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Searching for New Biologically Active Compounds Derived from Isoquinoline Alkaloids †

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Abstract: Many isoquinoline alkaloids are biologically active compounds and are successfully used as pharmaceuticals. Compounds belonging to isoquinolines and tetrahydroisoquinolines (TIQs) can be used as anesthetics, antihypertensive drugs, antiviral agents, and vasodilators. In the presented studies, the search for new compounds and synthesis of tetrahydroisoquinoline alkaloid derivatives was undertaken. Several dihydroisoquinolines were synthesized by Bishler-Napieralski reaction from the corresponding amides. Dihydroisoquinolines were reduced with sodium borohydride to obtain racemic tetrahydroisoquinolines. Asymmetric reduction of selected 3,4-dihydroisoquinolines was attempted with borane in the presence of chiral terpene spiroboranes.

Keywords: isoquinoline; alkaloids; biologically active compound

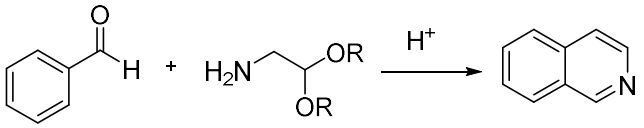
1. Introduction

Isoquinoline and its derivatives are used as starting materials in the synthesis of dyes, insecticides, and pharmaceuticals. Tetrahydroisoquinoline (TIQ) is one of many representatives of *N*-heterocyclic compounds. Its structure consists of a benzene ring fused with a piperidine ring. Isoquinolines and TIQs have a broad spectrum of biological activities, including anesthetic (Quinisocaine), antiviral (Saquinavir), antibacterial (protoberberine derivatives), antihypertensive (Quinapril, Debrisoquine), and vasodilation (papaverine) [1–3]. Tetrahydroisoquinoline derivatives have found numerous applications and became the object of interest of many synthetic chemists. It results from the modern view of science to create materials and chemical compounds with well-defined properties. Currently, studies on the synthesis and pharmacological properties of isoquinolines and TIQ derivatives are still widely conducted [4–6].

The beginnings of the chemistry of isoquinoline derivatives date back to the end of the 19th century. In 1885, isoquinoline was first isolated from coal tar by Hoogewerf and van Dorp [7].

2. Methods of Isoquinoline System Synthesis

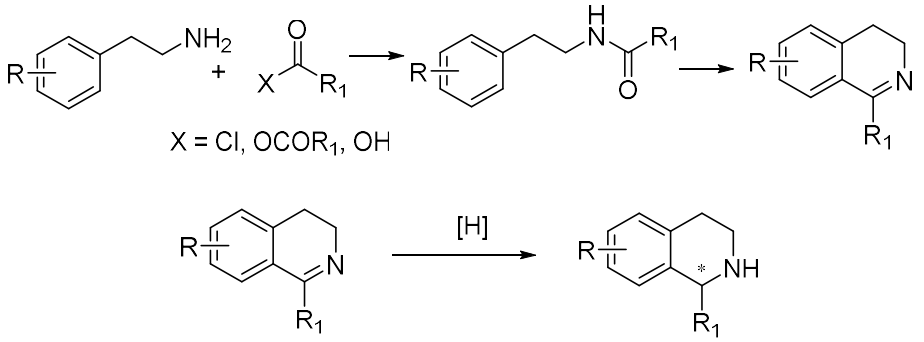
Although isoquinoline derivatives can be synthesized by several methods, relatively few direct methods furnish unsubstituted isoquinoline. The Pomeranz-Fritsch reaction provides an efficient method to produce isoquinoline. In this reaction benzaldehyde reacts with 2,2-dialkoxyethylamine in the presence of acidic catalyst to form isoquinoline (Scheme 1) [8]. Alternatively, benzylamine and glyoxal acetal can be used to obtain the same result using the Schlittler-Müller modification [8].



Scheme 1.

Asymmetric synthesis of (*R*)-(+)-salsolidine, TIQ derivative, was developed using Pomerantz-Fritsh reaction, followed by the diastereoselective reduction of Pomerantz-Fritsh chiral imine as the key step of the synthesis .

