Journal of International Scientific Publications:
Materials, Methods & Technologies, Volume 7, Part 1
ISSN 1313-2539, Published at: http://www.scientific-publications.net

SYNTHESIS OF 1-BIPHENYL-4-ARYL-1,2,3,4-TETRAHYDROISOQUINOLINE DERIVATIVES AS STRUCTURAL ANALOGUES OF THE ALKALOID CHERYLLINE

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Abstract

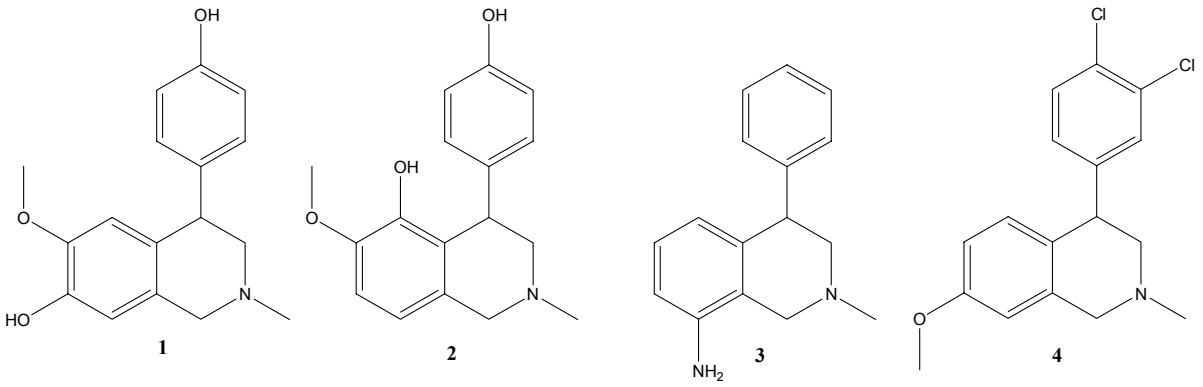
The biological activity of isoquinoline derivatives, as analogues of various drugs, has provided great deal of interest for the synthesis of new compounds.An application of Bischler-Napieralski reaction for the synthesis of new 1,2,3,4-tetrahydroisoquinolines with biphenyl substituent on the 1st position and aryl substituent on 4th position, is described.

Key words: *cherylline, 4-aryl-tetrahydroisoquinoline, 1-biphenyl-tetrahydroisoquinolines, Bischler-Napieralski reaction*

1. INTRODUCTION

The Amaryllidaceae alkaloids represent a large (over 300 alkaloids have been isolated) and still expanding group of biogenetically related isoquinoline alkaloids that are found exclusively in plants belonging to this family. [1]

Cherylline **1** is a naturally occurring optically active, 4-aryl-1,2,3,4- tetrahydroisoquinoline alkaloid, isolated from *Crinum Powelli*, *Amaryllidaceae* plant[2]. In the nature *Cherylline* occurs in (-) or (*S*) enantiomer.[3] Other 4-aryl-tetrahydroisoquinolines are *latifine* **2**, *nomifensine* **3** and *dichlorofensine* **4**. These alkaloids are of interest because of their various pharmacological activities.[4] For example, *nomifensine* **3** and *dichlofensine* **4** [5] exhibit central nervous system activity and inhibit serotonin and dopamine uptake mechanisms.



4-aryl-1,2,3,4-tetrahydroisoquinolines have attracted much attention from the synthetic community owing to the potential biological activities of this class of compounds and their increasing medicinal interest. Some of them are valuable medicines with centrally stimulating, thymoleptic, and

antiarrhythmic actions. Others exhibit broad spectrum calcium antagonistic, antibacterial, antiplasmodial, estrogen agonist/antagonist activity, and serotin (5-HT) re-uptake.

We report herein an alternative efficient synthesis of cherylline derivatives. The key steps involved are cyclization of amides **2** via Bischler-Napieralski reaction using phosphoryl chloride, dehydrogenation of the 1-substituted-4-aryl-3,4-dihydroisoquinolines using $NaBH_4$, and then acylation with different acyl chlorides of required 1,2,3,4-tetrahydroisoquinolines to obtain different 1-substituted cherylline derivatives.

