Chemistry of Heterocyclic Compounds, Vol. 45, No. 9, 2009

SYNTHESIS OF NOVEL 1,2-FUNCTIONALLY-SUBSTITUTED 6,7-DIMETHOXY-4-SPIROCYCLO-PENTANETETRAHYDROISOQUINOLINES

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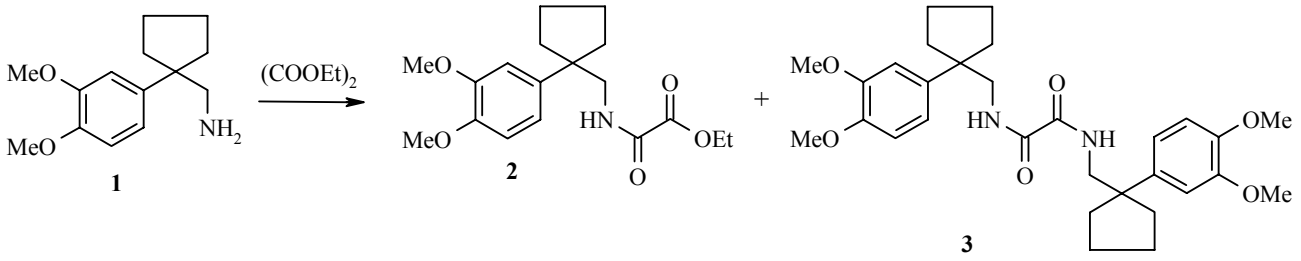
1-[(3,4-Dimethoxyphenyl)cyclopentyl]methylamine has been used in the synthesis of 6,7-dimethoxy-4-spirocyclopentane-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid N-methylamide which is employed in the preparation of novel derivatives with substituents in positions 1,2,6, and 7.

Keywords: 1-[(3,4-dimethoxyphenyl)cyclopentyl]methylamine, spirocyclopentane, tetrahydroisoquinoline, reduction.

Tetrahydroisoquinolines have long been known as biologically active substances [1] but interest in these structures has not lessened and studies of their biological properties continue without losing interest to the present day [2, 3].

The synthesis of isoquinolines containing methyl substituents in the one position and spiro rings in a quaternary position has been reported previously [4, 5]. The aim of this work was to preserve the spiro ring in the tetrahydroisoquinoline structure but to have functional groups like carbethoxy, amido, or hydroxymethyl in position one in order to prepare novel derivatives.

