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SYNTHESIS OF bis-TETRAHYDROISOQUINOLINES BASED ON HOMOVERATRYLAMINE AND A SERIES OF DIBASIC ACIDS. 3.

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Pyrido- and [1,4]-oxazinoisoquinolines, bis-tetrahydroisoquinolines, the alkaloid corydaldine, cleavage products, and a series of intermediates were prepared from homoveratrylamine and dibasic acids (glutaric and diglycolic) using a Bischler–Napieralski reaction. Their structures were confirmed using IR and NMR spectra and an x-ray crystal structure analysis.

Keywords: glutaric and diglycolic acids, homoveratrylamine, amides, Bischler–Napieralski reaction, isoquinolines.

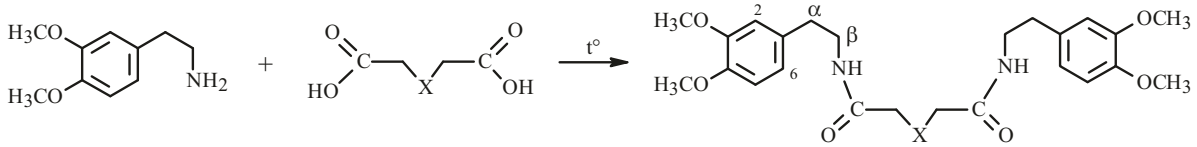
Organic chemists are faced with the problem of creating effective synthetic pathways to previously unknown compounds with useful properties. Such compounds include heterocyclic compounds such as isoquinoline derivatives. Despite the variety of known structures, research on the development of methods for preparing isoquinoline alkaloids and their synthetic analogs is critical according to the number of publications [1–3].

We showed earlier [4] that the cyclization of diamides obtained from homoveratrylamine (**1**) and a series of dibasic fatty acids (from C_6 to C_{10}) did not depend on the acid chain length whereas the cyclization of phthalic acid diamides depended on their structure [5]. In continuation of systematic research on the synthesis of bis-tetrahydroisoquinolines via the Bischler–Napieralski reaction, we used diamides of glutaric (**2**) and diglycolic acids (**3**) in the reaction.

Methods for preparing diglycolic acid from chloroacetic acid gave poor results [6, 7]. Diglycolic acid (**3**) was synthesized via oxidation of diethyleneglycol by HNO_3 according to the literature [8]. Use of 86% HNO_3 increased the yield of **3** to 90%.

Diamides **4** and **5** were synthesized by heating previously formed salts of **2** and **3** with **1** whereas others [9] prepared diglycolic acid diamide in several steps. In the first step, the cyclic anhydride of diglycolic acid was prepared and used to acylate an amine to form the monoamide. Then, the diamide was obtained through the acid chloride of the second carboxylic acid. This decreased significantly the yield. The synthetic method proposed by us was performed in one flask in two steps with 86% (**5**) and 79% (**4**) yields.

The structures of **4** and **5** were proved using IR and PMR spectra (see Experimental). IR spectra of **4** and **5** had strong absorption bands for amide carbonyl at 1638 and 1680 cm^{-1}, respectively.



1 **2, 3** **4, 5**

2, 4: X = CH_2; **3, 5**: X = O

An x-ray crystal structure analysis (XSA) confirmed the structure of **5** as 2,2′-oxo-bis[*N*-(3,4-dimethoxyphenylethyl)acetamide]. However, the molecular structure lacked symmetry [center, plane, and (or) axis of symmetry passing through O3] according to the XSA (Fig. 1). The molecule was situated in a general position without symmetry at the O3 position although the molecule was packed in the centrosymmetric triclinic system. The N–H groups in the crystal structure formed intermolecular H-bonds with the methoxy O atoms of centrosymmetrically situated molecules. The H-bond distances and angles were N1–H…O6, N1…O6, 3.118(4) Å, H…O6, 2.28 Å, and N–H…O, 164.0° and N2–H…O7, 3.238(4), 2.50 Å, and 145.0°, respectively.

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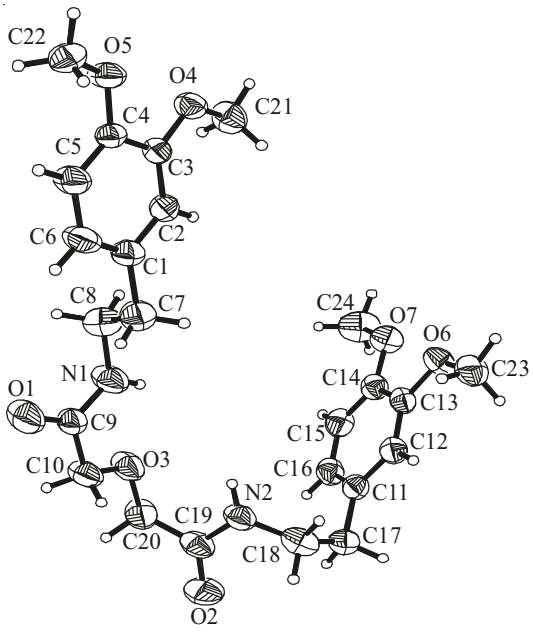


Fig. 1. Molecular structure of **5**.