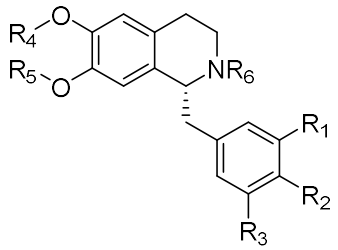
In the asymmetric synthesis of isoquinoline alkaloids, the most frequently used reaction is the Bischler-Napieralski reaction [8,10]. In the Bischler-Napieralski reaction, β-phenylethylamines are converted into the corresponding amides in the first step of the synthesis by acylation reaction with appropriate acid derivatives: chlorides, anhydrides or acids. *N*-Phenethyl amides are further cyclized using dehydrating agent ($POCl_3$, P_2O_5, PPA) to produce 1-substituted 3,4-dihydroisoquinolines.[11] In the last step, 3,4-dihydroisoquinolines are reduced, also stereoselectively, providing the desired tetrahydroisoquinolines (Scheme 2). The formation of 3,4-dihydroisoquinolines can be accomplished employing $SnCl_4$ and BF_3 etherate with phenethylamides, while Tf_2O and polyphosphoric acid (PPA) have been used with phenethylcarbamates. For substrates lacking electron-donating groups in the phenyl ring, phosphorus pentoxide (P_2O_5) in refluxing $POCl_3$ is most effective. Depending on the dehydrating reagent used, the reaction temperature varies from room temperature to 110 °C (boiling point of toluene, which is often used as a solvent).



Scheme 2.

There are a lot of 1-benzyl substituted isoquinoline alkaloids, which are in enantiomeric form and have diverse biological activity (Table 1).

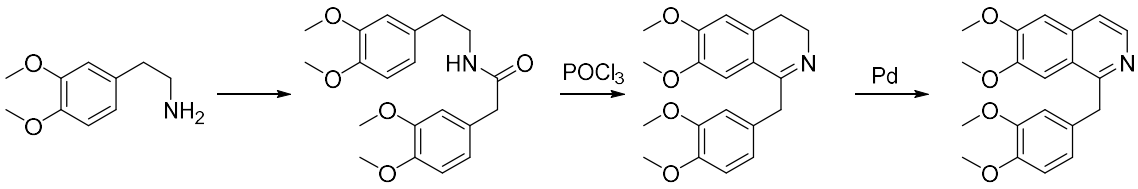
Table 1.



Alkaloid	R_1	R_2	R_3	R_4	R_5	R_6	Biological activity
(*R*)-Norcoclaurine	H	OH	H	H	H	H	Food supplements developed for weight management and sports supplements
(*R*)-Coclaurine	H	OH	H	Me	H	H	Nicotinic acetylcholine receptor antagonist[1]
(*R*)-Norreticuline	OH	OMe	H	Me	H	H	
(*R*)-Reticuline	OH	OMe	H	Me	H	Me	The precursor of morphine and many other alkaloids. It is also toxic to dopaminergic neurons

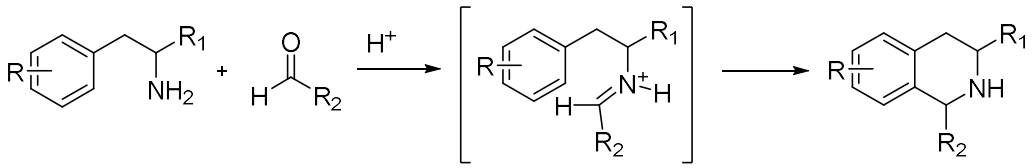
							causing a form of atypical parkinsonism
(*R*)-Trimetoquinol	OMe	OMe	OMe	H	H	H	Drug with a sympathomimetic effect, with a short duration of action, acting selectively on β2 adrenergic receptors
(*R*)-Norarmepavine	H	OH	H	Me	Me	H	
(*R*)-Armepavine	H	OH	H	Me	Me	Me	Anti-inflammatory effects on human peripheral blood mononuclear cells, but also immunosuppressive effects on T lymphocytes
(*R*)-Norprotosinomenine	OH	OMe	H	H	Me	H	
(*R*)-Protosinomenine	OH	OMe	H	H	Me	Me	
(*R*)-Norlaudanosine	OMe	OMe	H	Me	Me	H	
(*R*)-Laudanosine	OMe	OMe	H	Me	Me	Me	Interact with GABA receptors, glycine receptors, opioid receptors, and nicotinic acetylcholine receptors
(*R*)-nor-5-Methoxylaudanosine	OMe	OMe	OMe	Me	Me	H	
(*R*)-5-Methoxylaudanosine	OMe	OMe	OMe	Me	Me	Me	

Products obtained by the Bischler-Napieralski reaction can also be converted to the isoquinoline system using dehydrogenation reaction with palladium catalyst. In this way, papaverine is obtained, which is an agent with a strong relaxing effect on the smooth muscles of internal organs and acts directly on the muscle cells. The relaxing effect of papaverine occurs primarily in the bile, urinary tract, gastrointestinal tract, blood vessels and bronchi, and also reduces blood pressure (Scheme 3) [12].



Scheme 3.

Another reaction in which the isoquinoline system can be obtained is the Pictet-Spengler reaction, which is a variant of the Bischler-Napieralski reaction. In this reaction, the condensation of β-phenylethylamine and the corresponding aldehyde or its equivalent leads to the formation of an imine, which cyclizes to form tetrahydroisoquinoline instead of 3,4-dihydroisoquinoline (Scheme 4). In this method, the stereogenic C1 center is generated during ring closure in a one-pot reaction. If the reaction is carried out asymmetrically, the chirality transfer comes from the chiral auxiliary introduced to either the β-arylethylamine or the aldehyde substrate, thus involving a diastereoselective synthesis [13,14].