2. RESULTS AND DISCUTION

The syntheses of cherylline skeleton can be sorted by the nature of the bond formed in the heterocyclic ring closure (Fig. 1)

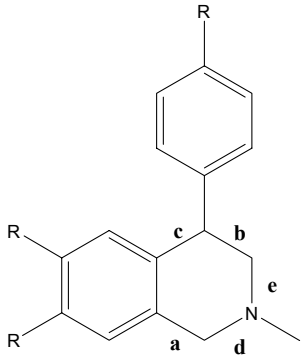
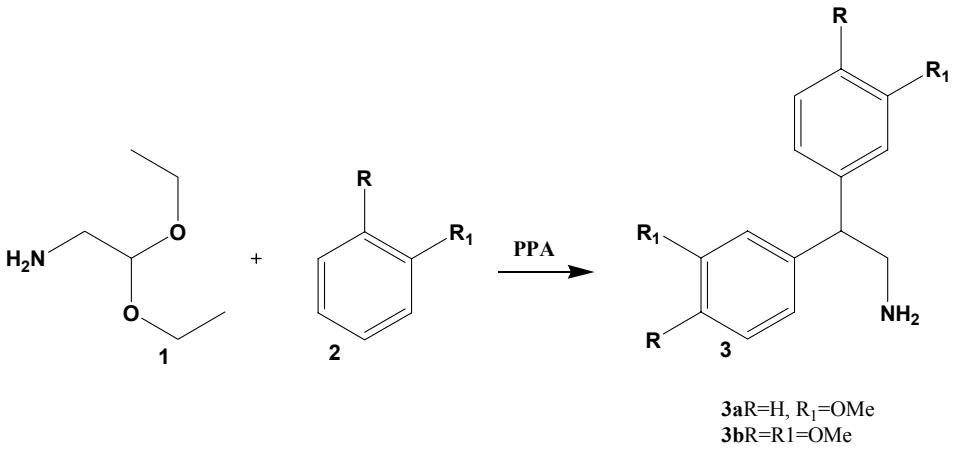


Figure 1

The C-C bond '**a**' was caused by a Bischler-Napieralski reaction of *N*-formyl derivatives of phenethylamines [6-8] or by cyclization of β-phenethylisocyanate [9, 10]. The C-C bond '**b**' was mainly formed by intramolecular Horner reaction [11]. The C-C bond '**c**' was achieved by several methods, such as photoinduced cyclization of ortho-halogenated *N*-acylbenzylamines [12], Friedel-Crafts type reactions [13-19], intramolecular coupling of quinonoid intermediates [20-23] or palladium-catalyzed intramolecular cyclization of amide-enolates [24]. Finally and less usually, the C-N bonds '**d**' or '**e**' were constructed mostly by *N*-alkylation [3, 25] .

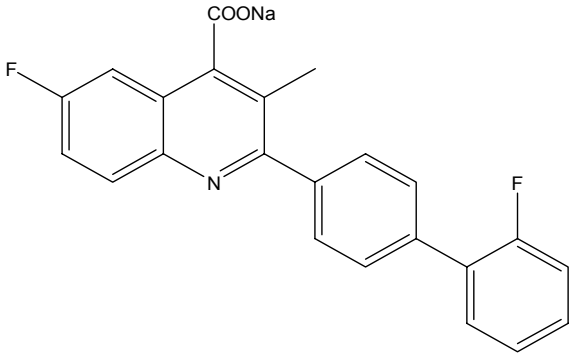
In 1969 Brossi, Grethe and Teitel first reported for isolation of the alkaloid Cherylline from Crinum Powelli. [26] They reported also the facile synthesis of *(+/-) O,O* – dimethyl-*N*-dimethyl cherylline. We successfully applied Klumpp's [27] protocol for the synthesis of required starting materials, between amino acetals and benzene veratrole in the presence of polyphosphoric acid instead of triflic acid. We have found that aminoacetaldehyd-dimethylacetal react with excess of 1,2-dimetoxybenzene (veratrol) in PPA at rt to give good (91%) yield of corresponding product **3** (Scheme 2). We obtained the amine 3 with 89-91% yields. [28]

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Scheme 1

The required amides **5** would arise from amines **3** and biphenyl-4-carbonyl chloride **4**. Biphenyl substituent was chosen because of its biological activity. Previous reports showed that nitrogen-containing six-membered heterocycles touched to a biphenyl substituent are inhibitors of dihydroorotate dehydrogenase (DHODH). DHODH is enzyme, identified in the *Plasmodium falciparum*. He is located in the mitochondrial membrane where it catalyses the oxidation of dihydroorotate to orotate, which is the rate-limiting step in pyrimidine biosynthesis.[29] Concomitant with dihydroorotate oxidation is electron transfer to ubiquinone (cofactor Q). Genes encoding all enzymes in the conserved pyrimidine pathway have been identified in the *Plasmodium falciparum* genome but genes encoding enzymes in pyrimidine salvage do not appear to be present. Human cells, in contrast to Plasmodium, synthesise and salvage pyrimidines.