Scheme 1



1 **2** **3**

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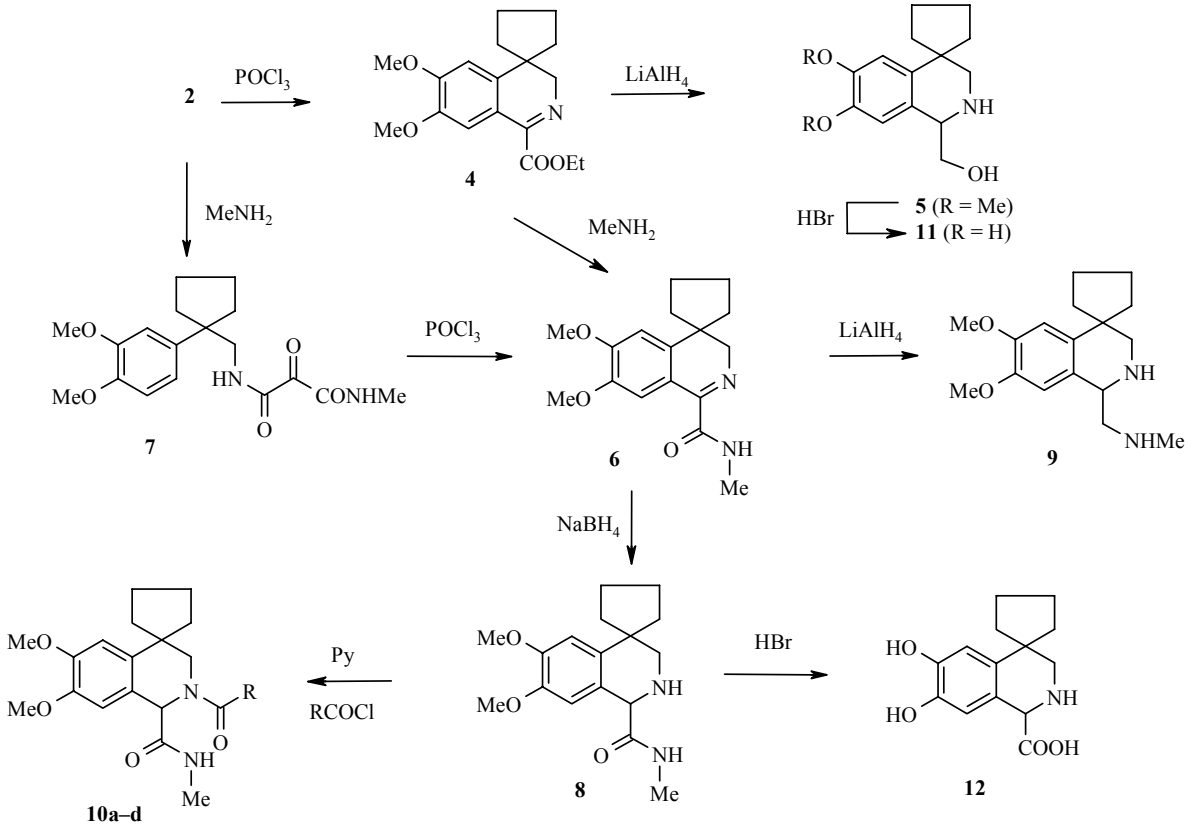
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1338-1344, September, 2009. Original article submitted November 5, 2007.

The 1-[(3,4-dimethoxyphenyl)cyclopentyl]methylamine **1** [6] was used as the starting material and condensed with diethyl oxalate to give the monoethyl ester of oxalic acid amide **2** together with a small amount (~ 5%) of the symmetrical diamine **3** (Scheme 1).

Under Bischler-Napieralski reaction conditions amide **2** underwent cyclization to give 1-ethoxycarbonyl-4-spirocyclopentane-3,4-dihydroisoquinoline **4** and this was confirmed by the presence in the ^{1}H NMR spectrum of signals for two rather than the three aromatic protons seen in the starting compound **2** (Scheme 2). Reduction of compound **4** with lithium aluminium hydride reduces both the double bond and also the ester group to give the tetrahydroisoquinoline **5** containing a hydroxymethyl group at the one position. Attempts to reduce the C=N bond in compound **4** selectively using sodium borohydride were unsuccessful and separation of the tetrahydroisoquinoline could not be achieved due to the instability of the ester group in basic medium. In order to retain a carbonyl fragment the dihydroisoquinoline **4** was treated with methylamine to give amide **6**. The same dihydroisoquinoline was separated after cyclization of the unsymmetrical oxalic acid diamide **7** which was prepared *via* condensation of amidoester **2** with methylamine. The yields from both routes were virtually the same (28% for the two stages).



10 a R = Me, **b** R = 2-furyl, **c** R = Ph, **d** R = 4-$O_2NC_6H_4$

Selective hydrogenation of the C=N double bond in compound **6** was achieved using sodium borohydride to give the tetrahydroisoquinoline **8** with retention of the amide functional group in the 1 position. The yield of the tetrahydroisoquinoline **8** can be increased by 5-7% if it is prepared from diamine **7** without isolation of the intermediate dihydroisoquinoline **6**.