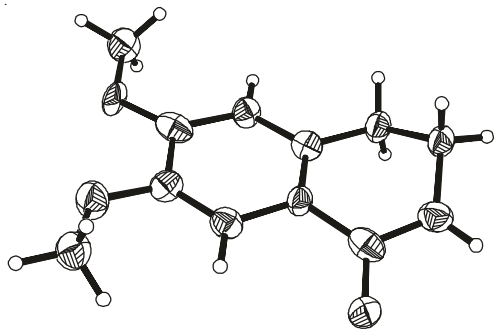
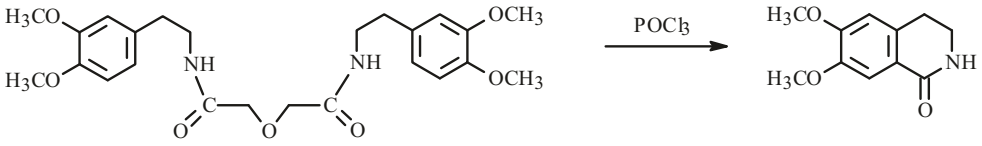


Fig. 2. Molecular structure of corydaldine (**6**).

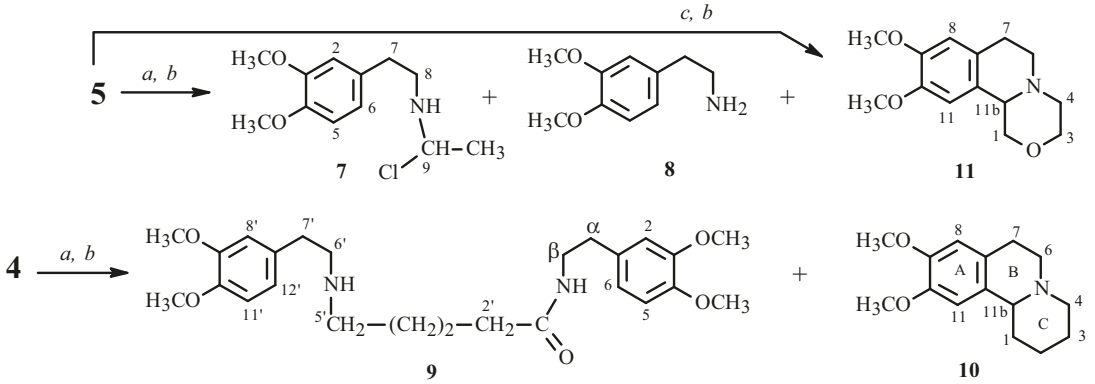
Subsequent cyclization of **4** and **5** by the Bischler–Napieralski method depended on the dehydrating agent and solvent. Cyclization in anhydrous benzene with $POCl_3$ produced a mixture of products, e.g., three compounds (R_f 0.3, 0.6, 0.9) for **5**. Only compound **6** could be isolated pure. The others could not be separated because of rapid oxidation.



5 **6**

The structure of **6** was proved using PMR spectra as 3,4-dihydro-6,7-dimethoxy-1(2*H*)-isoquinolinone and was identified as the known alkaloid corydaldine, which was previously isolated from *Berberis baluchistanica* [10]. An XSA of **6** (Fig. 2) showed that it was identical to the reported crystal structure of corydaldine isolated from *Corydalis solida* subs. *brachyloba* [11].

Cyclization of **4** and **5** in benzene with $POCl_3$ and subsequent reduction of the dihydroisoquinolines by $NaBH_4$ did not give the expected bis-tetrahydroisoquinolines, despite the fact that $POCl_3$ is a mild reagent. Instead, it gave various destruction products [**7** and **8** (**1**·H_2CO_3) for **5** and **9** for **4**] and tricyclic products **10** and **11**.



a. $POCl_3$, C_6H_6; *b.* $NaBH_4$; CH_3OH; *c.* $POCl_3$

Amine **7** gave a Beilstein test for halide. The IR spectrum of **7** had a band for active H at 3434 cm^{-1}. The PMR spectrum of **7** showed resonances at 1.51 ppm (3H, d, J = 6.5, CH_3) and 3.23 ppm (1H, m, CH) that were consistent with a CH–CH_3 group. Two multiplets at 3.07 ppm (2H, m) and 3.17 ppm (2H, m) corresponded to protons H-7 and H-8. The nature of the resonances at 3.79 and 3.80 ppm (3H each, s, OCH_3) and 6.71 and 6.72 ppm confirmed that two methoxyls were present in the trisubstituted benzene ring. Amine **7** was *N*-(1-chloroethyl)homoveratrylamine according to these results.

