$. Imide **3** (0.2 g) was dissolved in MeOH:$CHCl_3$ (3:2), treated at room temperature in portions with $NaBH_4$ (0.8 g), held at room temperature for 1 h, treated with conc. HCl until acidic, and refluxed on a water bath for 2 h. The course of the reaction was monitored by TLC. The solvent was distilled off. The residue was dissolved in H_2O and extracted with $CHCl_3$. The $CHCl_3$ was removed. The residue was crystallized from Me_2CO. Yield 100%, mp 173–175°C, R_f 0.2 (system 2).

^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.71 (1H, dt, J = 4, 7.8. H-5), 2.95 (1H, m, H-5), 3.36 (1H, m, H-6a), 3.79 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.44 (1H, m, H-6e), 5.56 (1H, s, H-13), 6.60 (1H, s, H-4), 7.10 (1H, s, H-1), 7.43* (1H, t, J = 7.3, H-10), 7.55* (1H, td, J = 1, 7.5, H-11), 7.77** (1H, d, J = 7.6, H-9), 7.82** (1H, d, J = 7.6, H-12).

2-Carboxy-*N*-(3,4-dimethoxy-β-phenylethyl)benzamide (8), $C_{18}H_{19}NO_5$. A solution of **3** (3 g) in NaOH (2 N, 60 mL) was refluxed at 100°C for 12 h and acidified by HCl solution until the pH was 2. The residue was separated and crystallized from Me_2CO. Yield 84% (2.65 g), mp 158–161°C (Me_2CO), R_f 0.88 (system 1) [3].

IR spectrum (KBr, ν, cm^{-1}): 3329 (NH), 2944 (Ar-C), 1730 (C=O), 1629 (N-C=O), 1602, 1519 (Ar-H). ^1H NMR spectrum (400 MHz, CD_3OD, δ, ppm, J/Hz): 2.79 (2H, t, J = 7.9, Hα), 3.48 (2H, t, J = 7.7, Hβ), 3.73 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 6.76 (1H, dd, J = 2, 8.3, H-6), 6.81 (1H, d, J = 8.3, H-5), 6.86 (1H, d, J = 2, H-2), 7.45 and 7.51 (each 1H, td, J = 7.6, 1.5, H-4′, 5′), 7.27 (1H, dd, J = 7.6, 1.5, H-6′), 7.88 (1H, dd, J = 1.3, 7.7, H-3′).

Preparation of Tetrahydroisoquinolines 12b and 12c. ***Method A.*** A mixture of dicarboxylic acid diamide (2.4 mmol), anhydrous C_6H_6 (30 mL), and $POCl_3$ (0.05 mol) was refluxed for 3 h. The course of the reaction was monitored by TLC. The C_6H_6 and $POCl_3$ were distilled off. The residue was dissolved in MeOH (60 mL), cooled to 0–5°C, and treated in portions with $NaBH_4$ (0.05 mol). The MeOH was distilled off. The residue was dissolved in H_2O and extracted with $CHCl_3$. The $CHCl_3$ was removed. The residue was crystallized from Me_2CO.

Method B. A suspension of PCl_5 (0.6 g, 0.0028 mol) in $CHCl_3$ (10 mL) was cooled in ice, treated with diamide (0.5 g, 0.001 mol), stirred at 0–5°C for 2 h, and left at room temperature for 1–2 d. The course of the reaction was monitored by TLC. The mixture was poured onto ice and extracted with $CHCl_3$. The $CHCl_3$ was distilled off. The resulting crystals were vacuum filtered. The residue was dissolved in MeOH (30 mL), cooled to 0–5°C, and treated in portions with $NaBH_4$ (0.05 mol). The MeOH was removed. The residue was treated with H_2O (30 mL) and extracted with $CHCl_3$. The $CHCl_3$ was removed. The product was crystallized from Me_2CO [11].

1,3-*bis*-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)benzene (12b), $C_{28}H_{32}N_2O_4$. ***Method A.*** Prepared from **7b** (1.2 g, 0.0024 mol) and $POCl_3$ (7.4 mL). Yield 71% (0.8 g), mp of hydrochloride 230–233°C (Me_2CO), R_f 0.3 (system 4).

IR spectrum (KBr, ν, cm^{-1}): 3376 (NH), 2952 (Ar-C), 1613 (Ar-H), 1519 (Ar-H), 1460 (Ar-H). ^1H NMR spectrum (400 MHz, CD_3OD, 50°C, δ, ppm, J/Hz): 3.05 (2H, m, H-4). 3.19* (2H, m, H-4′), 3.37 (4H, m, H-3), 3.58* (3H, s, OCH_3-6), 3.59* (3H, s, OCH_3-6′), 3.79** (6H, s, OCH_3-7), 3.81** (6H, s, OCH_3-7′), 5.68 (2H, s, H-1), 6.32 (2H, s, H-8), 6.81 (2H, s, H-5), 7.36–7.38 (2H, d, J = 7.4, H-4″, 6″), 7.45 (1H, s, H-2″), 7.51 (1H, t, J = 7.4, H-5″).

1,4-*bis*-(6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)benzene (11c), $C_{28}H_{30}N_2O_4$. ***Method B.*** Prepared from **7b** (1.2 g, 0.0024 mol) and PCl_5 (1.4 mL) without subsequent reduction by $NaBH_4$. Yield 71% (0.8 g), mp of hydrochloride 230–233°C (Me_2CO), R_f 0.3 (system 4).