Reduction of the dihydroisoquinoline **6** using lithium aluminium hydride also gave the tetrahydroisoquinoline **8** with a small admixture (~ 6%) of the fully hydrogenated product **9** and this could be separated due

to the difference in solubilities of the hydrochloride **8** and the dihydrochloride **9** in absolute ethanol. The presence of an active amino group in compound **8** allows the preparation of novel tetrahydroisoquinoline derivatives containing a spiro ring. In particular, condensation of compound **8** with acetyl, benzoyl, *p*-nitrobenzoyl, or 2-furoyl chlorides gave the series of amides **10a-d**. Study of the ^{1}H NMR spectra of these amides showed them to be mixtures of diastereomers in the ratio 70:30, 80:20, and 70:30 for **10a,c,d** respectively. In the case of compound **10b** fractional recrystallization gave the main isomer. Formation of diastereomers in the N-acyl tetrahydroisoquinoline series is apparently due to hindered rotation around the bond between the nitrogen atom of the tetrahydroisoquinoline and the carbonyl group.

It was also of interest to study the demethylation process of the 6,7-dimethoxytetrahydroisoquinolines **5** and **8** to give the dihydroxyisoquinolines. Demethylation was carried out using hydrobromic acid. As a result of this reaction compound **5** gave the 6,7-dihydroxytetrahydroisoquinoline hydrobromide **11** while demethylation of compound **8** simultaneously gave hydrolysis of the amide group to form the amino acid hydrobromide **12**.

EXPERIMENTAL

IR spectra were taken on a Carl Zeiss UR-20 instrument for a thin layer in vaseline oil and ^{1}H NMR spectra on a Varian Mercury 300 (300 MHz) instrument using DMSO-d_6 diluted with carbon tetrachloride and with TMS as internal standard. TLC was performed on Silufol UV-254 plates.

Ethyl Oxalate N-[1-(3,4-Dimethoxyphenyl)cyclopentylmethyl]amide (2). A solution of 3,4-dimethoxyphenylcyclopentylmethylamide **1** (23.5 g, 100 mmol) in chloroform (50 ml) was added dropwise to a refluxing solution of diethyl oxalate (29.2 g, 200 mmol) in chloroform (100 ml) and refluxed for 10 h. Chloroform and excess diethyl oxalate were distilled off and the residue was distilled to give the monoamide **2** (20.0 g, 62.7%) with mp 68ºC (hexane) and bp 227-230ºC (1 mm Hg), R_f 0.51 (benzene–acetone, 3:1). IR spectrum, ν, cm^{-1}: 1580, 1600 (C=C Ar), 1640 (NC=O), 1710 (OC=O), 3300 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.34 (3H, t, *J* = 7.1, CH_3); 1.62-1.97 (8H, m, C_4H_8); 3.31 (2H, d, *J* = 6.5, NCH_2); 3.78 (3H, s, OCH_3); 3.80 (3H, s, OCH_3); 4.22 (2H, q, *J* = 7.1, OCH_2); 6.73-6.80 (3H, m, C_6H_3); 7.49 (1H, br. t, *J* = 6.5, NH). Found, %: C 64.51; H 7.72; N 4.23. $C_{18}H_{25}NO_2$. Calculated, %: C 64.44; H 7.53; N 4.18.

After distillation of compound **2** the residue was recrystallized from ethanol to give the diamide **3** (2.6 g, 5%); mp 166-168ºC, R_f 0.75 (benzene–acetone, 2:1). IR spectrum, ν, cm^{-1}: 1590, 1605 (C=C Ar), 1690 (NC=O), 3390 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.65-1.94 (16H, m, 2 C_4H_8); 3.27 (4H, d, *J* = 6.5, 2 NCH_2); 3.78 (6H, s, 2 OCH_3); 3.80 (6H, s, 2 OCH_3); 6.70-6.79 (6H, m, 2 C_6H_3); 7.45 (2H, t, *J* = 6.5, 2 NH). Found, %: C 68.58; H 7.51; N 5.54. $C_{30}H_{40}N_2O_6$. Calculated, %: C 68.70; H 7.63; N 5.34.