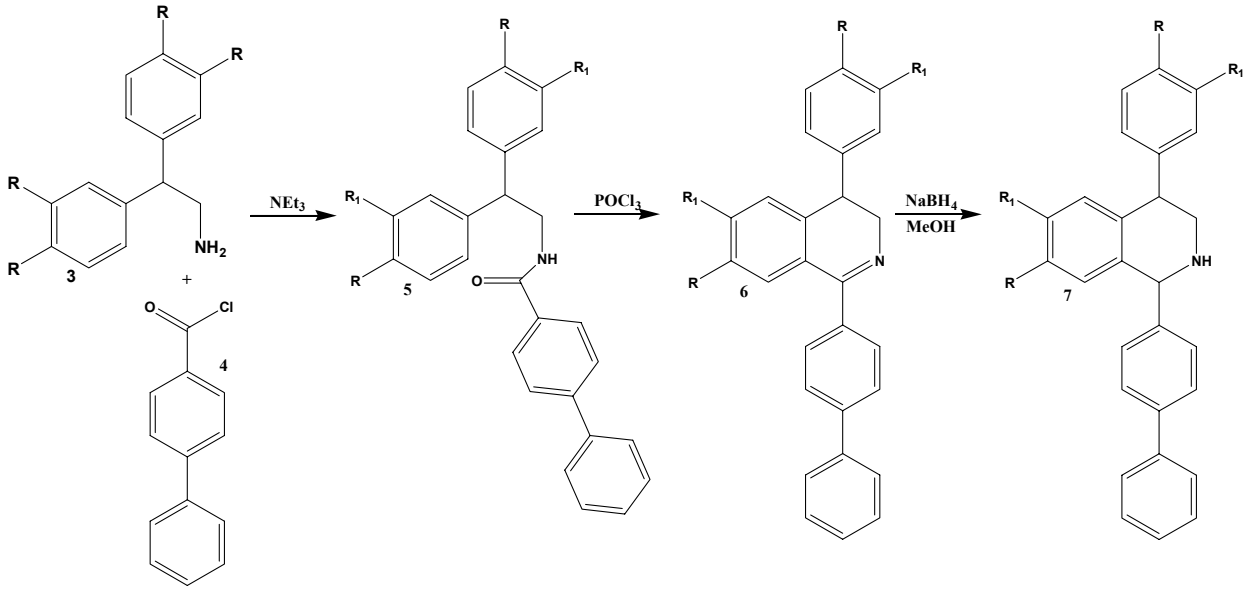
Brequinar

Inhibitors of DHODH show immunosuppressant and antiproliferative activities.[30, 31] Two well-described inhibitors of human dihydroorotate dehydrogenase (hDHODH) are *Leflunomide* and *Brequinar*, which are currently used to treat Malaria, rheumatoid arthritis, and analogs are in clinic to treat graft versus host disease and multiple sclerosis.

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Next step is cyclisation to corresponding 1-biphenyl-4-aryl-3,4-dihydroisoquinolines **6**. For this reaction we applied the classical *Bischler-Napieralski* reaction with phosphorus oxychloride as cyclisation agent. We found that this reaction obtained dihydroisoquinolines with more than 90% yield.

The last step involve reduction of 3,4-dihydro- to 1,2,3,4-tetrahydroisoquinolines. Using mild reaction conditions with sodium borohydride/methanol we successfully obtained compounds **7**.



Scheme 2

5	Yield, %	6	Yield, %	7	Yield, %
a	94	**a**	90	**a**	91
b	89	**b**	94	**b**	93
c	97	**c**	97	**c**	95

Table 1. Yields of amides 5, dihydroisoquinolines 6 and tetrahydroisoquinolines 7*

*For all compounds 5, 6 and 7: a) R=R_1=H; b) R=OMe, R_1=H; c) R=R_1=OMe.

