Synthesis of 1-(3,4-Dimethoxyphenylmethyl)-3-phenyl-6,7,8-trimethoxy-3,4-dihydroisoquinoline

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In an attempt to ascertain the scope of using ethyl polyphosphate in the Bischler-Napieralsky annelation reaction, a title compound was synthesized and reduced to the respective 1-(3,4-dimethoxyphenylmethyl)-3-phenyl-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline.

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Synthesis of 3,4-dihydroisoquinolines substituted at C-3 with a phenyl group is difficult to carry-out by a simple Bischler-Napieralski reaction using either P_2O_5 or $POCl_3$. It is clear that due to the presence of an electron withdrawing phenyl group the 3-arylisoquinolines are obtained in low yield. The simplest cases of the Bischler-Napieralski reaction are well documented and reviewed [1,5].

Nowadays, some of the more complex 3,4-dihydroisoquinolines are synthesized by other methods. Using those methods the title compound has not been reported. Furthermore, compounds that posses a substitution pattern like that of the title compound, with 6,7,8-trimethoxy groups, are present in natural products, and indeed represent an interesting synthetic target [3-5].

A mild agent such as ethyl polyphosphate was previously reported as a good reagent for the synthesis of 3-phenyl-isoquinoline compounds [6-13]. The present document describes the preparation of 3,4-dihydroisoquinoline compounds and their reduction behavior [14]. Thus, Scheme 1, shows the synthesis of 1-(3,4-dimethoxyphenylmethyl)-3-phenyl-6,7,8-trimethoxy-3,4-dihydroisoquinoline (**1**) and the reduction to 1-(3,4-dimethoxyphenylmethyl)-3-phenyl-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**2**).

The synthetic route was developed through the transformation of the 1-phenyl-2-(3,4,5-trimethoxyphenyl)ethylamine (**3**) to *N*-(3,4-dimethoxy phenylacetyl)-1-phenyl-3,4,5-trimethoxyphenylethylamine (**4**), which was then treated with a chloroform solution of ethyl polyphosphate to give 1-(3,4-dimethoxyphenylmethyl)-3-phenyl-6,7,8-trimethoxy-3,4-dihydroisoquinoline in good yield. Again showing the excellent performance of the ethyl polyphosphate (2.68 g/ml) in the cyclodehydratation of amides that undergo the Bischler-Napieralski reaction [6,11].

The electron impact mass spectra of 1-(3,4-dimethoxyphenylmethyl)-3-phenyl-6,7,8-trimethoxy-3,4-dihydroisoquinoline do not present a clear molecular ion peak ($M^{+\cdot}$, m/e: 447). The low intensity of the molecular ion peak, less than 5 %, is in agreement with the fragmentation observed in the electron impact mass spectra of 3,4-dihydroisoquinolines and 1,2,3,4-tetrahydroisoquinolines [3,12]. Fragment ion m/e: 446 $[M-H]^+$ appears with relative intensity of 1.9 %. The particularly important fragment ion m/e 327 likely involves the loss of a CH_3 and H radicals as well as neutral benzenenitrile.

As follows comparing 3,4-dihydroisoquinoline (**1**) with previously reported 1,2,3,4-tetrahydroisoquinolines, a significative difference due to presence of C=N bond is observed [9-11, 13].

Analysis of carbon-13 nuclear magnetic resonance spectra (cmr) of 3,4-dihydroisoquinoline compound (**2**) completely agree with those previously reported for 1,2,3,4-tetrahydrobenzylisoquinolines [9,13]. The signal corresponding to *C*-1 appears at δ: 54.9 ppm, *C*-3 signal appears at δ: 57.1 ppm and *C*-4 appears at δ: 39.6 ppm and *C*–9, which is the CH_2 signal, appears at δ: 42.6 ppm.

Proton nuclear magnetic resonance (pmr) spectra is observed as a complex coupling group of signals (ABX system) coincident with the intense signals corresponding to the five CH_3O groups.

In order to assign the structure of (**1**), Table 1 was constructed.