Oxalic Acid N-Methyl-N'-[1-(3,4-dimethoxyphenyl)cyclopentylmethyl]amide (7). A solution of methylamine (1.3 g, 4 mmol) in absolute ethanol (50 ml) was added to a solution of the amidoester **2** (6.7 g, 2 mmol) in ethanol (50 ml) and left for 10 h at room temperature. The crystals formed were filtered and recrystallized from ethanol to give the diamide **7** (4.8 g, 75.2%); mp 125-126ºC, R_f 0.44 (benzene–acetone, 3:1). IR spectrum, ν, cm^{-1}: 1590, 1610 (C=C Ar), 1657 and 1693 (NC=O, 3350 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.63-1.97 (8H, m, C_4H_8); 2.71 (3H, d, *J* = 5.0, NCH_3); 3.31 (2H, d, *J* = 6.5, NCH_2); 3.78 (3H, s, OCH_3); 3.80 (3H, s, OCH_3); 6.73-6.80 (3H, m, C_6H_3); 7.46 (1H, br. t, *J* = 6.5, NH); 8.45 (1H, br. q, *J* = 5.0, NH). Found, %: C 63.95; H 7.81; N 8.82. $C_{17}H_{24}N_2O_4$. Calculated, %: C 63.71; H 7.50; N 8.75.

Ethyl 6,7-Dimethoxy-4-spirocyclopentane-3,4-dihydrosioquinoline-1-carboxylate (4). A mixture of amidoester **2** (17.8 g, 53 mmol) and phosphorus oxychloride (50 ml) in acetonitrile (200 ml) was refluxed for 10 h. Solvent was distilled off, the residue was dissolved in water, and the product was basified with aqueous ammonia to pH 8.0. It was extracted with benzene (3×100 ml), dried over sodium sulfate, solvent was distilled off, and the residue was chromatographed on a II activity grade alumina column collecting the fraction with R_f 0.43 (benzene–diethyl ether, 2:1) to give the dihydroisoquinoline **4** (8.0 g, 47.6%). IR spectrum, ν, cm^{-1}: 1585,

1600 (C=C Ar), 1640 (C=N), 1720 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.41 (3H, t, *J* = 7.1, CH_3); 1.66-1.83 (8H, m, C_4H_8); 3.59 (2H, s, NCH_2); 3.80 (3H, s, OCH_3); 3.88 (3H, s, OCH_3); 4.35 (2H, q, *J* = 7.1, OCH_2); 6.78 (1H, s, CH arom); 7.10 (1H, s, CH arom). Found, %: C 68.02; H 7.55; N 4.25. $C_{18}H_{23}NO_4$. Calculated, %: C 68.13; H 7.32; N 4.41.

6,7-Dimethoxy-4-spirocyclopentane-3,4-dihydroisoquinoline-1-carboxylic Acid N-Methylamide Hydrochloride (6·HCl). A. A mixture of the dihydroisoquinoline **4** (6.4 g, 20 mmol) and methylamine (1.2 g, 40 mmol) in ethanol (100 ml) was left for 6 h at room temperature. Solvent was distilled off and the residue was dissolved in absolute diethyl ether and treated with an ether solution of hydrogen chloride to give the hydrochloride **6** (4.0 g, 58.8%).

B. Obtained similarly to compound **4** from the diamine **7** (3.2 g, 10 mmol) and phosphorus oxychloride (8 ml) in acetonitrile (50 ml) and converted to the hydrochloride by method A. Yield of the hydrochloride **6** 1.1 g (36.6%); mp 176-178ºC (acetone), R_f 0.55 (benzene–acetone, 2:1; ammonia vapor). IR spectrum, ν, cm^{-1}: 1590, 1600 (C=C Ar), 1640 (C=N), 1673 (NC=O), 3469 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.80-1.95 (8H, m, C_4H_8); 2.82 (3H, br. d, *J* = 4.8, NCH_3); 3.68 (2H, s, NCH_2); 3.84 (3H, s, OCH_3); 3.89 (3H, s, OCH_3); 6.96 (1H, s, CH arom); 7.33 (1H, s, CH arom); 9.88 (1H, br. m, NH). Found, %: C 60.48; H 6.85; Cl 10.52; N 8.11. $C_{17}H_{22}N_2O_3$·HCl. Calculated, %: C 60.23; H 6.79; Cl 10.47; N 8.27.