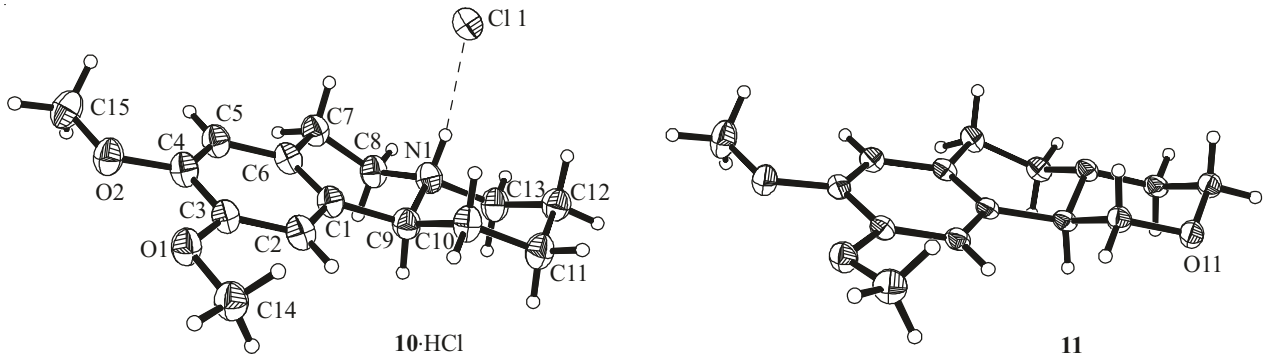


Fig. 3. Molecular structures of **10**·HCl and **11**.

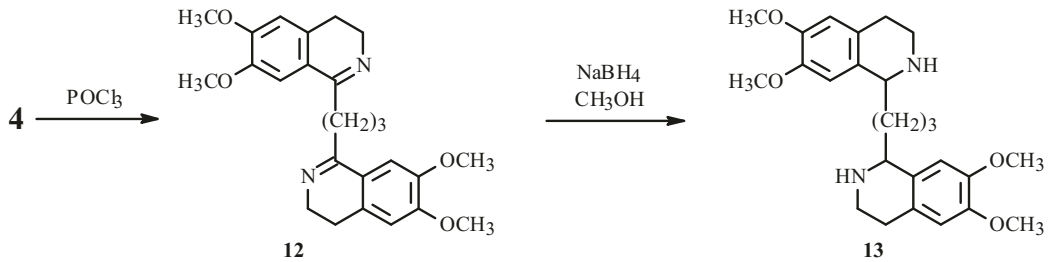
Compound **9** was *N*-(3,4-dimethoxyphenylethyl)-5-(3,4-dimethoxy-*β*-phenylethylamino)pentanamide according to PMR spectra.

Compounds **10** and **11** probably formed through a single mechanism. Their formation was determined by the number of atoms between the two amides and not their nature (CH_2–CH_2–CH_2 or CH_2–O–CH_2). The structures of **10** and **11** were established using PMR spectra. The spectrum of **11** showed two 1H singlets at 6.53 ppm (1H, s, H-8) and 6.61 ppm (1H, s, H-11) and one 1H doublet of doublets at 4.30 ppm with SSCC J = 10.5 and 2.8 Hz and indicated unambiguously that the ring had closed and formed the tetrahydroisoquinoline. Methylene protons H-1, -3, and -4 resonated in the PMR spectrum at 2.57 (1H, td, J = 11.5, 11.5, 4.2, H-4a), 2.80 (1H, dd, J = 11.9, 1.2, H-4b), 3.35 (1H, br.d, J = 10.5, H-1a), 3.43 (1H, t, J = 10.3, H-1b), 3.77 (1H, td, J = 11.3, 11.3, 2.6, H-3a), and 3.89 (1H, dd, J = 10.2, 3.1, H-3b). The pattern was analogous in the PMR spectrum of **10** with 1H singlets at 6.80 and 6.83 ppm (H-8, 11) and a broad resonance at 4.38 ppm (H-11b). The methylene protons appeared as multiplets at 1.78, 1.95, 3.04, 3.42, and 3.60 ppm. The results suggested that **10** and **11** were 9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline and 9,10-dimethoxy-1,3,4,6,7,11b-hexahydro[1,4]oxazino[3,4-*a*]isoquinoline, respectively. We did not find in the literature natural products with structures similar to **11**. However, a series of hexahydro[1,4]oxazino[3,4-*a*]isoquinolines were reported [12–14]. The structures of **10** and **11** were confirmed by XSA studies.

Figure 3 shows the molecular structures of **10**·HCl and **11** from the XSA studies. Rings B and C were *trans*-fused in both molecules. Ring B had a half-chair conformation in both molecules [N(1) and C(8) deviating from the C(9)–C(1)–C(6)–C(7) plane by –0.32(2) Å and 0.45(2) Å in **10** and by –0.425(5) Å and 0.356(5) Å in **11**]. Ring C had a chair conformation. The N–C bonds in **10** [N(1)–C(8) 1.493(2), N(1)–C(9) 1.508(2), and N(1)–C(13) 1.500(3) Å] were slightly elongated relative to the corresponding bonds in **11** [N(1)–C(8) 1.465(3), N(1)–C(9) 1.470(3), and N(1)–C(13) 1.463(4) Å] because the N atom was protonated. The N–C bond was also elongated in the *N*-oxide of **10** [15].

