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Synthesis of Isoquinolines from 2-Phenylethylamines, Amides, Nitriles and Carboxylic Acids in Polyphosphoric Acid

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Abstract: A convenient one pot synthesis of 1-, 1,3-substituted 3,4-dihydroisoquinolines **5**, enamines **10** and 3-oxo-2,3-dihydroisoquinolines **18** as well as of enamides **22** of isoquinoline from 2-phenyl-, 1,2-diphenylethylamines, phenylacetamides, phenylacetonitriles, N-acylphenylethylamines and carboxylic acids in nonaqueous media has been accomplished.

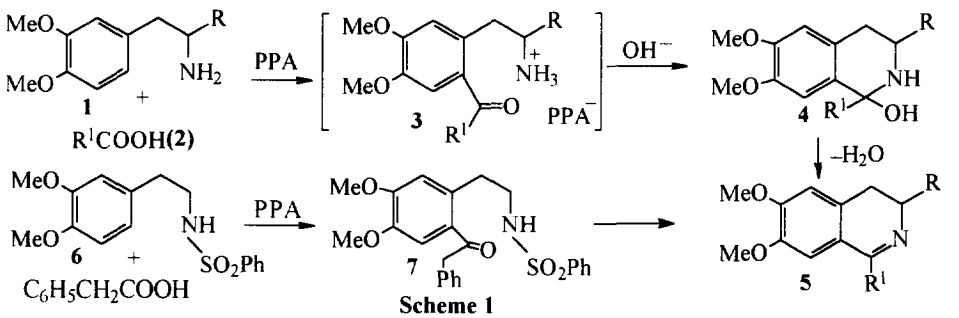
The biological activity attached to the isoquinoline nucleus has provided a great deal of interest in the synthesis of isoquinolines.[1a-c] The Bischler-Napieralski, Pictet-Spengler and Pomeranz-Fritsch reactions are methods of choice for the preparation of isoquinoline derivatives.[1b,c]

The Bischler-Napieralski reaction (B-N reaction) is one of the most effective methods for preparing 3,4-dihydroisoquinoline derivatives.[2] The reaction has been used in the synthesis of a variety of isoquinoline alkaloids and analogues of pharmacological interest.[1b,c,3] The mechanism of the B-N reaction has been shown by Fodor and Nagubandi to undergo dehydration before cyclization via the formation of nitrilium salt.[4] It is through this intermediate nitrilium salt that many side products of the B-N reaction have been reported. It is also known that B-N's cyclization of appropriate amides to 3-phenyl-3,4-dihydroisoquinolines have generally failed[5] and recently a modified procedure was reported.[6]

Accounts concerned with the reactions of carboxylic acids or their anhydrides and esters with 2-phenylethylamines, phenylacetamides, phenylacetonitrile, and N-acylphenylethylamines for synthesis of isoquinoline derivatives have remained suprisingly few in number. Carboxylic acids have been used only incidentally in Bischler-Napieralski reaction for synthesis of aromatic isoquinolines as papaverine.[7]

Now we wish to report on our investigations into the reaction of carboxylic acids with 2-(3,4-dimethoxyphenyl)ethylamine (homoveratrylamine), 1,2-diphenylethylamines, N-alkyl(alkylaryl)-2-phenylethylamines, phenylacetamides and/or phenylacetonitriles and N-acyl-2-phenylethylamines in nonaqueos acidic media as polyphosphoric acid (PPA).

We found that the reaction of equimolar amounts of homoveratrylamine with carboxylic acids **2** in PPA for 2 h at 80°C afforded very conveniently the corresponding 3,4-dihydroisoquinolines **5** in very good yields and purity (Scheme **1**, Table **1**, **5a-f**). The reactions to **5** can also be carried out with esters and anhydrides of carboxylic acids as well as with hydrochloric salt of homoveratrylamine. The reaction with anhydrides proceeded faster than with the corresponding carboxylic acids or their esters but depended on the order of mixing the reagents. For example, when acetic anhydride was mixed with homoveratrylamine and PPA was added after 5 min, the product of the reaction was N-(2-acetyl-4,5-dimethoxyphenylethyl) acetamide[8] that did not cyclize to **5a** after several hours at 80°C. However, when PPA was added to homoveratrylamine and then acetic anhydride, **5a** was obtained in a quantitative yield after 1 h at 80°C. We assumed that the reaction proceeded first with acylation of the activated aromatic ring of ammonium salt of **1** to **3** and then spontaneous cyclization between the carbonyl group and the amino group occurred to **5** at work up of the reaction mixture. Conformation of this assumption was the reaction of N-(3,4-dimethoxyphenylethyl)benzenesulphonamide **6** with phenylacetic acid in PPA. When the reaction was carried out for 30 min at 80°C, phenylacetyl-benzenesulfonamide **7** was obtained in 50% yield. Treatment of **7** with PPA for 3 h at 80°C or with conc.hydrochloric acid in dioxane for 3 h at room temperature afforded **5d** in 70% yield. The reaction of **6** with phenylacetic acid in PPA for 3 h at 80°C afforded directly **5d** in 70% yield.