This table contains spectral information corresponding to several (a total of 22) dimethoxy-3,4-dihydroisoquinolines [15]. The dimethoxy-3,4-dihydroisoquinolines models were constructed by changing the substitution pattern as depicted in the structure included with Table 1. From the theoretical values obtained with ACD-lab® it is simple to conclude that the experimental proton magnetic resonance signals obtained for (**1**), are correctly assigned. Data presented are in close agreement with all the 3-phenyl-

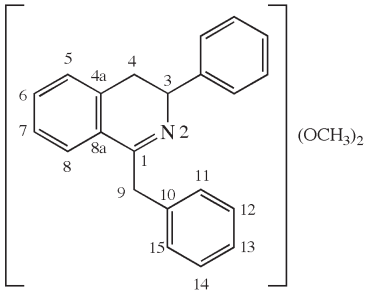
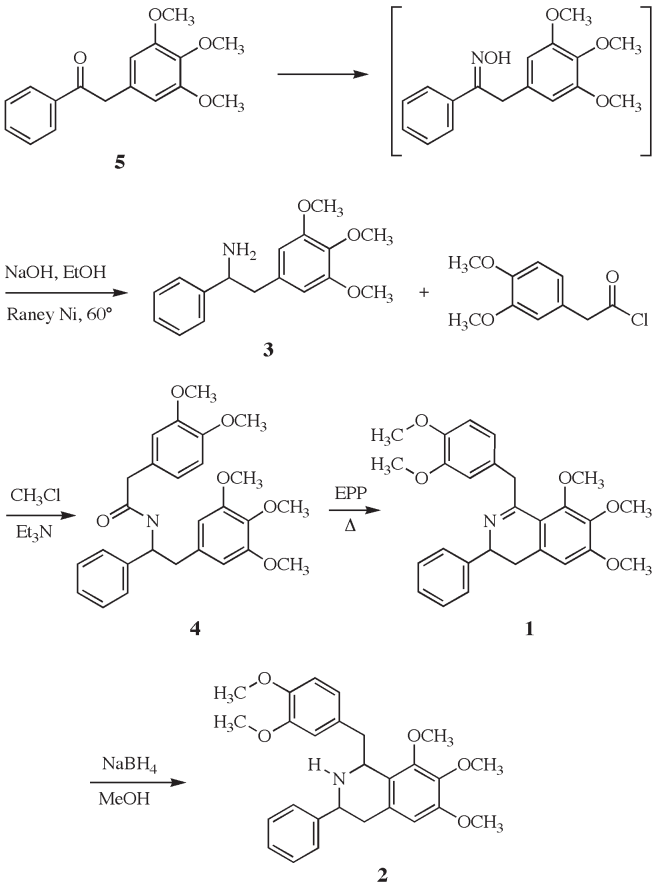