IR spectrum (KBr, ν, cm^{-1}): 2948 (Ar-C), 1604 (C=N), 1516 (C=N), 1474, 1446 (Ar-H). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.70 (4H, t, J = 7.4, H-4, 4′), 3.65 (6H, s, OCH_3-6, 6′), 3.78 (4H, q, J = 7.6, H-3, 3′), 3.89 (6H, s, OCH_3-7, 7′), 6.73 (2H, s, H-8, 8′), 6.75 (2H, s, H-5, 5′), 7.64 (4H, s, H-2″, 3″, 5″, 6′).

1,4-*bis*-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)benzene (12c), $C_{28}H_{32}N_2O_4$. ***Method A.*** Prepared from **7c** (1 g, 0.002 mol) and $POCl_3$ (1.5 mL). Yield 38% (0.36 g), (Me_2CO), R_f 0.2 (system 4).

Method B. Prepared from **7c** (0.5 g, 0.001 mol) and PCl_5 (0.6 g). Yield 85% (0.4 g), mp 235–238°C (Me_2CO), R_f 0.2 (system 4).

IR spectrum (KBr, ν, cm^{-1}): 3437 (NH), 2962 (Ar-C), 1519, 1443, 1046 (Ar-H). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.68 (2H, dt, J = 15.8, 4.5, H-4), 2.87 (2H, ddd, J = 15.5, 5.6, 8.2, H-4′), 3.00 (2H, ddd, J = 12.1, 4.5, 8.2, H-3), 3.16 (2H, dt, J = 12.1, 5.6, H-3′), 3.56 (6H, s, OCH_3-6, 6′), 3.80 (6H, s, OCH_3-7, 7′), 4.97 (2H, s, H-1, 1′), 6.18 (2H, s, H-8, 8′), 6.56 (2H, s, H-5, 5′), 7.15 (4H, s, H-2″, 3″, 5″, 6″).

Cyclization of 5a with $POCl_3$. A mixture of **5a** (2.4 mmol), anhydrous C_6H_6 (30 mL), and $POCl_3$ (0.05 mol) was refluxed for 3 h. The course of the reaction was monitored by TLC. The C_6H_6 and $POCl_3$ were distilled off. The residue was dissolved in MeOH (60 mL), cooled to 0–5°C, and treated in portions with $NaBH_4$ (0.05 mol). The MeOH was distilled off. The residue was dissolved in H_2O and extracted with $CHCl_3$. The $CHCl_3$ was removed. The residue was dissolved in Me_2CO and treated with conc. HCl until acidic. The resulting crystals of **3** were filtered off. The mother liquor was made basic with NH_4OH (25%) and extracted with Et_2O (fr. 1) and $CHCl_3$ (fr. 2). The resulting crystals of **6** from fr. 1 were filtered off. The mother liquor (0.35 g) after separation of **6** was placed on a column of silica gel and eluted by $CHCl_3$ to afford **13**. Fraction 2 (0.42 g) was separated over a column of silica gel with elution by $CHCl_3$:MeOH (100:1) to isolate **7**.

***N,N-bis*-(3,4-Dimethoxyphenylethyl)-*o*-phthalimide (13),** $C_{28}H_{32}N_2O_6$, oil, R_f 0.42 (system 3).

IR spectrum (oil, ν, cm^{-1}): 3456 (OH), 2941 (Ar-C), 1764, 1709, 1594, 1518, 1467, 1396 (Ar-H). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.87 (4H, t, J = 7.7, H-α), 3.74 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.84 (4H, m, H-β), 4.35 (2H, OH), 6.68–6.72 and 6.73–6.75 (6H, ArH), 7.62 and 7.74 (each 2H, m, system AA′BB′, H-2′, 3′, 4′, 5′).

REFERENCES

1. A. Sh. Saidov, M. Alimova, M. G. Levkovich, and V. I. Vinogradova, *Chem. Nat. Compd.,* **49**, 302 (2013).
2. F. M. Tursunkhodzhaeva, Sh. B. Rakhimov, F. N. Dzhakhangirov, V. I. Vinogradova, Zh. Rezhepov, and Sh. Sh. Sagdullaev, UzIAP 04590, 2012.
3. T. Kametani, T. Nakano, K. Shishado, and K. Fukumoto, *J. Chem. Soc. C*, 3350 (1971).
4. H. Iida, H.-C. Hsu, and T. Kikuchi, *Chem. Pharm. Bull.*, **21**, 1001 (1973).
5. V. S. Tolkunov, A. B. Eres′ko, and A. I. Khizhan, *Org. Khim.*, 99 (2011).
6. J. W. Huffman and E. G. Miller, *J. Org. Chem.*, **25**, 90 (1960).
7. N. S. Simpkins and C. D. Gill, *Org. Lett.*, **5**, 535 (2003).
8. R. Alonso, L. Castedo, and D. Dominguez, *Tetrahedron Lett.*, **26**, 2925 (1985).
9. Adams (ed.), *Syntheses of Organic Compounds* [Russian translation], No. 2, IL, Moscow, 1949, p. 547.
10. *Industrial Chloro-organic Products* [in Russian], L. A. Oshin (ed.), Khimiya, Moscow, 1978, pp. 495, 500.
11. R. Grewe and H. Fischer, *Chem. Ber.*, **96**, 1520 (1963).