Scheme 1

Table 1. 3,4-Dihydroisoquinolines **5a-j** Prepared

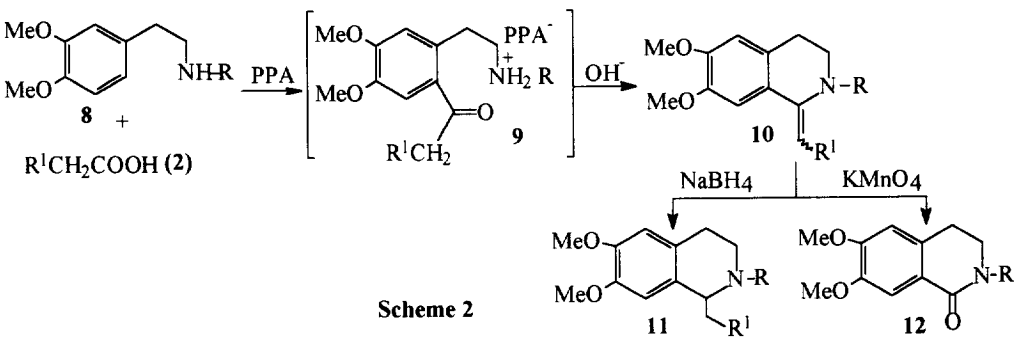
Entry	R	R^1	Yield (%)	mp °C	Mol. Formula or Lit. mp (°C)
5a	H	Me	96	104-105	104-105[8]
5b	H	C_6H_5	95	121-122	121-122[9]
5c	H	3,4-$(MeO)_2C_6H_3$	70	167-168	171[9]
5d	H	$C_6H_5CH_2$	80	82-84	84-85[10]
5e	H	4-NO_2-$C_6H_4CH_2$	80	120-121	122[11]
5f	H	3,4-$(MeO)_2C_6H_3CH_2$	20	103-104	105[12]
5g	3,4-$(MeO)_2C_6H_3$	Me	75	114-115	115-116[13]; 158-160[5a]
5h	4-MeO-C_6H_4	Me	80	102-103	$C_{19}H_{21}NO_3$ (311.4)
5i	3,4-$(MeO)_2C_6H_3$	C_6H_5	50	163-164	130-2[5a]; 124-126[5b]
5j	3,4-$(MeO)_2C_6H_3$	$C_6H_5CH_2$	60	57-59	170-180[5a]

The experiment showed that when the nucleophilicity of nitrogen in the amine **1** was decreased by an electron withdrawing group which is also a good leaving group, the o-acylated product **3** can be isolated as an intermediate of the reaction.

The procedure worked very well for synthesis of 3-phenyl-3,4-dihydroisoquinolines (Table **1**, **5g-j**). The acylation of aromatic ring of 1,2-diphenylethylamines was regioselective even for 1,2-bis-(3,4-dimethoxy-phenyl)ethylamine **1g** since the cyclization only to 3-phenyl-3,4-dihydroisoquinolines (Table **1**, **5g, i, j**) was observed as an additional proof for the accepted mechanism. The regioselectivety of acylation is probably due to electronic and stereochemical reasons.

The method worked for 2-phenylethylamines **1** with electron donating groups in the aromatic ring. The reaction of 2-phenylethylamine with carboxylic acids in PPA even at 120-130°C led to unchanged starting compounds after work up of the reaction mixture.

The preferred acylation of the aromatic ring of homoveratrylamine in PPA was found to be rather general and the reaction of N-methyl(benzyl)-2-phenylethylamines with carboxylic acids in PPA afforded the corresponding enamines of isoquinoline **10** after 4 h at 60° (Scheme **2**, Table **2**, **10a-d**). ^{1}H-NMR spectra clearly indicated that **10** were obtained as mixture of E and Z isomers (Table **5**, **10a-d**). Their reduction with $NaBH_4$ in MeOH afforded the corresponding tetrahydroisoquinolines (Table **2**, **11**), while the oxidation with $KMnO_4$ in $CHCl_3$ in the presence of 18-Crown-6 led to 2-alkyl-3,4-dihydro-1(2H)-isoquinolinones(Table **2**, **12**).



Scheme 2

Table 2. Enamines **10a-d** Prepared.