Scheme 4.

Many biologically active compounds were also obtained by this method using the Pictet-Spengler reaction. The reaction to form a heteroatomic cyclic system was one of the strategic steps in the total synthesis of these compounds (Figure 1): for example Cibrostatin-4 is described as anti-cancer, anti-fungal and anti-bacterial agent [15], Lemonemycin antitumor antibiotic [16] or (−)-Quinocarcin also antitumor antibiotic [17].

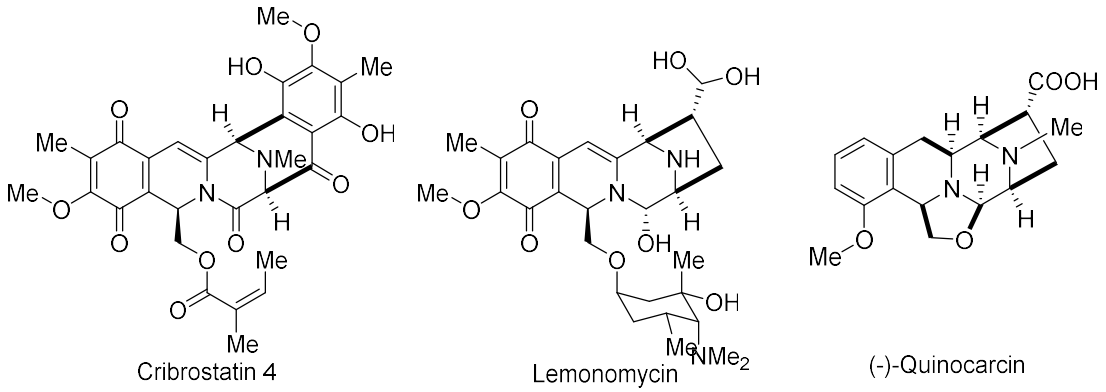
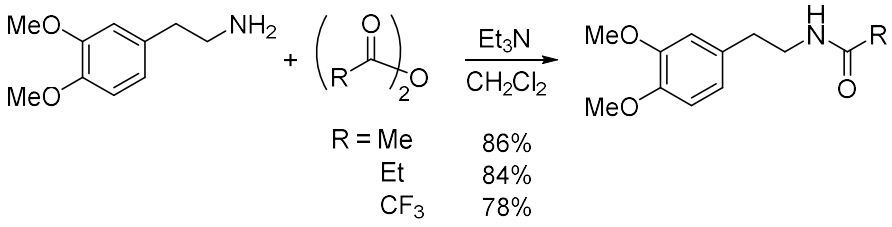


Figure 1.

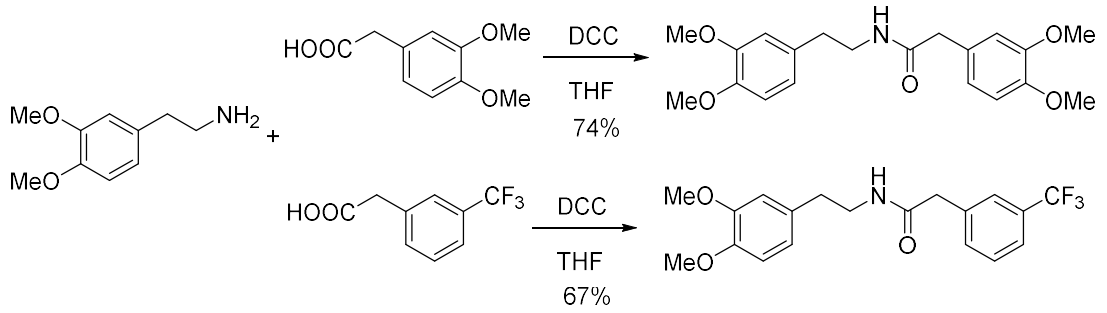
3. Results and Discussion

We started our studies from the synthesis of phenethyl amides, which we obtained in the reaction of 3,4-dimethoxyphenethylamine with acetic, propionic, and trifluoroacetic anhydrides (Scheme 5). Reactions were carried out in dichloromethane in the presence of triethylamine and the products were isolated in good yields.