2. EXPERIMENTAL SECTION

Reagents and chemicals were purchased from commercial sources [Fluka and Merck] and used as received. Melting points were determined on a Boetius hostage apparatus and are uncorrected. Spectra were recorded on a Bruker Avance DRX250 spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were taken in $CDCl_3$ (unless otherwise specified) at 250 or 600 MHz and 62.5 MHz respectively. Chemical shifts were given in part per million (ppm) relative and were referenced to TMS (□=0.00ppm) as an internal standard and coupling constants are indicated in Hz. All the NMR spectra were taken at rt (ac. 295 K). TLC was carried out on precoated 0.2 mm Fluka silica gel 60 plates. Merck silica gel 60 (0.063-0.2mm) was used for column chromatographic separation.

Synthesis of amines 3 [28].

Synthesis of amides 5 from starting 3 with biphenyl-4-carbonyl chloride 4:

To the solution of 1 mmol of amines **3** in dichloromethane equal amount of biphenyl-4-carbonyl chloride was added. After 10 min a little excess of triethylamine was added. After 30 min the solution was washed subsequent with diluted hydrochloric acid, saturated solution of Na_2CO_3 and water. The organic layer was dried (Na_2SO_4), filtered on short column with neutral Al_2O_3 and after removing of the solvent, the pure product **5** was isolated.

N-(2,2-diphenylethyl)-4-phenylbenzamide 5a [28].

N-[2,2-bis(4-methoxyphenyl)ethyl-4-phenylbenzamide 5b - ^{1}H-NMR: 3.77 (s, 6H), 4.04 (ddd, 2H, J=4.1, 6.8, 7.7), 4.23 (t, 1H, J=7.9), 6.14 (t, 1H, J=5.5), 6.84-6.88 (m, 4H), 7.17-7.22 (m, 4H), 7.36-7.40 (m, 2H), 7.43-7.47 (m, 1H), 7.53-7.55 (m, 2H), 7.57-7.59 (m, 2H), 7.65-7.68 (m, 2H); ^{13}C-NMR: 167.1, 158.4, 158.3, 157.1, 144.2, 140.0, 134.3, 133.8, 133.5, 133.3, 129.3, 129.0, 128.9, 128.0, 127.9, 127.4, 127.2, 114.2, 114.0, 55.6, 55.3, 49.0, 44.6.

N-[2,2-bis(3,4-dimethoxyphenyl)ethyl]-4-phenylbenzamide 5c [28].

Cyclisation of amide 5 to 1-biphenyl-4-aryl-3,4,-dihydroisoquinoline 6, typical procedure:

Solution of 1 mmol of amides **5** in 3 ml phosphorus oxychloride was refluxed for 30 minutes. The cool reaction mixture was washed with saturated solution of Na_2CO_3 and water. The organic layer was dried (Na_2SO_4), filtered on short column with basic Al_2O_3 and after removing of the solvent, the pure product with high yield was isolated.

4-phenyl-1-(4-phenylphenyl)-3,4-dihydroisoquinoline 6a - ^{1}H-NMR: 4.34 (d, 2H, J=7.8), 4.44 (dd, 1H, J=7.0, 9.4), 7.22-7.32 (m, 3H), 7.31 (s, 4H), 7.34-7.45 (m, 5H), 7.51-7.68 (m, 6H); ^{13}C-NMR: 148.6, 140.0, 138.5, 128.7, 128.3, 128.3, 127.7, 127.4, 127.2, 127.0, 126.6, 121.0, 112.0, 107.5, 49.8, 46.5. Anal. calc. for $C_{27}H_{21}N$ C 90.21; H, 5.89; N, 3.90; found C 90.27; H, 5.85; N, 3.87.

7-methoxy-4-(4-methoxyphenyl)-1-(4-phenylphenyl)-3,4-dihydroisoquinoline 6b - ^{1}H-NMR: 3.12 (s, 1H), 3.77 (d, 2H, J=5.2), 3.91 (d, 6H, J=2.6), 6.86 (d, 2H, J=17.6), 7.05-7.19 (m, 3H), 7.28-7.50 (m, 6H), 7.57-7.72 (m, 2H), 7.83 (dd, 3H, J=16.6, 7.2); ^{13}C-NMR: 167.5, 152.2, 151.7, 146.9, 145.2, 134.5, 133.6, 131.1, 130.6, 130.4, 128.4, 127.1, 126.9, 116.5, 116.1, 114.0, 113.5, 112.6, 111.7, 56.2, 56.0, 42.5, 29.5. Anal. calc. for $C_{29}H_{25}NO_2$ C 83.03; H, 6.01; N, 3.34; found C 83.09; H, 6.03; N, 3.28.