Entry	R	R^1	Yield (%)	mp (°C)	Mol.Formula[a] or Lit. mp(°C)
10a	Me	C_6H_5	74	94-95	$C_{19}H_{21}NO_2$ (295.4)
10b	$C_6H_5CH_2$	C_6H_5	66	104-105	$C_{25}H_{25}NO_2$ (371.5)
10c	4-NO_2-$C_6H_4CH_2$	C_6H_5	83	139-140	$C_{25}H_{24}N_2O_4$ (416.5)
10d	4-Cl- $C_6H_4CH_2$	C_6H_5	63	97-98	$C_{25}H_{24}ClNO_2$ (405.9)
11a	$C_6H_5CH_2$	C_6H_5	90	76-77	$C_{25}H_{27}NO_2$ (373.5)
11b	Me	H	60	212[b]	210-211[14]
12a	$C_6H_5CH_2$	-	90	101-102	102-103[9]
12b	Me	-	60	129-130	130[9]

[a] Satisfactory microanalysis obtained: C ±030, H ±0.22, N ±0.20; [b]as HCl salt

Enamine **10** (Scheme **2**, R=Me, R^1=H), obtained from N-methylhomoveratrylamine.HCl salt and AcOH in PPA for 3 h at 60°C was unstable and very difficult to purify. However, its reduction furnished the alkaloid (±)-carnegine (Table **2**, **11b**) and the oxidation afforded the alkaloid N-methylcorydaldine (Table **2**, **12b**). Oxidation of **10a** (Table **2**) also led to the same alkaloid in 82% yield.

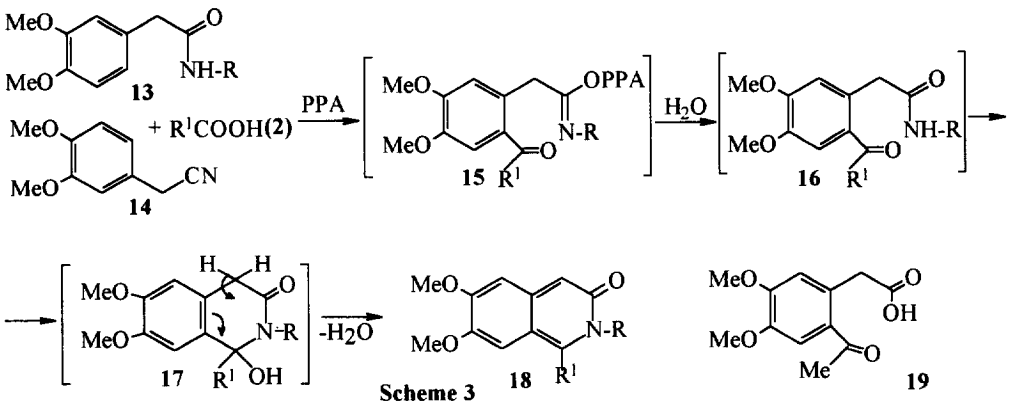
Phenylacetamides are known as unreactive with aldehydes in the intramolecular amidoalkylation reaction to 1,4-dihydro-3(2H)-isoquinolinones. The preferred intermolecular α-amidoalkylation of aromatics in the "phenylacetamide" series and the sluggishness of the cyclization reaction is attributed by D.Ben-Ishai to the deactivation of the phenyl ring in the intermediate N-acyliminium ion formed in the strong acid medium, to the preferred s-trans conformation of the amide bond in the reactive intermediate, and to the stereoelectronic effects.[15]

In order to obtain further information concerning the role of the various effects on the inter vs. Intramolecular α-amidoalkylation, the reaction of carboxylic acids with phenylacetamides in PPA was examined in expectation to obtain the corresponding o-acyl-phenylacetamides **16**. It was found, however, that the reaction of 3,4-dimethoxyphenylacetamide with phenylacetic acid in PPA for 6 h at 100°C afforded directly 3-oxo-2,3-dihydroisoquinoline in 66% yield (Scheme **3**, Table **3**, **18c**). The reaction of secondary amides as N-methyl-3,4-dimethoxyphenylacetamide (Scheme **3**, **13**, R=Me) with acetic acid in PPA also led to 1,2-dimethyl-6,7-dimethoxy 3-oxo-2,3-dihydroisoquinoline (Table **3**, **18f**). The reaction proceeded by the same mechanism as with phenylethylamines, since the reaction of N-(4-nitrophenyl)-6,7-dimethoxyphenylacetamide (Scheme **3**, **13**, R= 4-NO_2-C_6H_4) with acetic acid in PPA for 30 min at 60°C afforded N-(4-nitrophenyl)-2-acetyl-4,5-dimethoxyphenylacetamide (Scheme **3**, **16**, R= 4-NO_2-C_6H_4) in 89% yield. Its reflux in 1,2-dichloroethane in the presence of p-toluenesulphonic acid monohydrate (PTS) for 4 h afforded the corresponding isoquinolinone in 70% yield (Table **3**, **18g**).