6,7-Dimethoxy-4-spirocyclopentane-1,2,3,4-tetrahydroisoquioline-1-carboxylic Acid N-Methylamide (8). A. Sodium borohydride (1.1 g, 30 mmol) was added in small portions with stirring to a solution of the dihydroisoquinoline **6** (3.0 g, 10 mmol) in methanol (100 ml) at 0-5ºC. It was left overnight. Solvent was distilled off and the residue was treated with water and extracted with benzene (3×50 ml). The product was dried over sodium sulfate, solvent distilled off, and the residue was recrystallized from diethyl ether to give the tetrahydroisoquinoline **8** (2.0 g, 66.2%).

B. A mixture of diamide **7** (3.2 g, 10 mmol), phosphorus oxychloride (8 ml), and acetonitrile (50 ml) was refluxed for 5 h. After distillation of the solvent the residue was dissolved in methanol and reduced as in method A to give compound **8** (1.0 g, 33.3%); mp 100-102ºC, R_f 0.42 (benzene–acetone, 1:1). IR spectrum, ν, cm^{-1}: 1580, 1605 (C=C Ar), 1680 (NC=O), 3300 (NH). Mp of hydrochloride **8**·HCl 227-230ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.76-2.05 (8H, m, C_4H_8); 2.78 (3H, d, *J* = 4.6, NCH_3); 2.99, 3.59 (2H, two d, *J* = 12.5, NCH_2); 3.78 (3H, s, OCH_3); 3.79 (3H, s, OCH_3); 5.14 (1H, s, NCH); 6.72 (1H, s, CH arom); 7.06 (1H, s, CH arom); 9.31 (1H, br. q, *J* = 4.6, NH); 8.97 (1H, br. s, NH); 10.48 (1H, br. s, HCl). Found, %: C 67.32; H 7.65; N 9.45. $C_{17}H_{24}N_2O_3$. Calculated, %: C 67.10; H 7.89; N 9.21.

1-Hydroxymethyl-6,7-dimethoxy-4-spirocyclopentane-1,2,3,4-tetrahydroisoquinoline (5). The dihydroisoquinoline **4** (3.17 g, 10 mmol) in benzene (100 ml) was added dropwise to lithium aluminium hydride (1.1 g, 30 mmol) in absolute diethyl ether (50 ml). The mixture was refluxed with stirring for 12 h and decomposed with water. The product was filtered, solvent distilled off, and the residue was recrystallized from ether to give the amino alcohol **5** (1.4 g, 50.5%); mp 70-72ºC, R_f 0.41 (butanol–acetic acid–water, 5:3:3). IR spectrum, ν, cm^{-1}: 1580, 1600 (C=C Ar), 3500-3300 (NH, OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.61-1.91 (8H, m, C_4H_8); 2.31 (1H, br. s, NH); 2.56, 2.78 (2H, two d, *J* = 12.2, NCH_2); 3.50, 3.59 (2H, dd, *J* = 8.4 and *J* = 10.7, OCH_2); 3.74 (3H, s, OCH_3); 3.75 (1H, m, NCH); 3.75 (3H, s, OCH_3); 4.18 (1H, br. s, OH); 6.55 (1H, s, CH arom); 6.65 (1H, s, CH arom). Found, %: C 69.18; H 8.17; N 4.97. $C_{16}H_{23}NO_3$. Calculated, %: C 69.31; H 8.30; N 5.05.