Protonated N1 in the crystal of **10**·HCl formed an intermolecular H-bond with the Cl anion [N1…Cl 3.041(2) Å, H1…Cl 2.13(3) Å, N1–H…Cl 161(2)°].

The reaction of **4** in $POCl_3$ as the solvent and reagent occurred more selectively. In this instance, only one reaction product (**12**) was observed by chromatography. It was reduced to the target isoquinoline **13** whereas amide **5** cyclized under analogous conditions without undergoing substantial changes compared with those above and gave **11** in ~70% yield.

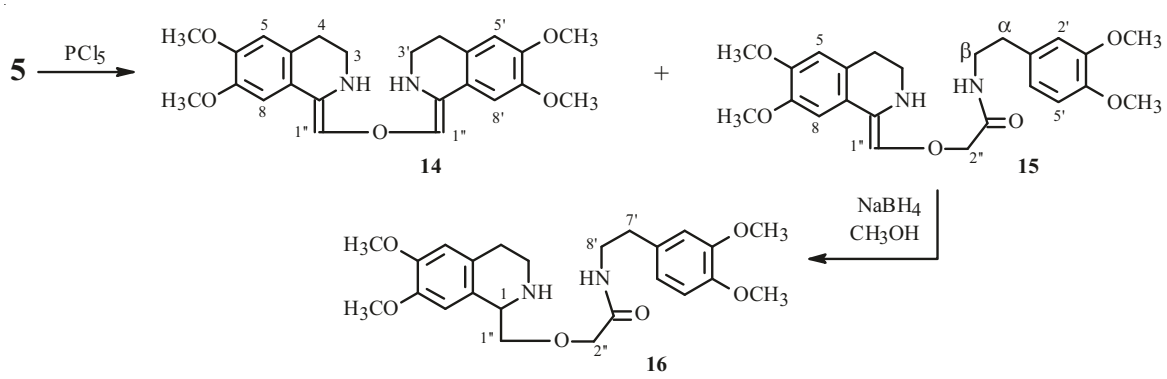


The absence of the bis-tetrahydroisoquinoline in the reactions of **5** with $POCl_3$ prompted us to study this reaction using PCl_5, P_2O_5, and polyphosphoric acid (PPA) instead of $POCl_3$.

It is well known that PCl_5 is a more forcing reagent than $POCl_3$. Therefore, syntheses involving it are carried out under milder conditions. Diamide **5** was cyclized by PCl_5 in anhydrous $CHCl_3$ at room temperature over 4 d. The reaction mixture was separated using the solubilities of the hydrochlorides. The hydrochloride of **14** precipitated from $CHCl_3$–Me_2CO (1:1, 20% yield). Subsequent work up of the dried mother liquor by Me_2CO separated **15** (35% yield).

TABLE 1. Principal Crystallographic Parameters and Characteristics of an X-ray Crystal Structure Analysis for **5**, **10**·HCl, and **11**

Parameter	**5**	**10**·HCl	**11**
Molecular formula	$C_{24}H_{32}N_2O_7$	$C_{15}H_{22}NO_2Cl$	$C_{14}H_{19}NO_3$
MW	460.52	283.79	249.30
Space group	P-1	$P2_1/n$	$P2_1/c$
Z	2	4	4
a, Å	9.0171 (6)	9.495 (1)	18.135 (5)
b, Å	11.7331 (9)	16.208 (2)	7.191 (3)
c, Å	12.2617 (9)	9.867(1)	10.170 (2)
α,°	97.836 (6)	90.00	90.00
β, °	90.062 (6)	105.67 (1)	95.25 (2)
γ, °	110.753 (6)	90.00	90.00
V, Å^3	1200.06 (15)	1462.0 (3)	1320.7 (7)
ρ, g/cm^3	1.274	1.289	1.254
Crystal size, mm	0.55 × 0.35 × 0.20	0.60 × 0.40 × 0.10	0.45 × 0.25 × 0.15
μ_{exp}, cm^{-1}	0.78	2.414	0.714
Number of reflections	4786	2585	2650
Number of reflections with $I > 2\sigma$ (I)	2844	2090	1333
R_1 (I > 2 σ (I) and total)	0.074	0.040 (0.053)	0.064 (0.120)
wR_2	0.235	0.108 (0.115)	0.165 (0.199)
GOOF	1.05	1.036	0.919
Electron density difference peaks, eÅ^{-3}	0.72 and –0.32	0.22 and –0.19	0.21 and –0.20
CCDC	998858	998859	998860



Reduction of **14** by $NaBH_4$ gave a mixture of greater than five products. This was possibly due to the instability of **14** in basic solution. Reduction of **15** by $NaBH_4$ produced the free base **16**. The structures of **14**–**16** were proved using PMR spectra.

The PMR spectrum of **14** had two 2H singlets at 7.09 ppm (2H, s, H-8, 8′) and 7.26 (2H, s, H-5, 5′) and a single 1H singlet at 5.47 ppm that indicated unambiguously that two rings had closed and formed the bis-dihydrohydroisoquinoline. The double bonds on C-1 and C-1′ caused the resonances of aromatic protons H-5 and H-8 to shift to weak field compared with those in **10**, **11**, and **13**.