It was found that 3-oxo-2,3-dihydroisoquinolines **18a-e**(Table **3**) can also be obtained from (3,4-dimethoxyphenyl)acetonitrile **14** (homoveratronitrile) and the corresponding carboxylic acids in PPA. For example, **18a** was obtained from **14** and phenylacetic acid in PPA under the same reaction conditions as from 3,4-dimethoxyphenylacetamide in 70% yield. The cyclization of **13** or **14** proceeded to 3-oxo-2,3-dihydro-isoquinoline **18** with quinonoid structure which is favoured to aromatic one as it has been shown by calculations of resonance energy of 3(2H) isoquinolinones.[16]

However, the reaction homoveratronitrile **14** with Ac_2O in PPA for 6 h at 80 °C (or 4 h at 100 °C) led only to acylated imide **16a** (Table **3**) The product did not cyclize to **18a** after 3 h at 130°C in PPA, but its hydrolysis with NH_4OH or with H_2SO_4-dioxane (1:1) for 3 h at room temperature afforded **18a** in yields of 96% and 75%, respectively. The hydrolysis with H_2SO_4-dioxane (1:1) for 15 min at 100°C led to 2-acetyl-4,5-dimethoxyphenylacetic acid **19**[17] and with aq. Na_2CO_3 produced a mixture of **18a** and **19.** It can be assumed that the hydrolysis of **16a** in milder conditions as at room temperature in acidic or alkali medium led to **16** (R=H, R^1=Me), which after that spontaneously cyclized to **18a**.

The reaction of phenylacetonitriles or phenylacetamides with electron donating groups in the aromatic ring with carboxylic acids in PPA provides an alternative route to 3-oxo-2,3-dihydroisoquinoline **18.**[17,18] The reaction from phenylacetonitriles or primary phenylacetamides afforded N-unsubstituted **18** (Table **3**, **18a-e**), while the reaction of secondary phenylacetamides provided N-substituted 3-oxo-2,3-dihydroisoquinolines (Table **3**, **18f,g**).



Scheme 3

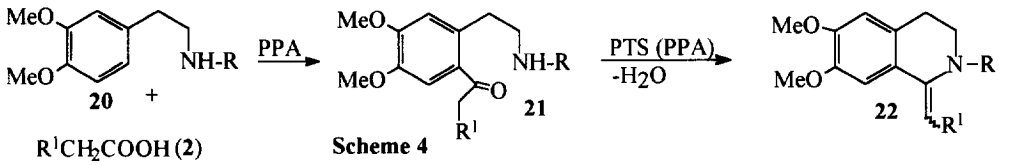
Table 3. 3-Oxo-2,3-dihydroisoquinolines **18a-g** Prepared.

Entry	R	R^1	Yield (%)	mp °C	Mol. Formula or Lit. mp (°C)
16a	COMe	Me	85	163-165	$C_{14}H_{17}NO_5$ (279.3)
16g	4-O_2N-C_6H_4	Me	89	172-173	$C_{18}H_{18}N_2O_6$ (358.4)
18a	H	Me	70	213-214	212-213[17]
18b	H	C_6H_5	55	204-206	204-206[17]
18c	H	$C_6H_5CH_2$	66	213-214	212-214[17]
18d	H	4-Cl-$C_6H_4CH_2$	72	240-243	$C_{18}H_{16}ClNO_3$ (329.8)
18e	H	4-O_2N-$C_6H_4CH_2$	44	245-248	249-250[17]
18f	Me	Me	64	181-182	182-183[17]
18g	4-O_2N-C_6H_4	Me	70	235-236	$C_{18}H_{16}N_2O_5$ (340.3)

It is known from the literature[19] that 1-methylene-2-acetyltetrahydroisoquinoline hydrolyzed in boiling hydrochloric acid to N-(2-acetyl-phenyl)ethyl acetamide. These compounds were recently obtained by Friedel-Crafts acetylation of N-acetylphenylethylamines and after treatment in boiling hydrochloric acid were converted to 1-substituted 3,4-dihydroisoquinolines.[8]

Bearing in mind these results, we carried out acylation of N-acylphenylethylamines **20** with carboxylic acids, their anhydrides or esters in PPA, and obtained the expected N-(2-acylphenylethyl)amides **21** (Scheme **4**, Table **4**, **21a-f**). Their cyclization in less acidic medium as in the presence of catalytic amount of p-toluene-sulfonic acid monohydrate (PTS) afforded the corresponding enamides of isoquinoline **22** (Table **4**, **22a-f**), since the N-acyl group is not a good leaving group.

The reaction of N-acylphenylethylamines **20** with aromatic carboxylic acids in PPA can be carried out directly to **22**, but the yields were a little low because of the unstability of enamides in more acidic medium. For example, **22b** was obtained from **21** (R=COOEt) and phenylacetic acid after 4 h at 100°C in 40% yield.



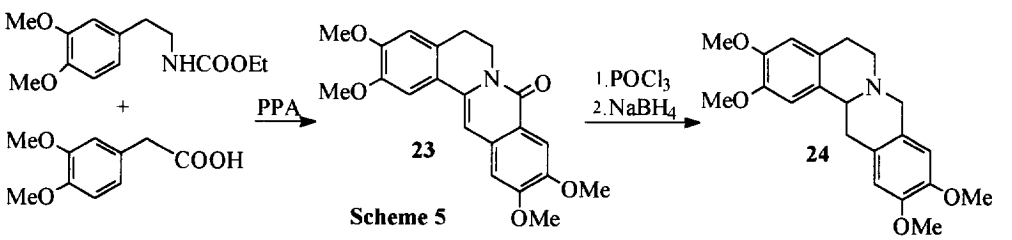
Scheme 4

Table 4. N-(2-Acyl-4,5-dimethoxyphenylethyl)amides **21a-g** and Enamides **22a-f** Prepared.