Table 1

Carbon Number, OCH_3 Positions, δ (H) ppm

Comp N°	OCH_3 Positions	C-3	C-4 (H4a)	C-4 (H4b)	C-5 (H5)	C-6 (H6)	C-7 (H7)	C-8 (H8)	C-9 (H9)	C-11 (H10)	C-12 (H11)	C-13 (H12)	C-14 (H14)	C-15 (H15)
6	8, 13	**4.0**	**2.9**	**2.6**	6.8	7.1	7.2		**3.9**	6.8	6.9		6.9	6.8
7	8, 12	**4.0**	**2.9**	**2.6**	6.8	7.1	7.2		**4.0**	6.5		6.8	7.1	6.8
8	8, 11	**4.0**	**2.9**	**2.6**	6.8	7.1	7.2		**4.1**		6.8	7.1	6.9	6.8
9	7, 13	**4.0**	**2.9**	**2.7**	6.8	7.1		7.4	**3.9**	6.9	6.9		6.9	6.9
10	7, 12	**4.0**	**2.9**	**2.7**	6.8	7.1		7.4	**4.0**	6.5		6.8	7.1	6.8
11	7, 11	**4.0**	**2.9**	**2.7**	6.8	7.1		7.3	**4.0**		6.8	7.1	6.9	6.8
12	6, 13	**4.0**	**2.9**	**2.6**	6.7		6.8	8.2	**3.9**	6.8	6.9		6.9	6.8
13	6, 12	**4.0**	**2.9**	**2.6**	6.7		6.8	8.2	**4.0**	6.5		6.8	7.1	6.8
14	6, 11	**4.0**	**2.9**	**2.6**	6.7		6.8	8.2	**4.0**		6.8	7.1	6.9	6.8
15	5, 13	**4.0**	**2.9**	**2.7**		6.8	7.3	7.4	**3.9**	6.8	6.9		6.9	6.8
16	5, 12	**4.0**	**2.9**	**2.7**		6.8	7.3	7.4	**4.0**	6.5		6.8	7.1	6.8
17	5, 11	**4.0**	**2.9**	**2.7**		6.8	7.3	7.4	**4.0**		6.8	7.1	6.9	6.8
18	11, 12	**4.0**	**2.9**	**2.7**	7.0	7.0	7.1	7.7	**4.1**			6.8	7.0	**6.6**
19	12, 13	**4.0**	**2.9**	**2.7**	7.0	7.0	7.1	7.7	**4.0**	6.8			6.9	**6.6**
20	12, 14	**4.0**	**2.9**	**2.7**	7.0	7.0	7.1	7.7	**4.0**	**6.2**		**6.2**		**6.2**
21	12, 15	**4.0**	**2.9**	**2.7**	7.0	7.0	7.1	7.7	**4.2**		**6.5**	7.1	**6.5**	
22		**4.0**	**2.9**	**2.7**	7.0	7.0	7.1	7.7	**3.9**	7.3	7.2	7.2	7.2	7.3
23	6, 7	**4.0**	**2.9**	**2.6**	6.6			7.0	**3.9**	7.3	7.2	7.2	7.2	7.3
24	7, 8	**3.9**	**2.9**	**2.7**	6.8	6.9			**4.0**	7.2	7.2	7.2	7.2	7.2
25	5, 8	**3.9**	**3.0**	**2.7**		7.0	6.8		**4.0**	7.2	7.2	7.2	7.2	7.2
26	5, 7	**3.9**	**2.9**	**2.7**		6.4		7.0	**3.9**	7.3	7.2	7.2	7.2	7.3
27	5, 6	**3.9**	**2.9**	**2.7**			6.7	7.9	**3.9**	7.3	7.2	7.2	7.2	7.3
1		**4.7**	**2.8**	**2.8**	**6.4**				**4.2**	**6.8**			**6.8**	**6.8**

Scheme 1



1,2,3,4-tetrahydroisoquinolines published and with those of the new compound (**2**).

EXPERIMENTAL

The pmr spectra were recorded on a Varian 80A or on a Bruker WOSYFT spectrometer in $CDCl_3$ using TMS as internal reference. IR spectra were recorded on a Jasco A-200 as Nujol mulls. Melting points (uncorrected) were obtained on a Thomas Hoover apparatus. The EI mass spectra were recorded in a Shimadzu CGQP 1000 mass spectrometer operating at ionizing electron energy of 70 eV or 20 eV, in all cases by direct injection of the samples as chloroform solution [12].

2-(3,4,5-Trimethoxyphenyl)-1-phenyl-ethylamine (**3**).

2-(3,4,5-Trimethoxyphenyl)-1-phenyl-ethanone oxime (3.00 g, 10 mmoles), was dissolved in 60 ml of ethanol and 60 ml of 2 *N* NaOH. The solution was heated at 60 °C while stirring and 4.5 g of raney nickel alloy was added. Once the addition was completed heat was removed and the solution stirred for another 60 minutes. The mixture was then filtered through 0.5 cm high bed celite and the filtrate extracted with diethyl ether. The solution containing the amine was dried with Na_2SO_4 and evaporated to give an oil, yield 93%, pmr: δ 1.75 (2 H, s, NH_2); 2,75 (2 H, s, CH_2); 3.70 (6 H, s, OCH_3); 3.75 (3 H, s, OCH_3); 4.10 (1 H, m, CH); 6.25 (2 H, m, Ar); 7.25 (5 H, m, Ar), ppm., ir, ν : 3390 (N-H); 1580 (HC=C); 700 (Ar-H) and 670 (Ar-H) cm^{-1}, [16].

