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SYNTHESIS OF *bis*-TETRAHYDROISOQUINOLINES BASED ON HOMOVERATRYLAMINE AND SEVERAL DIBASIC ACIDS. 4. REACTION WITH MALONIC AND SUCCINIC ACIDS

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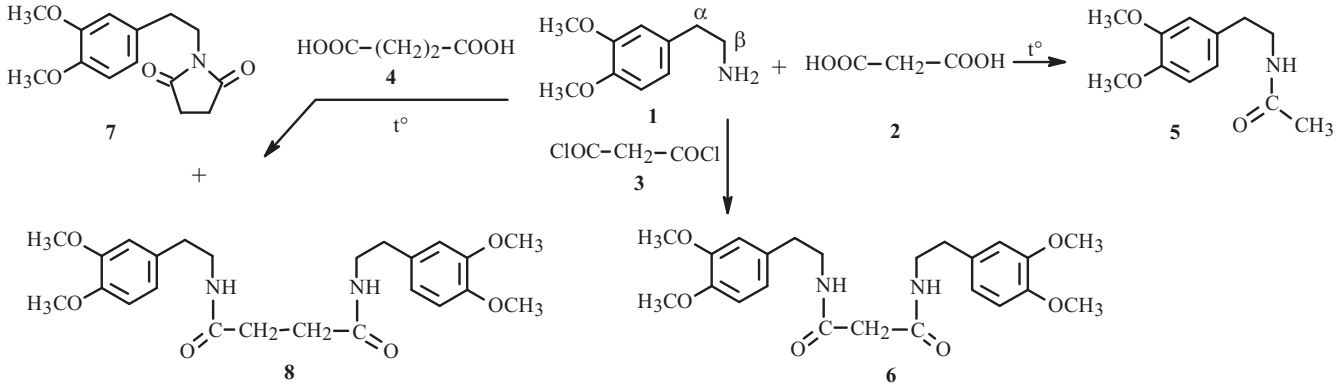
Bischler–Napieralski cyclization of amides synthesized from homoveratrylamine and malonic and succinic acids produced N-*(3,4-dimethoxy-*β*-phenylethyl)-succinimide, 1,1-*bis*-(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)methane, cleavage products, and several intermediates, the structures of which were confirmed using IR and NMR spectral data and x-ray crystal structure analysis.*

Keywords: malonic and succinic acids, homoveratrylamine, Bischler–Napieralski reaction.

Modern approaches to new drug discovery use reactions that are simple to perform and produce high yields of pure target compounds.

In continuation of previous research [1–3] on the synthesis of isoquinoline derivatives using the Bischler–Napieralski reaction, we used C3 and C4 dibasic acids in the present work.

We studied the reaction of homoveratrylamine (**1**) with malonic acid (**2**), malonic acid chloride (**3**), and succinic acid (**4**) in order to synthesize new derivatives.



Malonic acid diamide (**6**) was prepared using **3** because **2** decarboxylated at 110–120°C to form acetic acid, which produced acetamide **5**.

Amide **8** was obtained by heating **1** with **4** to 178°C for 1 h. The product was crystallized from Me_2CO. The resulting mixture of imide **7** and amide **8** was separated by fractional crystallization from C_6H_6. The yield of **8** was 48%; of **7**, 37%.

The structures of **5**–**8** were proved using PMR and IR spectra. IR spectra of **6** and **8** had strong bands at 1640 and 1630 cm^{-1}; 3246 and 3305 cm^{-1}; 2875 and 2837–2935 cm^{-1} that corresponded to stretching vibrations of C=O, NH, and aromatic rings. PMR spectra of **6** and **8** exhibited 2H resonances for α- and β-methylene protons at 2.77, 3.04, 3.23, 3.37 and 2.67, 3.40 ppm, respectively, and for methylene protons at 3.15 and 2.39 ppm. The nature of the methylene resonances indicated that **8** was totally symmetric. However, the symmetry was destroyed in **6**, possibly because of the formation of an intramolecular H-bond as a six-membered ring between N–H…O=C. The presence of this bond caused a redistribution of electron density among the bond participants, i.e., from the labile H atom to the proton-accepting O atom, which affected subsequent ring closure by $POCl_3$.