The PMR spectrum of **15** exhibited 1H singlets at 7.06 ppm (1H, s, H-8) and 7.17 (1H, s, H-5) in addition to resonances at 6.71 ppm (2H, d, J = 8, H-6′), 6.76 (2H, s, H-2′), and 6.79 (2H, d, J = 8, H-5′). This indicated that only one cyclization occurred and formed not the bis-isoquinoline but amidodihydroisoquinoline **15**. The incomplete cyclization was also confirmed by PMR spectra of free base **16**. Distinguishing features of the latter were a resonance at 4.12 ppm (H-1) and the lack of a resonance at 5.10 ppm (H-1″) that was characteristic of free base **15**.

P_2O_5 is a more energetic condensing agent and is used for amides if they are poor cyclized. We used xylene as the solvent because **5** did not dissolve in toluene. The reaction was carried out for 4 h with constant stirring. Product **15** was insoluble in xylene and precipitated and mixed with the P_2O_5. This may have reduced the activity of the P_2O_5. The yield of pure **15** was 20% whereas the mixture of other compounds could not be separated.

We started with a temperature of 60–70°C for the cyclization with PPA. However, **5** did not dissolve at this temperature. The mixture became homogeneous if the temperature was increased gradually to 110°C (**5** had mp 112°C). The comparatively

low (0.2 g, 13%) yield of **14** was explained by the fact that PPA is a very active reagent. This led to side reactions and the formation of organophosphorus compounds.

Our research showed that the Bischler–Napieralski reaction of dibasic acids with a chain of five atoms depended on both the type of atoms in the chain and the used solvents and reagents. Simple methods for preparing both hexahydropyrido- (**10**) and hexahydro[1,4]oxazino (**11**) -isoquinolines in addition to bis-isoquinoline derivatives (**13**, **14**) could be proposed by varying the reaction conditions.

EXPERIMENTAL

IR spectra were recorded from KBr pellets on an FTIR system 2000 instrument (PerkinElmer). PMR spectra were recorded on a Unity-400+ Varian spectrometer (400 MHz, $CDCl_3$ solvent, HMDS internal standard). R_f values were determined on LS 5/40 silica gel plates (Czechoslovakia) using solvent systems $CHCl_3$–MeOH (12:1, system 1; 10:1, 2; 8:1, 3; 6:1, 4; and 4:1, 5). Melting points of all synthesized compounds were determined on a Boetius apparatus.

***N,N′*-(3,4-Dimethoxy-*β*-phenylethyl)glutardiamide (4)**, $C_{25}H_{34}N_2O_6$. A mixture of **1** (5 g, 0.027 mol) and **2** (2 g, 0.011 mol) was dissolved in MeOH (5 mL). Then, the salt was heated on an oil bath at 178°C for 2 h. The reaction mixture was 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. The resulting crystals were filtered off. Yield 79% (5 g), mp 132–135°C (Me_2CO), R_f 0.76 (system 3). IR spectrum (KBr, ν, cm^{-1}): 3290 (NH), 2931 (Ar-CH), 1638 (N-C=O), 1591, 1551, 1519 (Ar-H). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.82 (2H, t, J = 6.9, H-2′), 2.10 (4H, t, J = 7, H-1′, 3′), 2.70 (4H, t, J = 7, H-*α*), 3.41 (4H, q, J = 6.2, H-*β*), 3.79 (6H, s, OCH_3), 3.80 (6H, s, OCH_3), 5.69 (2H, t, NH), 6.64 (2H, d, J = 2, H-2), 6.66 (2H, dd, J = 2, 8.6, H-6), 6.74 (2H, d, J = 8.6, H-5).

Preparation of 2,2′-oxy-bis**[*N*-(3,4-dimethoxyphenyl)acetamide] (5)**, $C_{24}H_{32}N_2O_7$. A solution of **1** (2 g, 0.011 mol) in MeOH (5 mL) was treated with **3** (0.8 g, 0.006 mol) to form the salt. The reaction mixture was heated at 180°C for 1.5 h after complete crystallization. When the reaction was finished, the mixture was dissolved in $CHCl_3$ (100 mL) and washed with aqueous NaOH (5%) and HCl (10%). The $CHCl_3$ was removed *in vacuo*. The oily product was dissolved in Me_2CO (25 mL) with added H_2O (3 mL) and left to crystallize slowly. The crystalline amide was filtered off and washed with H_2O. Yield 86% (2 g), mp 110–112°C (Me_2CO), R_f 0.8 (system 5). IR spectrum (KBr, ν, cm^{-1}): 3365 (H-N), 1680 (N-C=O), 1464 (-CH_2-C=O), 1261 (C-N), 1141 (C-O-C). ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.75 (4H, t, J = 7.2, H-*α*), 3.44 (4H, t, J = 7.2, H-*β*), 3.77 (6H, s, OCH_3), 3.80 (6H, s, OCH_3), 3.96 (4H, s, H-1′), 6.74 (2H, d, J = 8.2, H-6), 6.83 (2H, s, H-2), 6.84 (2H, d, J = 8.2, H-5). Crystals for the XSA were grown from Me_2CO–C_6H_6.