Reduction of 6,7-Dimethoxy-4-spirocyclopentane-3,4-tetrahdroisoquinoline-1-carboxylic Acid N-Methylamide (6). A solution of the dihydroisoquinoline **6** (1.5 g, 5 mmol) in benzene (50 ml) was added dropwise to lithium aluminium hydride (1.1 g, 30 mmol) in absolute diethyl ether (50 ml). The mixture was refluxed with stirring for 20 h and decomposed with water. The product was filtered, the solvent distilled off, and the residue was dissolved in absolute diethyl ether and treated with an ether solution of hydrogen chloride to yield the hydrochloride. It was refluxed in ethanol and the dihydrochloride **9** (0.1 g, 5.6%) insoluble in the hot alcohol was filtered off. Mp 265-267ºC, R_f 0.30 (benzene–acetic acid–water, 5:3:3). IR spectrum, ν, cm^{-1}: 1590, 1605 (C=C Ar); 3250-3400 (NH, NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.56-1.91 (6H, m, C_4H_8);

2.01-2.14 (2H, m, C_4H_8); 2.64 (3H, s, CH_3); 3.12, 3.22 (2H, two d, J = 13.6, NCH_2); 3.37(1H, dd, J = 14.2 and J = 2.1, $NC\underline{H}_2CH$); 3.74 (1H, dd, J =14.2 and J = 9.3, $NC\underline{H}_2CH$); 3.77 (6H, s, $2OCH_3$); 4.78 (1H, dd, J = 9.3 and J = 2.1, CH); 6.81 (1H, s, CH arom); 7.01 (1H, s, CH arom); 9.60 (4H, br. s, NH, HCl). Found, %: C 56.41; H 7.59; Cl 19.65; N 7.82. $C_{17}H_{26}N_2O_2 \cdot 2HCl$. Calculated, %: C 56.20; H 7.76; Cl 19.56; N 7.71.

Cooling the alcohol solution gave crystals of the hydrochloride **6** which were filtered off to give **6**·HCl (0.9 g, 53.0%) with parameters agreeing with those reported before.

1-Hydroxymethyl-6,7-dihydroxy-4-spirocyclopentane-1,2,3,4-tetrahydroisoquinoline Hydrobromide (11·HBr). A solution of the isoquinoline **5** (1.0 g, 3.6 mmol) in hydrobromic acid (30 ml) was refluxed for 4 h. After cooling, the crystalline product was filtered off and washed with cold water to give the hydrobromide **11** (0.9 g, 75.0%); mp 272-273ºC. IR spectrum, ν, cm^{-1}: 1590, 1610 (C=C Ar), 3200-3500 (NH, OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.73-2.02 (8H, m, C_4H_8); 2.99, 3.15 (1H, two m, NCH_2); 3.73 (1H, dd, J = 12.1 and 8.6, OCH_2); 3.93 (1H, dd, J = 12.1 and J = 4.0, OCH_2); 4.34 (1H, m, NCH); 6.57 (1H, s, CH arom); 6.68 (1H, s, CH arom); 8.40 (3H, br. s), 8.65 (1H, br. s), and 9.40 (1H, br. s, NH, OH, NBr). Found, %: C 51.05; H 5.89; Br 24.13; N 4.51. $C_{14}H_{19}NO_3 \cdot HBr$. Calculated, %: C 50.90; H 6.06; Br 24.24; N 4.24.

