Searching for New Biologically Active Compounds Derived from Isoquinoline Alkaloids †

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Abstract: Many isoquinoline alkaloids are biologically active compounds and successfully used as pharmaceuticals. Compounds belonging to the 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 become objects of interest as many synthetic chemists seek 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 for producing it. In this reaction benzaldehyde reacts with 2,2-dialkoxymethylamine in the presence of an 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. Synthesis of isoquinoline by the Pomeranz–Fritsch reaction.

The asymmetric synthesis of (R)-(−)-salsolidine, TIQ derivative, was developed using the Pomerantz–Fritsch reaction, followed by the diastereoselective reduction of Pomerantz–Fritsch 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 [9,10]. In the first step of the synthesis, β-phenylethylamines are converted into the corresponding amides by an acylation reaction with appropriate acid derivatives: chlorides, anhydrides or acids. N-Phenethyl amides are further cyclized to produce 1-substituted 3,4-dihydroisoquinolines by using a dehydrating agent: phosphorus oxychloride (POCl₃), phosphorus pentoxide (P₂O₅), and polyphosphoric acid (PPA).[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 SnCl₄ and BF₃ etherate with phenethylamides, while Tf₂O and PPA have been used with phenethylcarbamates. For substrates lacking electron-donating groups in the phenyl ring, P₂O₅ in refluxing POCl₃ was most effective. Depending on the dehydrating reagent used, the reaction temperature varied from room temperature to 110 °C (boiling point of toluene, which is often used as a solvent).

Scheme 2. Synthesis of 3,4-dihydro- and tetrahydroisoquinolines.

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

<table>
<thead>
<tr>
<th>Alkaloid</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>R₅</th>
<th>R₆</th>
<th>Biological Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R)-Norcoclaurine</td>
<td>H</td>
<td>OH</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Food supplements developed for weight management and sports supplements</td>
</tr>
<tr>
<td>(R)-Coclaurine</td>
<td>H</td>
<td>OH</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>Nicotinic acetylcholine receptor antagonist</td>
</tr>
<tr>
<td>(R)-Norreticuline</td>
<td>OH</td>
<td>OMe</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>The precursor of morphine and many other alkaloids. It is also toxic to dopaminergic neurons causing a form of atypical parkinsonism</td>
</tr>
<tr>
<td>(R)-Reticuline</td>
<td>OH</td>
<td>OMe</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>Drug with a sympathomimetic effect, with a short duration of action, acting selectively on β2 adrenergic receptors</td>
</tr>
<tr>
<td>(R)-Trimetoquinol</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Anti-inflammatory effects on human peripheral blood mononuclear cells, but also immunosuppressive effects on T lymphocytes</td>
</tr>
<tr>
<td>(R)-Norarmepavine</td>
<td>H</td>
<td>OH</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>(R)-Armepavine</td>
<td>H</td>
<td>OH</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td></td>
</tr>
<tr>
<td>(R)-Norprotosinomenine</td>
<td>OH</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>(R)-Protosinomenine</td>
<td>OH</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td></td>
</tr>
<tr>
<td>(R)-Norlaudanosine</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>(R)-Laudanosine</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>Interacts with GABA receptors, glycine receptors, opioid receptors, and nicotinic acetylcholine receptors</td>
</tr>
<tr>
<td>(R)-nor-5-Methoxylaudanosine</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>(R)-5-Methoxylaudanosine</td>
<td>OMe</td>
<td>OMe</td>
<td>OMe</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td></td>
</tr>
</tbody>
</table>

Products obtained by the Bischler–Napieralski reaction can also be converted to the isoquinoline system using dehydrogenation reaction with a 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 it also reduces blood pressure (Scheme 3) [12].

Scheme 3. Synthesis of papaverine.

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 tetrahydroisoquin-
oline 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-arylthethylamine or the aldehyde substrate, thus involving a diastereoselective synthesis [13,14].

Scheme 4. Synthesis of tetrahydroisoquinolines by the Pictet–Spengler reaction.

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. Biologically active compounds obtained by the Pictet–Spengler reaction.

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. Synthesis of amides from 3,4-dimethoxyphenethylamine and acid anhydrides.

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. Synthesis of amides from 3,4-dimethoxyphenethylamine and substituted phenylacetic acids.

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. Synthesis of 1-substituted 6,7-dimethoxy-3,4-dihydroisoquinolines.

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 ammonium chlorides by the addition of hydrogen chloride.

Scheme 8. Reduction of C=N double bond in 1-substituted 6,7-dimethoxy-3,4-dihydroisoquinolines.

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) [20,21] 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. Asymmetric reduction 1-substituted 6,7-dimethoxy-3,4-dihydroisoquinolines.](image)

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.

References