N-(3,4-Dimethoxyphenylacetyl)2-(3,4,5-trimethoxyphenyl)-1-phenylethylamine (**4**).

A solution of homoveratroyl chloride (3,4-dimethoxyphenylacetyl chloride) (2.10 g, 12 mmoles), in 5 ml of $CHCl_3$ was added to a solution of the amine (**3**) (2.70 g, 10 mmoles) and 1.2 ml of Et_3N in 20 ml $ClCH_3$. The resulting mixture was stirred for 60 minutes, after which the solvent was evaporated and the resulting residue was diluted in 50 ml of water and the residue was collected by filtration to give compound (**4**), yield 62 %, mp, 152-154° (ethanol / H_2O) as white plate crystals, pmr: δ 2.90 (2H, m, CH_2); 3.45 (3H, s, OCH_3); 3.63 (6H, s, OCH_3) 3.75 (6H, s, OCH_3); 3.85 (3H, s, OCH_3); 5.25 (1H, br. q., CH); 5.70 (1H, br.d., NH); 6,05 (2H, s, Ar); 6,65 (3H, m, Ar); 7.20 (5H, m, Ar), ir : ν 3330 (N-H); 1660 (C=O) cm^{-1}.

Anal. Calcd. for: $C_{27}H_{31}NO_6$ (465): C, 69.66; H, 6.71; N, 3.01. Found: C, 66.68, H, 6.67, N, 3.00.

1-(3,4-Dimethoxyphenylmethyl)-3-phenyl-6,7,8-trimethoxy-3,4-dihydroisoquinoline (**1**).

N-(3,4-Dimethoxyphenylacetyl)2-(3,4,5-trimethoxyphenyl)-1-phenylethylamide (1.0 mmol) and ethyl polyphosphate (EPP), 2 ml (cc 2.68 g/ml as chloroform solution) were heated for 8 hs at 80 °C in an oil bath. The solvent was evaporated, the residue poured in 20 ml of water and extracted with CH_2Cl_2 (2 x 5 ml), the alkaline material was extracted with HCl (3 x 5 ml) and the aqueous solution was alkalinized to pH 11. The solution was extracted with CH_2Cl_2 (2 x 5 ml) and the 3,4-dihydroisoquinoline purified by tlc, Silica gel GF254 plates, chloroform:methanol:ammonia (20%) as proportion 95:5:I, [9,13] to yield 87 % of an amber oil, compound (**1**) described by pmr: δ 2.75 (2H, m, CH_2); 3.75 (3H, s, OCH_3); 3.80 (3H, s, OCH_3); 3.87(3H, s, OCH_3); 3.90 (6H, m, OCH_3); 4.25 (2H, m, CH_2); 4.70 (1H, m, CH); 6,40 (1H, d, Ar); 6,80 (3H, m, Ar); 7.30 (5H, m, Ar) ppm; MS (m/e): 446 (1.9 %), 329 (24.5 %), 328 (23.7 %), 327 (100 %), 149 (30 %).

Anal. Calcd. for: $C_{27}H_{29}NO_5$ (447): C, 72.46; H, 6.53; N, 3.13. Found: C,72.48, H, 6.48, N, 3.13.

1-(3,4-Dimethoxyphenylmethyl)-3-phenyl-6,7,8-trimethoxy-1,2,3,4-tetrahydro isoquinoline (**2**).