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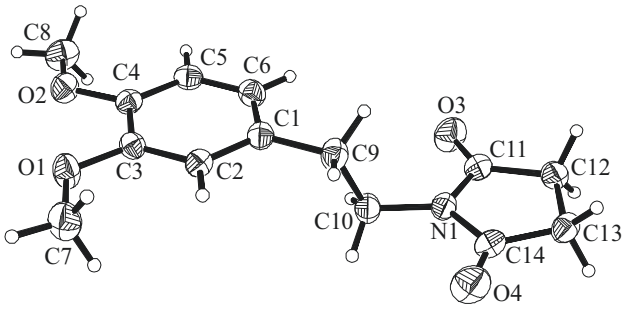
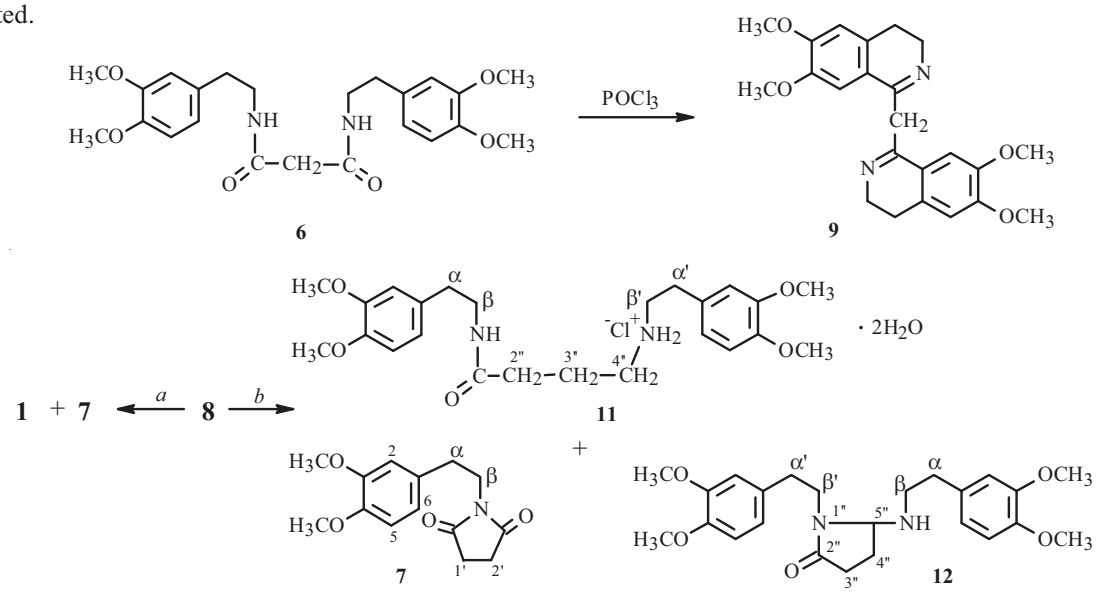


Fig. 1. Molecular structure of **7** from an XSA.

Amide **6** was cyclized into *bis*-dihydroisoquinoline **9**, reduction of which gave a mixture of compounds that could not be separated.



Bischler–Napieralski cyclization [4] of amide **8** followed by $NaBH_4$ reduction gave a mixture of three products, i.e., imide **7**, *N*,*N*′-disubstituted 4-aminobutanamide **11** and 5-aminopyrrolidin-2-one **12**.

The structures of synthesized **7**, **11**, and **12** were confirmed using IR and PMR spectroscopy. Their IR spectra contained strong bands at 1640, 1651, and 1673 cm^{-1} and at 3246–3434, 3258, and 3316 cm^{-1} that corresponded to CO and NH stretching vibrations.

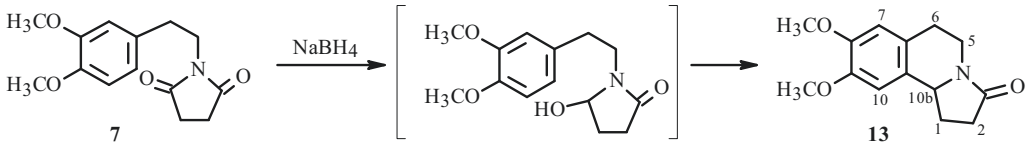
Resonances for aromatic protons in PMR spectra of **7**, **11**, and **12** at δ 6.68 (1H, d, J = 1.8, H-2), 6.69 (1H, d, J = 8, H-5), 6.73 (1H, dd, J = 8, 1.8, H-6), 6.73-6.85 (6H, m, Ar-H), and 6.65-6.79 (6H, 1,3,4-substituted aromatic ring) indicated that there was no isoquinoline ring. PMR spectra of these derivatives had resonances for α- and β-protons and methylene protons at δ 2.12, 2.49, and 3.00 ppm for **11** and at 2.60 (4H, s, $2CH_2$) and 2.69 (2H, m, H-4″), 2.79 (2H, m, H-3″), 4.23 (1H, m, H-5″) for **7** and **12**, respectively.