Entry	R	R^1	Reaction conditions	Yield (%)	mp (°C)	Mol. Formula[a] or Lit. mp (°C)
21a	COOEt	H	3h, 80°C	95	90-91.5	$C_{15}H_{21}NO_5$ (295.3)
21b	COOEt	C_6H_5	4h, 80°C	65	78-80	$C_{21}H_{25}NO_5$ (371.4)
21c	MeCO	C_6H_5	20h, 60°C	62	120-122	120-121[8]
21d	C_6H_5CO	C_6H_5	20h, 60°C	82	141-142	$C_{25}H_{25}NO_4$ (403.5)
21e	4-O_2N-C_6H_4CO	C_6H_5	2h, 60°C	86	146-147	$C_{25}H_{24}N_2O_6$ (448.5)
21f	$MeSO_2$	C_6H_5	4h, 80°C	58	157-158	$C_{19}H_{23}NO_5S$ (377.5)
22a	COOEt	H	6h, 140°C	95	86-88	89-91[20c]
22b	COOEt	C_6H_5	5h, 80°C	75	120-122	122-124[20d]
22c	MeCO	C_6H_5	3h, 80°C	81	163-164	$C_{20}H_{21}NO_3$ (323.4)
22d	C_6H_5CO	C_6H_5	2h, 80°C	72	202-203	$C_{25}H_{23}NO_3$ (385.5)
22e	4-O_2N-C_6H_4CO	C_6H_5	2h, 80°C	71	212-213	$C_{25}H_{22}N_2O_5$ (430.5)
22f	$MeSO_2$	C_6H_5	1h, 80°C	54	188-189	$C_{19}H_{21}NO_4S$ (359.4)

[a] Satisfactory microanalysis obtained: C ±025, H ±0.16, N ±0.18

These results provided a convenient procedure for synthesis of isoquinoline enamides as important intermediates in the alkaloid synthesis.[20a-d] The method was applied for the synthesis of alkaloid xylopinine **24** in a two step procedure (Scheme **5**). The reaction of N-ethoxycarbonyl 2-(3,4-dimethoxyphenyl)ethylamine with homoveratric acid in PPA for 5 h at 80°C led directly to 2,3,10,11-tetramethoxy-8-oxo-protoberberine **23** in 50% yield which after treatment with $POCl_3$ and following reduction with $NaBH_4$ in methanol afforded 2,3,10,11-tetramethoxyberberine **24**.



Scheme 5

In conclusion, the reaction of 2-phenylethylamines, their amides, phenylacetamides or homoveratronitrile with carboxylic acids in PPA proceeds via acylation of the activated aromatic ring to the corresponding acylated intermediates. Their trend to the formation of N-heterocycle allows the synthesis of a variety of isoquinoline derivatives depending on the starting compounds. The approach provides an alternative route to the isoquinoline ring formation and is a useful addition to the methodology for synthesizing of 3,4-dihydro-isoquinolines and especially of those with 1,3-substitutents, enamines and enamides of isoquinoline as well as of

Table 5. ^{1}H-NMR ($CDCl_3$/TMS), δ (ppm), J (Hz)[a]