6,7-Dihydroxy-4-spirocyclopentane-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid Hydrobromide (12·HBr). was prepared similarly to compound **11·HBr** from isoquinoline **8** (1.0 g, 3.3 mmol) to give a yield of 0.7 g (65.0%); mp 263-265ºC. IR spectrum, ν, cm^{-1}: 1600, 1615 (C=C Ar); 1730 (C=O), 3300-3600 (NH, OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.64-1.94 (7H, m, C_4H_8); 2.01-2.11 (1H, m, C_4H_8); 3.17, 3.34 (1H, two d, J = 12.8, NCH_2); 4.96 (1H, s, NCH); 6.69 (1H, s, CH arom); 6.86 (1H, s, CH arom); 8.70 (3H, br. s); 9.25 (1H, br. s), and 9.77 (1H, br. s, NH, OH, HBr). Found, %: C 48.55; H 5.05; Br 23.27; N 4.29. $C_{14}H_{17}NO_4 \cdot HBr$. Calculated, %: C 48.83; H 5.23; Br 23.25; N 4.07.

Acylation of 6,7-Dimethoxy-4-spirocyclopentane-1,2,3,4-tetrahydroisoquinolinecarboxylic Acid N-Methylamide (8). The corresponding acid chloride (5 mmol) was added dropwise to a solution of the isoquinoline **8** (1.52 g, 5 mmol) and pyridine (0.4 g, 5 mmol) in benzene (50 ml). In the preparation of amide **10a** the reaction mixture was held with stirring for 5 h at room temperature and for the remainder refluxed for 5 h with stirring. The pyridine hydrochloride was filtered off and the filtrate was washed with water, 10% HCl, a 10% solution of sodium carbonate, and again water. Distillation of solvent gave a crystalline precipitate which was recrystallized from ethanol.

2-Acetyl-6,7-dimethoxy-4-spirocyclopentane-1,2,3,4-tetrahydroisoquinolinecarboxylic Acid N-Methylamide (10a). Yield 1.0 g (58.8%); mp 125-126ºC, R_f 0.35 (benzene–acetone, 2:1). IR spectrum, ν, cm^{-1}: 1600, 1610 (C=C Ar), 1660, 1680 (NHCO, NCO), 3320 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.26-2.20 (8H, m, C_4H_8); 2.09 (0.9H, s, $C(O)CH_3$) and 2.11 (2.1H, s, $C(O)CH_3$); 2.67 (2.1H, d, J = 4.5, $NHC\underline{H}_3$) and 2.69 (0.9H, d, J = 4.5, $NHC\underline{H}_3$); 3.55, 3.77 (0.7H, two d, J = 13.5, NCH_2) and 3.75, 4.39 (0.3H, two d, J = 13.0, NCH_2); 3.76 (2.1H, s, OCH_3); 3.78 (2.1H, s, OCH_3) and 3.79 (1.8H, s, OCH_3); 5.16 (0.3H, s, NCH) and 5.60 (0.7H, s, NCH); 6.69 (0.7H, s, CH arom) and 6.71 (0.3H, s, CH arom); 6.88 (1H, s, CH arom); 7.75 (0.3H, q, J = 4.5, NH) and 7.95 (0.7H, q, J = 4.5, NH) (Two isomers in the ratio 70:30). Found, %: C 65.64; H 7.40; N 8.22. $C_{19}H_{26}N_2O_4$. Calculated, %: C 65.89; H 7.51; H 8.09.

2-Furoyl-6,7-dimethoxy-4-spirocyclopentane-1,2,3,4-tetrahydroisoquinolinecarboxylic Acid N-Methylamide (10b). Yield 1.1 g (56.1%); mp 145-147ºC, R_f 0.51 (benzene–acetone, 2:1). IR spectrum, ν, cm^{-1}: 1580, 1605 (C=C Ar), 1650 and 1670 (NC=O); 3400 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.36-2.20 (8H, m, C_4H_8); 2.71 (3H, d, J = 4.6, NCH_3); 3.78 (3H, s, OCH_3); 3.79 (3H, s, OCH_3); 3.92, 4.32 (2H, two br. d, J = 13.0, NCH_2); 5.65 (1H, br. s, NCH); 6.54 (1H, dd, J = 3.4 and J = 1.8, H-4 furan); 6.70 (1H, s, CH arom); 6.93 (1H, s, CH arom); 7.01 (1H, d, J = 3.4, H-3 furan); 7.63 (1H, d, J = 1.8, H-5 furan); 8.10 (1H, br. s, NH). Found, %: C 66.15; H 6.39; N 7.21. $C_{22}H_{26}N_2O_5$. Calculated, %: C 66.30; H 6.53; N 7.03.