The structure of **11** was confirmed by an x-ray crystal structure analysis (XSA) [5].

Figure 1 shows the molecular structure of **11** from the XSA. The six-membered and five-membered rings were planar (deviations of atoms from least-squares planes of the rings were less than 0.004 and 0.003 Å, respectively). They were almost mutually coplanar with an angle of 3.17(8)° between the planes. As a result, stacking interactions between the five- and six-membered rings of neighboring molecules along the *x* axis with a distance of 3.713(2) Å between ring centroids was observed in the crystal.

Reduction of imide **7** and amide **8** by $NaBH_4$ under the usual conditions [6] followed by acidification and heating for 2 h occurred differently. Amide **8** gave two cleavage products, i.e., **7** and 3,4-dimethoxy-β-phenylethylamine (**1**), whereas **7** formed pyrroloisoquinoline **13** [7].

Alkaloid **13** was the dimethyl ether of trolline [8] and the methyl ether of erythrinarbine [9], which were isolated from *Trollius chinensis* and *Erythrina arborescens*.



The structure of **13** was proved using the PMR spectrum, which showed singlets for two aromatic protons at δ 6.57 and 6.62 ppm and resonances for eight methylene protons at δ 1.84–4.31 ppm and one methine proton H-10b at 4.73 ppm.

EXPERIMENTAL

IR spectra were taken from KBr pellets on an FTIR system 2000 instrument (PerkinElmer). PMR spectra were recorded on a Varian Unity-400+ (400 MHz, $CDCl_3$ and CD_3OD solvents, HMDS internal standard). The XSA was performed on a STOE STADI-IV diffractometer (Cu Kα-radiation, 300 K, graphite monochromator, θ/2θ-scanning). R_f values were determined on LS 5/40 silica gel plates (Czechoslovakia) using $CHCl_3$–MeOH solvent systems.

Melting points of all synthesized compounds were determined on a Boetius apparatus.

***N*-(3,4-Dimethoxy-*β*-phenylethyl)acetamide (5)**, $C_{12}H_{17}NO_3$. A mixture of homoveratrylamine (4 g, 0.022 mol) and malonic acid (1.15 g, 0.011 mol) was dissolved in MeOH (10 mL). The resulting salt was heated on an oil bath for 1 h at 178°C, cooled, 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 solid was crystallized from Me_2CO. Yield 71% (1.75 g), mp 99–101° (Me_2CO), R_f 0.67 (8:1 system). IR spectrum (ν, cm^{-1}): 3253 (NH), 3080, 2992, 2928 (Ar–CH), 1634 (N–C=O), 1567, 1518. ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.88 (3H, s, CH_3), 2.70 (2H, t, J = 7, H-*α*), 3.43 (2H, q, J = 7, H-*β*), 3.80 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 5.52 (1H, br.s, NH), 6.65 (1H, d, J = 2, H-2), 6.66 (1H, dd, J = 2, 8, H-6), 6.75 (1H, d, J = 8, H-5).

***N*,*N*′-(3,4-Dimethoxy-*β*-phenylethyl)malondiamide (6)**, $C_{23}H_{30}N_2O_6$. A mixture of homoveratrylamine (1 g, 0.005 mol), C_6H_6 (10 mL), and K_2CO_3 (0.4 g) was treated dropwise over 1 h with a solution of malonic acid chloride (**3**, 0.4 g, 0.013 mol) in C_6H_6 (10 mL). The reaction mixture was diluted with $CHCl_3$ (50 mL) and washed with H_2O until neutral. The $CHCl_3$ was distilled off. The solid was crystallized from Me_2CO. The resulting crystals were filtered off. Yield 33% (0.4 g), mp 156–158°C (Me_2CO), R_f 0.5 (8:1 system). IR spectrum (ν, cm^{-1}): 3246 (NH), 2875, 2837 (Ar–CH), 1640 (N–C=O), 1591, 1519. ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 3.15 (s, CH_2), 2.77 (2H, t, J = 7, H-*α*), 3.04 (2H, t, J = 7, H-*α*), 3.23 (2H, m, H-*β*), 3.37 (2H, q, J = 7, H-*β*), 3.83, 3.85 (each 3H, s, OCH_3), 3.87 (6H, s, OCH_3), 6.71 (1H, s, H-2), 6.73 (1H, d, J = 7.6, H-6), 6.78 (2H, d, J = 7.6, H-5, 6), 6.79 (1H, s, H-2), 6.8 (1H, d, J = 7.6, H-5).