5h	2.37(d,3H,J=2),2.59-2.82(d,2H,J=8),3.66(s,3H),3.78(s,6H),4.18-4.43(m,1H),6.45(s,1H),6.60(s,1H), 6.75(d,2H,J=8),7.10(d,2H,J=8)
5i	2.67-2.93(m,2H),3.68(s,3H),3.80(s,6H),3.86(s,3H),4.38-4.78(m,1H),6.70(s,1H),6.80(s,1H),6.85(s,1H), 6.90(s,1H),6.98(s,1H),7.27-7.38(m,3H),7.45-7.62(m,2H)
5j	2.73-2.95(m,2H),3.70(s,3H),3.85(s,9H),4.07(s,2H),4.44-4.78(m,1H),6.57(s,1H),6.85-7.00(m,4H), 7.12-7.35(m,5H)
10a	2.74(s,6H),2.78(t,2H,J=6),2.95-3.05(m,2H),3.18(t,2H,J=6),3.20-3.30(m,2H),3.86(s,3H),3.89(s,3H), 3.91(s,3H)3.92(s,3H),5.48(s,1H),5.94(s,1H),6.58(s,1H),6.62(s,1H),6.92(s,1H),7.06(t,1H,J=8),7.16 (d,2H,J=4),7.21(s,2H)7.25(s,2H),7.29(d,2H,J=8),7.51(d,2H,J=8)
10b	2.58(t,2H,J=6),2.84(t,2H,J=6),3.15(t,2H,J=6),3.26(s,3H),3.35(t,2H,J=6),3.87(s,6H),3.94(s,3H),4.17 (s,2H),4.62(s,2H),5.46(s,1H),6.10(s,1H),6.56(s,1H),6.61(s,1H),6.93(s,2H),7.01-7.13(m,4H),7.21-7.35 (m,14H), 7.57(d,2H,J=8)
10c	2.52(t,2H,J=6),2.76(t,2H,J=6),3.05(t,2H,J=6),3.12(s,3H),3.26(t,2H,J=6),3.70(s,6H),3.78(s,3H),4.08 (s,2H),4.50(s,2H),5.07(s,1H),5.87(s,1H),6.32(s,1H),6.37(s,1H),6.60(s,1H),6.72-6.77(m,6H),6.88-6.97 (m,3H),7.07(s,2H)7.17(d,4H,J=6),7.76(d,2H,J=8),7.87(d,2H,J=8)
10d	2.6(t,2H,J=6),2.78(t,2H,J=6),3.06(t,2H,J=6),3.15(s,3H),3.35(t,2H,J=6),3.73(s,6H),3.8(s,3H),4.0(s,2H), 4.56(s,2H),5.37(s,1H),5.94(s,1H),6.38(s,2H),6.71(s,1H),6.82-7.21(m,17H),7.35(d,2H,J=8)
11a	2.46-2.52(m,1H),2.78-2.92(m,3H),3.13-3.33(m,2H),3.55(s,3H),3.76(s,2H),3.78(t,1H,J=3),3.82(s,3H), 6.03(s,1H),6.58(s,1H),7.03-7.08(m,2H),7.17-7.23(m,8H)
16a	2.16(s,3H),2.52(s,3H),3.81(s,3H),3.85(s,3H),4.00(s,2H),6.92(s,1H),7.46(s,1H)
16g	2.65(s,3H),3.71(s,2H),3.84(s,3H),3.88(s,3H),6.06(s,1H,br.),6.84(s,1H),7.09(s,1H),7.49(d,2H,J=9),7.99 (d,2H,J=9)
18d	3.75(s,3H),3.80(s,3H),4.35(s,2H),6.55(s,1H),6.95(s,1H),7.05(s,1H),7.23(s,4H)
18g	2.31(s,3H),3.85(s,3H),3.91(s,3H),6.41(s,1H),6.52(d,2H,J=4),7.26(d,2H,J=8),8.29(d,2H,J=8)
21a	1.21(t,3H,J=7),2.56(s,3H),2.87-3.15(m,2H),3.39(t,2H,J=6),3.93(s,6H),4.08(q,2H,J=8),5.35(s,1H,br.), 6.75(s,1H)7.21(s,1H)
21b	1.82(t,3H,J=8),2.90(d,2H,J=6),3.28(t,2H,J=6),4.02(s,6H),4.02(q,2H,J=6),4.14(s,2H),5.15(t,1H,J=5) 6.55(s,1H),6.65(s,1H),7.18(s,5H)
21d	2.95(t,2H,J=6),3.5-3.7(m,2H),3.76(s,3H),3.79(s,3H),4.14(s,2H),6.61(s,1H),6.95(s,1H,br.),7.06(s,1H), 7.07(s,2H),7.10(s,4H),7.21(d,2H,J=6),7.58(d,2H,J=6)
21e	2.93(t,2H,J=6),3.63-3.83(m,2H),3.85(s,3H),3.89(s,3H),4.20(s,2H),6.76(s,1H),6.8(s,1H,br.),7.14(s,1H) 7.20(s,5H),7.78(d,2H,J=8),8.13(d,2H,J=8)
21f	2.70(s,3H),2.90(t,2H,J=8),3.24(t,2H,J=8),3.78(s,3H),3.83(s,3H),4.10(s,2H),4.91(t,1H,J=5),6.58(s,1H) 6.90(s,1H),7.08(s,3H),7.10(s,2H)
22c	1.70(s,3H),2.77(d,1H,J=12),3.13(d,ABq,J=12,1H),3.16(d,ABq,J=14,1H),3.80(s,3H),3.89(s,3H),4.92 (d,1H,J=8)6.48(s,1H),6.65(s,1H),7.00(s,1H),7.10-7.28(m,5H)
22d	2.93(d,1H,J=10), 3.28(d,ABq,J=12,1H), 3.37(d,ABq,J=12,1H),3.9(s,3H),3.94(s,3H),5.03-5.25(m,1H) 6.34(s,1H),6.64(s,1H),6.79-7.20(m,11H)
22e	3.01(d,1H,J=10),3.20(d,ABq,J=14,1H),3.30(d,ABq,J=15,1H),3.89(s,3H),3.93(s,3H),5.05-5.25(m,1H) 6.40(s,1H),6.69(s,1H),6.83(s,1H),6.88(s,3H),6.98(s,1H),7.16(s,1H),7.18(d,2H,J=8)7.73(d,2H,J=8)
22f	2.44(s,3H),2.96(t,2H,J=6),3.77(s,3H),3.85(s,3H),3.95(t,2H,J=6),6.44(s,1H),6.77(s,1H),6.97(s,1H), 7.09-7.19(m,3H),7.46(d,2H,J=8)

[a] Some of signals are doubled because of stereoisomers.