Reaction of 4 with $POCl_3$ in C_6H_6. A mixture of **4** (1.5 g, 0.006 mol), anhydrous C_6H_6 (30 mL), and $POCl_3$ (2 mL) was refluxed for 2 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 (30 mL), cooled to 0–5°C, and treated in portions with $NaBH_4$ (0.015 mol). The MeOH was distilled off. The residue was treated with H_2O and extracted with $CHCl_3$. The $CHCl_3$ was removed. The residue was separated over a column of silica gel (25 g) with elution by $CHCl_3$ and $CHCl_3$–MeOH (100:0.5–0:100) to afford two crystalline compounds **9** and **10**.

***N*-(3,4-Dimethoxyphenylethyl)-5-(3,4-dimethoxy-*β*-phenylethylamino)pentanamide (9)**, $C_{25}H_{36}N_2O_5$. Mass spectrum *m/z* 445.2678 $(M + 1)^+$. Yield 22% (0.2 g), mp 147–149°C (Me_2CO), R_f 0.41 (system 3). IR spectrum (KBr, ν, cm^{-1}): 3325 (NH), 2942, 2777, 2461, 1642 (NC=O), 1591, 1519, 1470. ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.77, 1.91 (each 2H, t, J = 7, H_2-3′, 4′), 2.24 (2H, t, J = 7, H_2-2′), 2.77 (2H, t, J = 7, H_2-5′), 2.98 (2H, m, H-*β*), 3.18 (4H, m, H-*α*, 7′), 3.44 (2H, q, J = 7, H-6′), 3.83 (3H, s, OCH_3), 3.84 (6H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.58 (1H, broad, NH), 6.72 (2H, d, J = 8, H-6, 12′), 6.77 (2H, s, H-2, 8′), 6.78 (2H, d, J = 8, H-5, 11′), 9.70 (2H, br.s, NH).

9,10-Dimethoxy-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline (10), $C_{15}H_{21}NO_2$, Yield 55% (0.5 g), hydrochloride mp 201–203°C (Me_2CO), R_f 0.55 (system 3). IR spectrum (KBr, ν, cm^{-1}): 2962, 2450, 1611, 1709, 1525. ^1H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.78 (2H, m, CH_2), 1.95 (4H, m, $2CH_2$), 3.04 (2H, m, CH_2), 3.42 (2H, m, CH_2), 3.60 (2H, m, CH_2), 3.81 (6H, s, OCH_3), 4.38 (1H, broad, H-11b), 6.80 (1H, s, H-8), 6.83 (1H, s, H-11). Crystals of **10**·HCl for the XSA were grown from MeOH.

Reaction of 4 with $POCl_3$. A mixture of **4** (0.5 g, 0.6 mmol) and $POCl_3$ (1.5 mL) was refluxed on a water bath for 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%) to pH 9, and extracted with $CHCl_3$. The $CHCl_3$ was removed. The residue was crystallized from Me_2CO to afford **12** (0.4 g, 87%).

1,3-Bis(6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)propane (12), $C_{25}H_{32}N_2O_4$. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.02 (2H, m, CH_2), 2.57 (4H, t, J = 7.3, $2CH_2$), 2.81 (4H, t, J = 7.5, H-4, 4′), 3.57 (4H, t, J = 7.5, H-3, 3′), 3.84 (6H, s, OCH_3), 3.85 (6H, s, OCH_3), 6.62 (2H, s, H-8, 8′), 7.00 (2H, s, H-5, 5′).

1,3-Bis(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)propane (13), $C_{25}H_{34}N_2O_4$. Compound **12** (0.39 g) 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 to afford **13**. Yield **13** 84% (0.33 g), mp 99–101°C (Me_2CO), R_f 0.35 (system 5). IR spectrum (ν, cm^{-1}): 3378, 2917, 1612, 1520, 1468, 1257, 1223. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.57 (4H, q, J = 7.4, H-1′, 2′), 1.83 (2H, m, CH_2), 2.63 (4H, dt, J = 6, H-4, 4′), 2.89 (2H, dt, J = 5, 2, H-3), 3.14 (2H, dt, J = 5.4, 2.4, H-3′), 3.77 (6H, s, OCH_3), 3.78 (6H, s, OCH_3), 3.87 (2H, dd, J = 3.5, 8.5, H-1, 1′), 6.50 (2H, s, H-8, 8′), 6.55 (2H, s, H-5, 5′).

Reaction of 5 with $POCl_3$ in C_6H_6. A solution of **5** (1.5 g, 0.003 mol) in C_6H_6 (20 mL) was treated with $POCl_3$ (2.72 g, 0.017 mol) and refluxed for 2 h. The course of the reaction was monitored by TLC. The resulting mixture was made basic with NH_4OH solution (10%) to pH 8–9 and extracted with $CHCl_3$. The $CHCl_3$ was distilled off. The resulting product mixture consisted mainly of three compounds with R_f 0.3, 0.6, and 0.9 (system 4). The resulting mixture was divided into two portions (A and B).