Preparation of 7 and 8. The salt obtained from homoveratrylamine (3.83 g, 0.0212 mol) and succinic acid (1.5 g, 0.01 mol) was heated on an oil bath for 1 h at 178°C, cooled, 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 to afford **7** and **8**.

***N*-(3,4-Dimethoxy-*β*-phenylethyl)succinimide (7)**, $C_{14}H_{17}NO_4$. Yield 37% (1.84 g), mp 129–131°C (Me_2CO), R_f 0.9 (8:1 system). IR spectrum (ν, cm^{-1}): 3246 (NH), 2875, 2837 (Ar–CH), 1640 (N–C=O), 1591, 1519. ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.60 (4H, s, H-1′, 2′), 2.77 (2H, t, J = 8, H-*α*), 3.66 (2H, t, J = 8, H-*β*), 3.79 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 6.68 (1H, d, J = 1.8, H-2), 6.69 (1H, d, J = 8, H-5), 6.73 (1H, dd, J = 1.8, 8, H-6).

***N*,*N*′-(3,4-Dimethoxy-*β*-phenylethyl)succindiamide (8)**, $C_{24}H_{32}N_2O_6$. Yield 48% (2.4 g), mp 175–177°C (Me_2CO), R_f 0.6 (8:1 system). IR spectrum (ν, cm^{-1}): 3305 (NH), 2935 (Ar–CH), 1630 (N–C=O), 1591, 1542, 1518. ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.39 (4H, s, $2CH_2$), 2.67 (4H, t, J = 7.1, H-*α*), 3.40 (4H, qn, J = 7.1, H-*β*), 3.79 (6H, s, OCH_3), 3.80 (6H, s, OCH_3), 5.90 (2H, br.s, NH), 6.65 (2H, d, J = 2, H-2), 6.66 (2H, dd, J = 2, 8.6, H-6), 6.73 (2H, d, J = 8.6, H-5).

1,1-*bis*(6,7-Dimethoxy-3,4-dihydroisoquinolin-1-yl)methane (9). A mixture of **6** (0.1 g, 2.54 mmol) and $POCl_3$ (0.25 mL) was refluxed on a water bath for 6 h. The course of the reaction was monitored by TLC. The reaction mixture was poured into ice, made basic to pH 9 with NH_4OH solution (25%), and extracted with $CHCl_3$. The $CHCl_3$ was distilled off. The solid was purified over a column of silica gel. R_f 0.6 (4:1 system). IR spectrum (ν, cm^{-1}): 1615, 1567, 1511, 1463, 1455, 1410, 1353, 1324, 1284, 1262, 1223, 1094, 1024, 805. ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.76 (2H, s, H-1′), 2.75 (4H, t, J = 7.1, H-4), 3.71 (12H, s, 6, 7-OCH_3), 3.90 (4H, br.t, H-3), 6.75 (2H, s, H-8), 6.85 (2H, s, H-5).

Reaction of 8 with $POCl_3$. A solution of **8** (2 g, 0.004 mol) in anhydrous C_6H_6 (30 mL) was treated with $POCl_3$ (0.05 mol) and refluxed for 2 h. The course of the reaction was monitored by TLC. When the reaction was finished, the reflux condenser was replaced by a collecting condenser. The C_6H_6 and $POCl_3$ were distilled off. The solid was dissolved in MeOH

(30 mL), chilled to 0–5°C, and treated in portions with $NaBH_4$ (0.025 mol) with ice cooling. The MeOH was distilled off. The solid was dissolved in H_2O and extracted with $CHCl_3$. The solvent was distilled off. The mixture consisted mainly of three compounds with R_f 0.9, 0.5, and 0.2 (8:1 system). The $CHCl_3$-soluble compounds (1.6 g) were separated over a column of silica gel (30 g) to afford three compounds with R_f 0.9, 0.5, and 0.2, i.e., **7** (0.3 g, R_f 0.9, mp 129–131°C); **11** (0.075 g, R_f 0.2, mp 133–135°C), and **12** (0.5 g, oil, R_f 0.5).