2-Benzoyl-6,7-dimethoxy-4-spirocyclopentane-1,2,3,4-tetrahydroisoquinolinecarboxylic Acid N-Methylamide (10c). Yield 1.2 g (60.3%); mp 245-246ºC (benzene), R_f 0.58 (benzene–acetone, 1:1). IR spectrum, ν, cm^{-1}: 1595, 1615 (C=C Ar), 1640, 1660 (NC=O), 3350 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.96-2.20 (8H,

m, C_4H_8); 2.67 (0.6H, d, J = 4.5, NCH_3) and 2.75 (2.4H, d, J = 4.5, NCH_3); 3.78 (6H, s, $2OCH_3$); 3.14 (0.2H, d, J = 13.2, NCH_2) and 3.48 (0.8H, d, J = 13.2, NCH_2); 3.86 (0.8H, d, J = 13.2, NCH_2) and 4.56 (0.2H, d, J = 13.2, NCH_2); 4.87 (0.2H, s, NCH) and 5.84 (0.8H, s, NCH); 6.68 (0.8H, s, CH arom) and 6.72 (0.2H, s, CH arom); 6.80 (0.2H, s, CH arom) and 6.96 (0.8H, s, CH arom); 7.31-7.44 (5H, m, C_6H_5); 7.61 (0.2H, br. q, J = 4.5, NH) and 8.20 (0.8H, br. q, J = 4.5, NH). (Two isomers in the ratio 80:20). Found, %: C 70.78; H 7.12; N 6.68. $C_{24}H_{28}N_2O_4$. Calculated, %: C 70.55; H 6.93; N 6.86.

6,7-Dimethoxy-2-(4-nitrobenzoyl)-4-spirocyclopentane-1,2,3,4-tetrahydroisoquinolinecarboxylic Acid N-Methylamide (10d). Yield 1.4 g (63.5%); mp 165-166ºC, R_f 0.55 (benzene–acetone, 1:1). IR spectrum, ν, cm^{-1}: 1590, 1605 (C=C Ar), 1640 and 1650 (NC=O), 3350 (NH). ^{1}H NMR spectrum, δ, ppm (J, Hz): 0.98-2.20 (8H, m, C_4H_8); 2.66 (0.9H, d, J = 4.5, NCH_3) and 2.76 (2.1H, d, J = 4.5, NCH_3); 3.20, 4.53 (0.6H, two d, J = 13.2, NCH_2) and 3.31, 3.92 (1.4H, two d, J = 13.2, NCH_2); 3.70, 3.78, 3.79, and 3.80 (6H, s, $2OCH_3$); 4.77 (0.3H, s, NCH) and 5.82 (0.7H, s, NCH); 6.67 (0.7H, s, CH arom) and 6.71 (0.3H, s, CH arom); 6.74 (0.3H, s, CH arom) and 6.99 (0.7H, s, CH arom); 7.58 (0.6H, d, J = 8.6, CH arom) and 7.65 (1.4H, d, J = 8.6, CH arom); 8.27 (0.6H, d, J = 8.6, CH arom) and 8.31 (1.4H, d, J = 8.6, CH arom); 7.54 (0.3H, br. q, J = 4.5, NH) and 8.28 (0.7H, br. q, J = 4.5, NH). (Two isomers in the ratio 70: 30). Found, %: C 63.65; H 5.81; N 9.11. $C_{24}H_{27}N_3O_6$. Calculated, %: C 63.54; H 5.97; N 9.27.

This work was carried out with the financial support of the International Science Technology Centre (grant A-960).

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