Sample A. The crude oily product (0.8 g) was placed onto a column of silica gel (15 g) and eluted by $CHCl_3$ with a gradient of MeOH from 0 to 100%. A total of 25 fractions were collected. Fractions 8–10 afforded pure **6** (0.25 g), R_f 0.6.

6,7-Dimethoxy-3,4-dihydroisoquinoline-1(2*H*)-oxo (6), $C_{11}H_{13}NO_3$. Yield 36% (0.25 g). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.86 (2H, t, J = 7, H-4), 3.49 (2H, m, H-3), 3.82 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.42 (1H, s, N-H), 6.61 (1H, s, H-8), 7.50 (1H, s, H-5).

Sample B. The crude oily product (0.8 g) was dissolved in MeOH (20 mL), cooled with ice, and treated in small portions with $NaBH_4$ (2 g). The MeOH was distilled off. The mixture was dissolved in H_2O and extracted with $CHCl_3$. The total $CHCl_3$ compounds (1 g) were separated over a column of silica gel (40 g). A total of 29 fractions were collected to afford **11** (0.3 g), R_f 0.8; **7** (0.04 g), R_f 0.66; and **8** (0.075 g), R_f 0.2 (system 4).

9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro[1,4]oxazino[3,4-*a*]isoquinoline (11), $C_{14}H_{19}NO_3$, mp 113°C. IR spectrum (KBr, ν, cm^{-1}): 2879 (H_3C-O), 1226 (C-N), 1132 (C-O-C). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.57 (1H, td, J = 11.5, 11.5, 4.2, H-4a), 2.61 (1H, td, J = 11.5, 11.5, 3.5, H-7b), 2.66 (1H, dd, J = 16.5, 5.0, H-7a), 2.80 (1H, dd, J = 11.9, 1.2, H-4b), 2.95 (1H, ddd, J = 10.5, 5.0, 1.1, H-6b), 3.11 (1H, td, J = 16.5, 11.8, 5.6, H-6a), 3.35 (1H, br.d, J = 10.5, H-1a), 3.43 (1H, t, J = 10.3, H-1b), 3.77 (1H, td, J = 11.3, 11.3, 2.6, H-3a), 3.89 (1H, dd, J = 10.2, 3.1, H-3b), 3.84 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.30 (1H, dd, J = 10.5, 2.8, H-11b), 6.53 (1H, s, H-8), 6.61 (1H, s, H-11). Crystals of **11** for the XSA were grown from Me_2CO.

***N*-(1-Chloroethyl)homoveratrylamine (7)**, mp 200°C. IR spectrum (KBr, ν, cm^{-1}): 3434 (N-H). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.51 (3H, d, J = 6.5, CH_3), 3.07 (2H, m, H-7), 3.17 (2H, m, H-8), 3.23 (1H, m, H-9), 3.79 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 6.71 (2H, d, J = 8.2, H-6), 6.72 (1H, s, H-2), 6.73 (1H, d, J = 8.2, H-5).

Homoveratrylamine (8) was isolated as the salt **1**·H_2CO_3. IR spectrum (KBr, ν, cm^{-1}): 3174 (N-H). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.89 (2H, t, J = 8, H-*α*), 3.08 (2H, t, J = 8, H-*β*), 3.79 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 6.74 (2H, d, J = 8.2, H-6), 6.75 (2H, s, H-2), 6.78 (2H, d, J = 8.2, H-5).

(1*Z*,1′*Z*)-1,1′-Oxa-bis(methane-1-ylidene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline) (14), $C_{24}H_{28}N_2O_5$. A suspension of PCl_5 (1.6 g, 0.008 mol) in anhydrous $CHCl_3$ (10 mL) was cooled with ice and treated over 10 min with small portions of **5** (1.5 g, 0.003 mol). The solution was red after **5** was totally added. Then, the reaction mixture was stored for 3 d at room temperature. The course of the reaction was monitored by TLC. The mixture was made basic with NH_4OH solution (10%) to pH 9 and extracted with $CHCl_3$. The $CHCl_3$ was removed. The resulting oily product was converted to the hydrochloride by adding HCl-saturated MeOH. The resulting mixture of hydrochlorides was dried in vacuo. Addition to the dry residue of $CHCl_3$–Me_2CO (1:1) isolated **14** (0.3 g) with R_f 0.25 (system 3), mp 185–186°C. The crystals were separated. The mother liquor was dried. The residue was dissolved in Me_2CO to afford **15** (0.5 g) with R_f 0.83 (system 3), mp 183–184°C.

Compound 14, mp 185–186°C. IR spectrum (KBr, ν, cm^{-1}): 3429 (H-N), 1276 (C-N), 1141 (C-O-C). ^{1}H NMR spectrum (400 MHz, CD_3OD, δ, ppm, J/Hz): 3.14 (4H, s, H-4, 4′), 3.86 (6H, s, OCH_3), 3.93 (2H, m, H-3, 3′), 3.94 (6H, s, OCH_3), 5.47 (2H, s, H-1″), 7.09 (2H, s, H-8, 8′), 7.26 (2H, s, H-5, 5′).

