Synthesis of disubstituted 1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acids derivatives

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Abstract: 1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid derivatives are of interest for pharmaceutical research as a core structure for synthesis of biological active substance - Etodolac (selective Cyclooxygenase-2 inhibitor, which belongs to the Nonsteroidal Anti-inflammatory Drug, NSAID, that shows a clinically effective analgesic and anti-inflammatory activity). Here the way of synthesis of two 1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid derivatives, impurities of Etodolac generated during drug production process, is presented. The title compounds were prepared in eight steps procedure which differs from previously reported with respect to the way of constructing 1,3,4,9-tetrahydropyranyring in molecule. Moreover, reaction conditions have been optimised and more efficient purification methods were introduced.

1. Introduction

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) defines drug impurity as all kinds of undesirable substances which are present in biologically active substance used in drug formulation, generated during drug production process or related with drug aging. According to ICH guidelines, based on patients' safety, all of the substances present in drugs have to be characterized in chemical structure and biological activity (genotoxicity). The content of the known impurity in drug product cannot exceed 0.15%. In the case of unknown impurities the limit is below 0.10% (in the case of genotoxicity the limit is still lower). The sum of content of all undesirable substances in ready drug product cannot exceed 1%. Impurities related with biologically active substance production can be divided into three general groups: 1) organic compounds (e.g. by-products), 2) inorganic compounds (e.g. by-products, fragments of filters) and

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3) solvents. In the case of drug formulation process, impurities also can be divided into three groups: 1) related with production method, 2) reaction medium condition (e.g. temperature, pressure) and 3) related with drug dosage form (e.g. powder, liquid). Impurities generated during drug aging can be organic and inorganic compounds or solvents which are released during passage of time (Basak, 2007; Jiben, 2002).

Two 1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid (1) derivatives, namely compounds (3) and (4) were obtained. Both of them are impurities of biologically active substance Etodolac (2) generated during synthesis process realized on technical scale. The structures of both 1,8-substituted 1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid derivatives (3) and (4) are presented in Fig. 1.

![Fig. 1.](image)

Etodolac 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid (2) showed in Fig. 1 is one of the anti-inflammatory drugs which belong to the large group of Nonsteroidal Anti-inflammatory Drugs (NSAID) that are inhibitors of both Cyclooxygenase (Cox) isoforms (Cox-1 and Cox-2). The advantage of Etodolac among the NSAID depends on the fact that this drug is selective Cox-2 inhibitor, whose enzyme is responsible for biosynthesis of prostaglandins that act in inflammation process. Cox-1 is rather inactive in inflammation and pain generation process, furthermore, this isoform of cyclooxygenase acts in inhibition of gastric ulceration process (Brater, 1989; Dubois, 1998; Humber, 1987; Neuman, 1987; Zvaifler, 1989). The impurities (3) and (4) are each others isomers.

2. Results and discussion

Etodolacs impurities (3) and (4) were obtained according to slightly modified procedure described in literature (Demerson, 1976). The synthesis of compound (3) was not described in the mentioned literature. The general synthetic pathway is presented in Fig. 2. The first step of synthesis is condensation of compound (5) with chloral hydrate in the presence of anhydrous Na$_2$SO$_4$. As a result of this reaction oxime derivative (6) is obtained. Subsequently the cyclization of oxime (6) to isatine (7) is accomplished in the presence of concentrated sulphuric acid as reaction medium. In the next step compound (7) is reduced to indole derivative (8) with LiAlH$_4$/anhydrous
EtOH suspension. Condensation of compound (8) with oxalyl chloride in anhydrous condition allowed to obtain substance (9). Subsequent change of solvent from Et₂O to absolute EtOH gave as a result product (10), which is reduced in LiAlH₄/anhydrous THF suspension to tryptophol (11). Condensation of tryptophol (11) with ester (12) in azotropically removal of water lead to obtain the ester derivative (13). Finally, ester obtained in the previous step is hydrolysed in alkali medium to impurity (3) or (4).

It should be mentioned that the synthesis of compound (3) was carried out straightly to the pathway showed in Fig. 2, but the synthesis of impurity (4) failed at the step of constructing 1,3,4,9-tetrahydropyran ring in molecule. To obtain compounds (4) the condensation step was modified. Instead of p-toluenesulfonic acid and toluene MeOH saturated with HCl(µ) and trimethyl orthoformate (12a) were used. This change contributed to obtaining ester (13) with satisfying yield. Fig. 3 describes the reaction sequence. The hydrolyse of ester (13) was carried out in basic conditions.

In conclusion two Etodolacs impurities (3) and (4) were obtained. The synthesis was carried out according to literature procedure, which was slightly modified. This synthetic pathway was used in the original form to synthesize compound (3), which was not described in the mentioned literature. In the case of compound (4) modification in one of the steps was introduced.
Fig. 3.

References