3-oxo-2,3-dihydroisoquinoline utilising readily available starting materials and convenient experimental procedures.

The prepared compounds were characterized by their m.p., IR, ^{1}H-NMR (Table **5**) and MS data or by comparison with products obtained by an independent synthesis.

Experimental

Polyphosphoric acid was obtained from 85% phosphoric acid and P_2O_5 (1:1 w/w).

3,4-Dihydroisoquinolines 5 (Table 1, 5a-j); Typical procedure: Homoveratrylamine (3 mmol) and the corresponding carboxylic acid (3.5 mmol) were dissolved in CH_2Cl_2 (3-5 mL) in an open flask and polyphosphoric acid (10g) was added. The mixture was stirred carefully at 80°C for 2-3 h, then poured on crushed ice. The solution was carefully alkalized with Na_2CO_3, then extracted with CH_2Cl_2 (3x20 mL) and combined extracts were dried (Na_2SO_4). The products, after evaporation of the solvent, were purified by recrystalization or fitration on short column with basic Al_2O_3 using CH_2Cl_2 as eluent.

The product **5f** was obtained after 3 days at room temperature in PPA.The yield of **5f** is low because of the preferable intermolecular acylation of 3,4-dimethoxyphenylacetic acid to 2-(3,4-dimethoxyphenylacetyl)-4,5-dimethoxyphenylacetic acid.[17]

N-(2-acyl-4,5-dimethoxyphenylethyl) benzenesulphonamide **7** was obtained from N-(3,4-dimethoxyphenyl-ethyl)benzenesulphonamide **6** (2 mmol) and phenylacetic acid (2 mmol) in PPA for 30 min at 80°C in 50% yield; mp 148-148.5°C. ^{1}H-NMR ($CDCl_3$/TMS), δ (ppm), J (Hz): 2.75(t,2H,J=6), 3.09(t,2H,J=6), 3.70(s,3H), 3.75(s,3H), 4.05(s,2H), 5.56(t,1H,J=5),6.36(s,1H), 6.97 (s,1H), 7.02-7.51(m,10H); MS, m/e (M^+):440 (Calc. for $C_{24}H_{25}NO_5S$, 439.5)

Enamines of tetrahydroisoquinoline 10 (Table 2, 10a-d); Typical procedure: A mixture of N-alkyl-homoveratrylamines **8** (3 mmol), the corresponding carboxylic acid (3.5 mmol) and polyphosphoric acid (10g) was stirred for 4 h at 60°C and worked up as above. The products were purified by recrystalisation or fitration on short column with basic Al_2O_3 using Et_2O or CH_2Cl_2 as eluents.

Synthesis of (±)-carnegine (Table 2, 11b) and N-methylcorydaldine (Table 2, 12b): A mixture of N-methylhomoveratrylamine.HCl (3 mmol), AcOH (1 mL) in PPA (10 g) was stirred for 3 h at 60^{0}C. The cooled mixture was poured portionwise to a cooled aq. Na_2CO_3 (100 mL) and the alkilized solution was extracted with CH_2Cl_2 (3x10mL), then the combined extracts were dried (Na_2SO_4) and filtered. The solution of the obtained enamine **10** (Scheme **2**, R=Me, R^1=H) was used further for preparation of (±)-carnegine or N-methylcorydaldine.

For synthesis of (±)-carnegine, to the solution of enamine **10** (R=R=Me, R^1=H) was added MeOH (10 mL) and then $NaBH_4$ (0.2 g) portionwise. The solution was stirred for 30 min at room temperature, then the solvent was removed under vacuum. Water (30 mL) was added to the residue and the solution was extracted with CH_2Cl_2 (3x20 mL), then the combined extracts were dried (Na_2SO_4) and the solvent distilled. The product was dissolved in MeOH (5 mL) and the solution was saturated with gaseous HCl. The obtained crystals of (±)-carnegine were separated; yield 0.630 g (60%); mp 212°C.

For synthesis of N-methylcorydaldine, to the stirred solution of enamine **10** (R=R=Me, R^1=H) at room temperature was added 18-Crown-6 (30 mg) and then $KMnO_4$ (3 mmol) portionwise. The colour of the

reaction mixture turned from violet to brown from the formed MnO_2. Saturated aqueous sodium metabisulfite solution (50mL) was then carefully added after 30 min. The resulting mixture was treated with aq.10% HCl (20 mL) and the solution was extracted with $CHCl_3$ (3x20mL). The combined extracts were dried (Na_2SO_4), the solvent evaporated under vacuum and the product purified by recrystallization from Et_2O; yield 60%.