Compound 15, mp 183–184°C. IR spectrum (KBr, ν, cm^{-1}): 3205 (H-N), 1651 (C=O), 1469 (-CH_2-C=O), 1274 (C-N), 1130 (C-O-C). ^{1}H NMR spectrum (400 MHz, CD_3OD, δ, ppm, J/Hz): 2.74 (2H, t, J = 7.5, H-*α*), 3.10 (2H, t, J = 7.5, H-4), 3.44 (2H, t, J = 7.5, H-*β*), 3.68 (3H, s, 6-OCH_3), 3.74 (3H, s, 7-OCH_3), 3.83 (2H, t, J = 7.5, H-3), 3.83 (3H, s, 3′-OCH_3),

3.92 (3H, s, 4′-OCH_3), 4.22 (2H, s, H-2″), 5.10 (1H, s, H-1″), 6.71 (2H, d, J = 8, H-6′), 6.76 (2H, s, H-2′), 6.79 (2H, d, J = 8, H-5′), 7.06 (1H, s, H-8), 7.17 (1H, s, H-5).

2[(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methoxy]-*N*-(3,4-dimethoxyphenylethyl)acetamide (16). Compound **15** (0.3 g) was dissolved in MeOH (5 mL), cooled with ice, and reduced by $NaBH_4$. The MeOH was removed. The product was extracted with $CHCl_3$ to afford **16** (0.25 g) with R_f 0.55, mp 173°C, $C_{24}H_{32}N_2O_6$. The yield of the reduced product was 0.25 g (90%). IR spectrum (KBr, ν, cm^{-1}): 3272 (HN), 1672 (C=O), 1455 (-CH_2-C=O), 1261 (CN), 1133 (C-O-C). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.74 (2H, t, J = 7.5, H-7′), 3.10 (2H, s, H-4), 3.40 (2H, m, H-8′), 3.43 (2H, m, H-3), 3.73 (3H, s, 6-OCH_3), 3.74 (3H, s, 7-OCH_3), 3.75 (3H, s, 3′-OCH_3), 3.76 (3H, s, 4′-OCH_3), 3.83 (2H, d, J = 8, H-4), 3.91, 4.02 (each 1H, d, J = 15.5, H-2″), 4.12 (1H, dd, J = 3, 8, H-1″), 6.46 (1H, s, H-5), 6.54 (1H, s, H-8), 6.60 (2H, d, J = 8, H-6′), 6.64 (2H, s, H-2′), 6.70 (2H, d, J = 8, H-5′).

(*Z*)-2-[(6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)methoxy]-*N*-(3,4-dimethoxyphenylethyl)acetamide (15), $C_{24}H_{30}N_2O_6$. A suspension of P_2O_5 (1 g, 0.007 mol) in xylene (25 mL) was stirred, treated with **5** (1.5 g, 0.003 mol), stirred on a magnetic stirrer, and refluxed for 3 h. The course of the reaction was monitored by TLC. When the reaction was finished, the mixture was made basic with NH_4OH solution (10%) to pH 9 and extracted with $CHCl_3$. The resulting total compounds were dried *in vacuo*, dissolved in MeOH, and reduced by $NaBH_4$. The resulting mixture (0.7 g) was separated over a column of silica gel (15 g). A total of 20 fractions were collected. The 8th fraction afforded pure **15** (0.2 g, 20%), R_f 0.8 (system 3).

Reaction of 5 with P_2O_5. P_2O_5 (1.3 g) was treated with stirring with H_3PO_4 (0.9 mL) and heated at 100–110°C on a glycerin bath in a flask with a stopper for 2 h. The freshly prepared PPA (2.6) was treated with **5** (1.5 g) and heated at 110°C on a glycerin bath for 2 h. When the reaction was finished, the mixture was neutralized with NH_4OH solution (10%) to pH 9 and extracted with $CHCl_3$ to afford a mixture (0.2 g) consisting of five compounds. The extracted aqueous part was acidified with HCl to pH 2 and again extracted with $CHCl_3$ to afford pure **14** (0.2 g), R_f 0.25.

X-ray Crystal Structure Analysis. Transparent crystals of **5**, **10**·HCl, and **11** were prepared as elongated prisms by slow evaporation of the corresponding solvents at room temperature. Unit-cell constants were determined and refined on a CCD Xcalibur Ruby diffractometer (Oxford Diffraction) using Cu Kα-radiation (300 K, graphite monochromator). A three-dimensional data set of reflections was obtained on the same diffractometer. Absorption corrections were applied using a semi-empirical method in the SADABS program [16]. Table 1 presents the principal crystallographic parameters and the characteristics of the XSA experiments and crystal structure refinement calculations.

The structures were solved by direct methods using the SHELXS-97 program set. The structures were refined using the SHELXL-97 program [17]. All non-hydrogen atoms were refined by anisotropic full-matrix least-squares methods (over F^2). Positions of H atoms were found geometrically and refined with fixed isotropic thermal parameters $U_{iso} = nU_{eq}$, where n = 1.5 for methyls and 1.2 for others and U_{eq} is the equivalent isotropic thermal parameter of the corresponding C atoms.

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

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