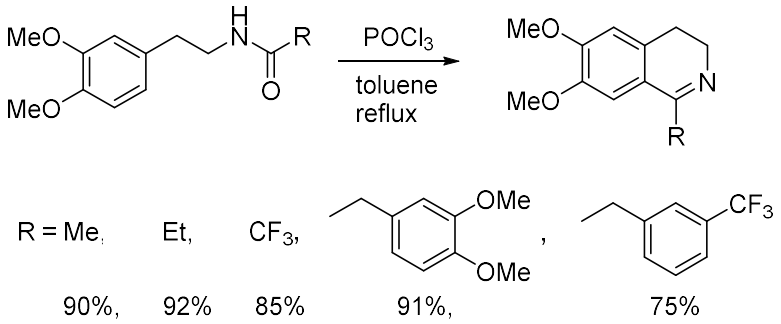
Scheme 5.

Two additional amides were synthesized in condensation reaction with *N,N'*-dicyclohexyl-carbodiimide (DCC) of 3,4-dimethoxyphenethylamine with 3,4-dimethoxyphenylacetic acid and 3-(trifluoromethyl)phenylacetic acid. Products were purified and separated in good yields (Scheme 6).



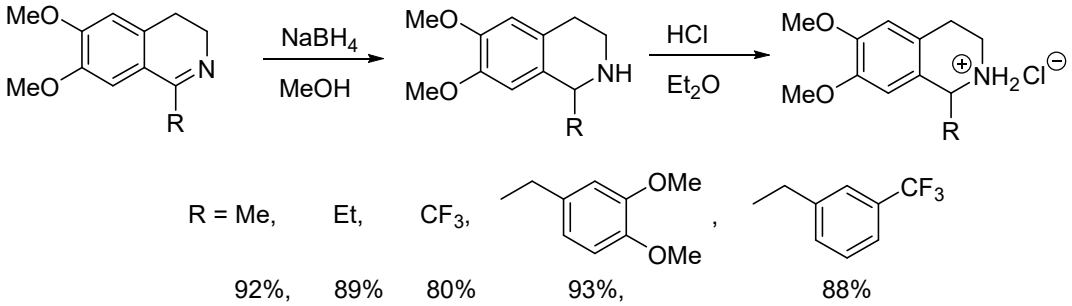
Scheme 6.

The Bishler-Napieralski reaction was performed under standard conditions. The obtained amides were cyclized in the presence of phosphoryl chloride in refluxing toluene (Scheme 7). 3,4-Dihydroisoquinolines substituted at C1 with methyl, ethyl, and trifluoromethyl groups were isolated as pure imines. On the other hand, 3,4-dihydroisoquinolines with benzyl groups at C1, due to their instability, were obtained as iminium hydrochlorides [18]. The instability of substituted 1-benzyl-3,4-dihydroisoquinoline is related to the reactivity of the benzyl position and the ease of oxidizing this position to the carbonyl group [19]. The structures and purity of imines were confirmed by NMR spectra analysis.



Scheme 7.

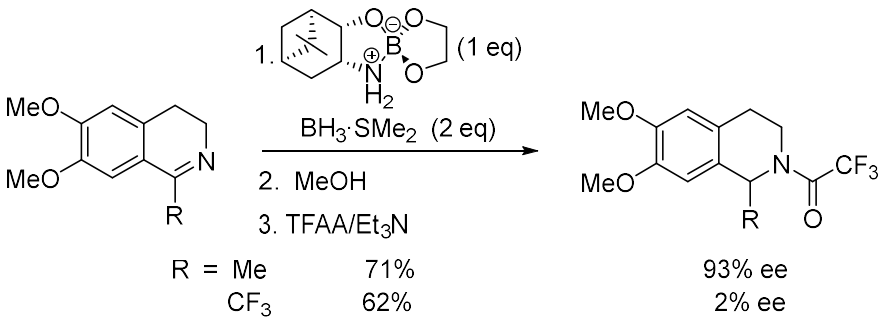
All 3,4-dihydroisoquinolines were reduced using standard procedure with sodium borohydride in methanol to the corresponding racemic tetrahydroisoquinolines (Scheme 8). Reduced products were isolated and converted into amonium chlorides by the addition of hydrogen chloride.



Scheme 8.

Finally, asymmetric reduction of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline and its fluorinated analog were carried out in THF with borane (2 molar equivalents) and the chiral terpene spiroborate ester (1 molar equivalent) [20] at room temperature under inert atmosphere (Scheme 9). The solution of imine was added dropwise to the reaction flask containing spiroborate ester with **borane-dimethyl** sulphide adduct. After the reaction mixture was quenched with methanol,

products converted into trifluoroacetamides and purified by column chromatography on silica gel. The formation of TFA derivatives allowed to separate enantiomers by HPLC analysis on chiral column.



Scheme 9.

4. Conclusions

In conclusion, we have described the synthesis of the selected 1-substituted 6,7-dimethoxy-3,4-dihydroisoquinolines and their reduced analogs. Attempts to reduce dihydroisoquinolines asymmetrically have been partially successful. An optically active salsolidine with an enantiomeric excess of 93% was obtained. The obtained compounds were submitted to evaluate their biological activity.

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