4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1-(4-phenylphenyl)-3,4-dihydroisoquinoline 6c - ^{1}H-NMR: 3.04 (t, 2H), 3.80 (d, 1H, J=5.4), 3.90 (s, 6H), 6.86-7.12 (m, 5H), 7.41 (d, 5H, J=7.0), 7.62 (d, 1H, J=7.2), 7.88 (d, 2H, J=7.6), 8.27 (s, 1H); ^{13}C-NMR: 167.6, 158.7, 151.5, 146.7, 142.4, 134.5, 133.5, 132.3, 131.4, 131.0, 129.0, 128.3, 127.1, 126.9, 123.4, 120.9, 113.4, 112.0, 111.3, 56.2, 56.0, 55.6, 42.7, 31.2. Anal. calc. for $C_{31}H_{29}NO_4$ C 77.64; H, 6.10; N, 2.92; found C 77.60; H, 6.12; N, 2.94.

General procedure for reduction of dihydroisoquinoline 6 to 6,7-dimethoxy-1-biphenyl-1,2,3,4-tetrahydroisoquinolines 7:

To solution of 1 mmol of the 3,4-dihydroisoquinoline **6** in 15 mL methanol, $NaBH_4$ (2 mmol, 0,1 g) was added portionwise. The solution was stirred 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). The products, after evaporation of the solvent, were obtained with high yields.

4-phenyl-1-(4-phenylphenyl)-1,2,3,4-tetrahydroisoquinoline 7a - ^{1}H-NMR: 2.42 (s, 1H, CH), 2.79 (d, 2H, J=4.9, CH_2), 3.31 (td, 1H, J=5.2, 11.4, CH), 5.14 (s, 1H, NH), 6.81-7.05 (m, 5H), 7.43 (d, 5H, J=7.0), 7.60-7.68(m, 2H) 7.73 (d, 1H, J=7.2), 7.84-7.96 (m, 4H), 8.27 (s, 1H); ^{13}C-NMR: 147.9, 147.1,

143.8, 140.5, 140.0, 136.2, 129.3, 129.0, 128.7, 127.6, 127.2, 127.1, 127.0, 121.6, 115.8, 111.1, 44.6, 41.4, 29.9. Anal. calc. for $C_{27}H_{23}N$ C 89.71; H, 6.41; N, 3.87; found C 89.75; H, 6.39; N, 3.91.

7-methoxy-4-(4-methoxyphenyl)-1-(4-phenylphenyl)-1,2,3,4-tetrahydroisoquinoline 7b –

^{1}H-NMR: 2.31 (s, 1H), 2.79 (d, 2H, J=4.9), 3.31 (td, 1H, J=5.2, 11.4), 3.69 (s, 3H), 3.91 (s, 3H), 5.06 (s, 1H), 6.30 (s, 1H), 6.65 (s, 1H), 7.34-7.40 (m, 5H), 7.43-7.49 (m, 4H), 7.48-7.60 (m, 5H); ^{13}C-NMR: 147.9, 147.1, 143.8, 140.5, 140.0, 136.2, 129.3, 129.0, 128.7, 127.6, 127.2, 127.1, 127.0, 121.6, 115.8, 111.1, 55.9, 55.85, 44.8, 41.2, 29.5. Anal. calc. for $C_{29}H_{27}NO_2$ C 82.63; H, 6.46; N, 3.32; found C 82.59; H, 6.50; N, 3.29.

4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1-(4-phenylphenyl)-1,2,3,4-tetrahydroisoquinoline 7c - ^{1}H-NMR: 2.23 (s, 1H), 2.77 (d, 2H, J=4.9), 2.86-3.11 (m, 2H), 3.23 (td, 1H, J=5.2, 11.4), 3.65 (s, 6H), 3.87 (s, 6H), 5.10 (s, 1H), 6.30 (s, 1H), 6.65 (s, 1H), 7.30-7.36 (m, 4H), 7.40-7.46 (m, 3H), 7.53-7.61 (m, 5H); ^{13}C-NMR: 147.8, 147.2, 143.7, 140.8, 140.2, 136.3, 129.5, 129.3, 128.7, 127.6, 127.2, 127.1, 127.0, 121.6, 115.8, 111.1, 61.0, 56.2, 55.9, 55.85, 45.0, 41.7, 29.2. Anal. calc. for $C_{31}H_{31}NO_4$ C 77.31; H, 6.49; N, 2.91; found C 77.35; H, 6.52; N, 2.93.

ACKNOWLEDGEMENTS:

We acknowledge financial support from the National Fund for scientific research DO-02-131 and Fund for scientific research of the Plovdiv University.

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