***N,N′-bis*(3,4-Dimethoxyphenylethyl)-4-aminobutanamide (11)**, mp 133–135°C. IR spectrum (KBr, ν, cm^{-1}): 3434, 3258, 2940, 1651, 1590, 1519. ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.12 (2H, br.s, H-3″), 2.49 (2H, t, J = 6.5, H-2″), 2.78 (2H, t, J = 7.1, H-α), 3.00 (2H, br.s, H-4″), 3.15 (4H, br, H-α′, β), 3.46 (2H, t, J = 7, H-β′), 3.83 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 6.73–6.85 (6H, m, Ar–H).

1-(3,4-Dimethoxyphenylethyl)-5-(3,4-dimethoxyphenylethylamino)pyrrolidin-2-one (12), oil. IR spectrum (ν, cm^{-1}): 3359, 2935, 1672, 1591, 1516, 1461. ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.13 (1H, m, H-α), 2.29 (1H, m, H-α′), 2.42 (1H, m, H-α), 2.69 (2H, m, H-4″), 2.76 (2H, m, H-α′, β), 2.79 (2H, m, H-3″), 3.08 (1H, m, H-β), 3.76 (1H, m, H-β′), 3.79 (1H, m, H-β′), 3.85 (12H, s, 4-OCH_3), 4.23 (1H, m, H-5″), 6.65 (1H, dd, J = 2, 8, H-6), 6.70 (2H, br.s, H-2, 2′), 6.72 (1H, dd, J = 2, 8, H-6′), 6.77 (1H, d, J = 8, H-5), 6.79 (1H, d, J = 8, H-5′).

Reaction of 8 with $NaBH_4$. A solution of **8** (0.8 g) in MeOH (20 mL) at room temperature was treated in portions with $NaBH_4$ (4 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 solid was dissolved in H_2O and extracted with $CHCl_3$ to afford two crystalline compounds, i.e., imide **7** and amine **1**.

Compound 7. Yield 50% (0.4 g), mp 129–131°C.

Compound 1. Yield 30% (0.15 g). IR spectrum (KBr, ν, cm^{-1}): 3325, 2935, 2838, 1590, 1519. ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.43 (2H, br.s, NH_2), 2.70 (2H, t, J = 8, H-α), 2.95 (2H, t, J = 8, H-β), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 6.73 (2H, d, J = 8, H-5), 6.81 (2H, dd, J = 8, 2, H-6), 6.80 (2H, d, J = 2, H-2).

8,9-Dimethoxy-1,2,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline-3(10b*H*)-one (13). A solution of **7** (0.3 g) in MeOH (20 mL) at room temperature was treated in portions with $NaBH_4$ (1.2 g), held at room temperature for 1 h, treated with conc. HCl until acidic, and refluxed for 2 h. The course of the reaction was monitored by TLC. The solvent was distilled off. The solid was dissolved in H_2O and extracted with $CHCl_3$. The $CHCl_3$ was removed to afford **13**. Yield 64% (0.18 g), oil, R_f 0.68 (10:1 system). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.84 (1H, m, H-2), 2.48 (1H, m, H-2), 2.55–2.70 (2H, m, H-1), 2.90 (2H, m, H-6), 3.00 (1H, m, H-5), 3.84 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.31 (1H, m, H-5), 4.73 (1H, t, J = 5.2, H-10b), 6.57 (1H, s, H-10), 6.62 (1H, s, H-7).

XSA. Crystals of **7** were triclinic, space group *P*1, a = 7.305(2), b = 7.527(2), c = 13.070(3) Å; α = 78.57(3), β = 74.36(3), γ = 70.00(3)°; V = 645.8(2) $Å^3$; $C_{14}H_{17}NO_4$; MW = 263.29; Z = 2; d_{calcd} = 1.354 g/cm^3; μ = 0.075 mm^{-1}; crystal size 0.55 × 0.45 × 0.30 mm; 2θ < 120°. Absorption corrections were applied empirically using ψ-curves (transmission 0.89–0.99).

The structure was solved using the SHELXS-97 program and refined to wR2 = 0.1448, S = 1.125 for all 1755 independent reflections [R = 0.0554 for 1512 F0 > 4σ(F)].

The XSA was performed on a STOE STADI-IV diffractometer (Cu Kα-radiation, 300 K, graphite monochromator, θ/2θ-scanning). The structure was refined by anisotropic least-squares methods using the SHELXL-97 program [10]. Parameters of H atoms were calculated geometrically in each refinement cycle.

Data from the XSA were deposited in the Cambridge Crystallographic Data Centre (CCDC 1040323).

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