1-(3,4-Dimethoxyphenylmethyl)-3-phenyl-6,7,8-trimethoxy-3,4-dihydroisoquinoline, (**1)** was reduced with sodium borohydride in methanol. Thus, 1.2 mmol of compound **1** was dissolved in 10 ml of methanol while stirring and then 200 mg of $NaBH_4$ was added. After stirring for 10 minutes the solvent was evaporated and the residue treated with water and extracted with ethyl ether (2 x 20 ml). The combined extracts were dried with sodium sulafet and concentrated *in vacuo* to give **2** quantitatively as oil [6]. Compound **2** was purified by tlc, Silicagel GF254, chloroform:methanol:ammonia (20%): as proportion 95:5:I, nmr: 1.85 (1 H, s, NH); 2.50 (2 H, m, CH_2); 2.75 (1 H, dd, CH); 3.75 (3 H, s, OCH_3); 3.80 (3 H, s, OCH_3); 3.87 (3 H, s, OCH_3); 3.90 (6 H, m, OCH_3); 4.25 (2 H, m, CH_2); 4.60 (1 H, m, CH); 6,35 (1 H, s, Ar); 6,40 (1 H, s, Ar); 6,75 (2 H, s, Ar); 7.30 (5 H, m, Ar) ppm, cmr: δ 39.6 C-4, 42.6 C-9, 54.9 C-1, 55.5 C-O, 55.8 C-O, 57.1 C-3, 60.4 C-O, 60.4C-O, 111.1 C-5, and 107.4 , 113.4, 121.8, 123.6, 126.4, 127.0, 128.2, 132.0, 132.7, 144.5, 148.5, 151.0, 151.8 ppm, as described in the text.

Anal. Calcd. for: $C_{27}H_{31}NO_5$ (449): C, 72.14; H, 6.95; N, 3.12. Found: C, 72.16 %, H, 6.90 %, N, 3.10 %.

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REFERENCES AND NOTES

[1] A. Bischler and B. Napieralski, *Ber*, **26**,1903 (1893).

[2] W. Whaley, and T. Govindachari, *Organic Reaction*, Vol. **IV**, pp. 74, Roger Adams Eds. John Wiley & Sons, Inc. N. Y. (1951).

[3] J. Comin, M. Vernengo, and V. Deulofeu, *The alkaloids*, Vol. **X**, pp 401, (1968) Academic Press inc. N.Y.

[4] A. Brossi, and S. Teitel, *Helvetica Chim. Acta*., **49** (207), 1757, (1960).

[5] S. Kubota, T. Masui, E. Fujita, and M. Kupchan, *J. Org. Chem*., **31**, 516 (1966).

[6] J. M. Aguirre, E. N. Alesso, C. Somoza, D. G. Tombari, G. Y. Moltrasio and J. D. Bonafede, *Ann. Asoc. Quim. Arg*., **73**, 391 (1985).

[7] J. M. Aguirre, E. N. Alesso, C. Somoza, D. G. Tombari, A. F. Ibañez, G. Y. Moltrasio and J. D. Bonafede, *Ann. Asoc. Quim. Arg*., **75**, 393 (1987).

[8] E. N. Alesso, D. G. Tombari, A. F. Ibañez, G. Y. Moltrasio Iglesias, and J. M. Aguirre, *Chem. Pharm. Bull*, **36** (8), 2802 (1988).

[9] A. F. Ibañez, G. B. Yaculiano, G. Y. Moltrasio Iglesias, *J. Heterocyclic Chem.*, **26,** 907 (1989).

[10] J. M. Aguirre, E. N. Alesso, A. F. Ibañez, D. G. Tombari, and G. Y. Moltrasio Iglesias, *J. Heterocyclic Chem.*, **26,** 25 (1989).

[11] J. M. Aguirre, E. N. Alesso, A. F. Ibañez, and G. Y. Moltrasio Iglesias, *Trends in Heterocyclic Chem.*, **3**, 95 (1993).

[12] A. F. Ibañez, and G. Y. Moltrasio Iglesias, *Org. Mass Spectrometry*, **26**, 136 (1991).

[13] J. M. Delfino, A. F. Ibañez, and G. Y. Moltrasio Iglesias, *J. Heterocyclic Chem*.**, 33,** 265 (1996).

[14] G. J. Kapadia, and M. B. E. Fayez, *J. Pharm. Chem. Sci*. **59**, 1699 (1970).

[15] Acdlab® 133 Richmond St. West Suite 605 Toronto, ON. M5H 2L3 Canada.

[16] B. Reitchert and W. Hoffmann, *Arch. Pharm.* **247,** 217, 21 (1936).