3-Oxo-2,3-dihydroisoquinolines 18 (Table 3, 18a-g); Typical procedure: A mixture of 3,4-dimethoxyphenylacetamide **13** (3 mmol) or homoveratronitrile **14** (3 mmol), the corresponding carboxylic acid (3.5 mmol) and polyphosphoric acid (10g) was stirred for 6 h at 100°C, then cooled and poured on crushed ice (30 g). The solution was basified with about 50 mL 26% aq. NH_4OH and evaporated to the half of volume, then cooled and the product was allowed to crystallize. After the separation of crystals, the solution was extracted with CH_2Cl_2 (3x30 mL), the organic solvent was evaporated and some new amount of the product was obtained. All products **18** were purified by recrystallization from MeOH.

Synthesis of enamides of tetrahydroisoquinoline 22:

Typical procedure for preparation of N-(2-acyl-4,5-dimethoxyphenylethyl)amides 21 (Table 4, 21 a-f): A mixture of N-(3,4-dimethoxyphenylethyl)amide **20** (3 mmol), the corresponding carboxylic acid (3.5 mmol) and polyphosphoric acid (10g) was stirred at temperature and the time given (Table **4, 21a-g**), then poured on crashed ice. The solution was carefully alkalized with Na_2CO_3, then extracted with CH_2Cl_2 (3x20 mL) and combined extracts were dried (Na_2SO_4). The products, after evaporation of the solvent, were purified by recrystalisation or fitration on short column with neutral Al_2O_3 using CH_2Cl_2 as eluent.

Synthesis of Enamides 22 (Table **4, 22a-f**); **Typical procedure**: Solution of N-(2-acyl-4,5-dimethoxyphenylethyl)amides **21** (3 mmol) and catalytic amount of PTS (20 mg) in 20 mL 1,2-dichloroethane (xylenes for **22a**) was reflux for the time given (Table **4, 22a-f**). The solution was washed with water (30 mL), aq. Na_2CO_3 (30 mL) and dried (Na_2SO_4). The products, after evaporation of the solvent, were purified by column chromatography on neutral Al_2O_3 using Et_2O as eluent.

Synthesis of 2,3,10,11-tetramethoxy-8-oxo-protoberberine 23: N-ethoxycarbonyl-3,4-dimethoxy-phenylethylamine (urethane) (1.12g, 4mmol) and homoveratric acid (0.784g, 4 mmol) were dissolved in CH_2Cl_2 (3 mL) and polyphosphoric acid (10 g) was added. The mixture was stirred for 30 min at 60°C, then at 100°C for 5 h. The cooled mixture was poured on crushed ice and extracted with CH_2Cl_2 (3x30 mL). The extract was washed sequentially with 20% aq. NaOH (20 mL), water (30 mL), 10% aq. HCL (20 mL), water (30 mL) and dried (Na_2SO_4). The product after evaporation of the solvent was purified by recrysatallization from Et_2O; yield 1.83g (50%); mp 198.5-200°C (lit.[20d,21] mp 198-199°C). ^{1}H-NMR ($CDCl_3$/TMS), δ (ppm), J (Hz): 2.91(t,2H, J=6), 3.92(s,3H), 3.95(s,6H), 4.23-4.42(m,2H), 6.75(s,1H), 6.81(s,1H), 7.15(s,1H), 7.68(s,1H); MS, m/e (M^+):367(Calc. for $C_{21}H_{21}NO_5$, 367.4)

2,3,10,11-Tetramethoxyberberine 24 (Xylopinine): 2,3,10,11-tetramethoxy-8-oxo-protoberberine **23** (0.367g, 1 mmol) was dissolved in dry 1,2-dichloroethane (15 mL) and $POCl_3$ (5 mL) was added to the cooled and stirred solution. The solution was stirred for 30 min at 80°C, then evaporated under vacuum to dry residue and dissolved in dry MeOH (30 mL). $NaBH_4$ (0.5g) was added portionwise to the cooled and stirred solution. After stirring for 30 min at room temperature, the solvent was removed under vacuum and water (30 mL) was added to the residue. The solution was extracted with CH_2Cl_2 (3x20 mL),the combined extract was dried (Na_2SO_4) and the solvent distilled. The product crystallized from Et_2O, yield: 0.285g (80%); mp 147-148.5°C (lit. mp 142-3°C[22a] and 157-158°C[22b]); ^{1}H-NMR ($CDCl_3$/TMS), δ (ppm), J (Hz): 2.55-3.68(m,9H), 3.85(s,9H), 3.88(s,3H), 6.57(s,1H), 6.59(s,1H), 6.64(s,1H), 6.71(s,1H); MS, m/e (M^+): 355 (Calc. for $C_{21}H_{25}NO_4$, 355.4).

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