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Review

Hydrogenation of ecdysteroids

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ABSTRACT

Catalytic hydrogenation is extensively used in steroid chemistry. The interest in transformations to the steroid skeleton of ecdysteroids has been increasing in the past years. Essential interest in the chemistry of ecdysteroids is caused by the selective reduction of Δ7 bond with the formation of 7,8-dihydro analogues, because this process allows one to obtain modified structures with new biological activity. Catalytic hydrogenation of isolated and conjugated double bonds and functional groups in ecdysteroids derivatives has been considered in review.

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1. Introduction

Ecdysteroids are hormones of molting and metamorphosis of insects and other arthropods. They are widespread in animal and plant worlds [1]. Plants contain these polyhydroxysteroids in much higher concentrations (up to 2% in some plant species) and can be isolated in order to study their properties and chemical transformations. Such studies were at first undertaken in the hope of developing safer and more specific insecticides, and it was quickly shown that ecdysteroids are not toxic to mammals. On the other hand, they displayed a wide array of rather beneficial pharmacological effects [2].

Ecdysteroids are structurally quite different from mammalian steroids. The carbon skeleton of ecdysteroids is termed cyclopentano–perhydro-phenanthrene with beta side-chain at C17, which is the product of terpene biosynthesis through mevalonic acid, cholesterol and related sterols. Annelation of the rings are characteristic: C/D is *trans*, and A/B is generally *cis*. Essential characteristics of ecdysteroids are α-hydroxyl at position C14, β-hydroxyl at C3 and C2, a 7-en-6-one chromophore in the B-ring. Ecdysteroids are highly hydroxylated sterines. 20-Hydroxyecdysone is the major biologically active ecdysteroid (Fig. 1) [3].

Chemical transformations of readily available phytoecdysteroid 20-hydroxyecdysone represent the most efficient pathway to other ecdysteroids and their analogues seldom encountered in nature [3]. Essential interest in the chemistry of ecdysteroids is caused by the selective reduction of Δ7 bond with the formation of 7,8-dihydro analogues, because this process allows one to obtain modified structures with new biological activity (for example, seven-membered lactones in ring B – analogues of brassinosteroids). The simplest approach to the reduction of the double bond of Δ^7-keto group in steroids is catalytic hydrogenation. However, in the case of ecdysteroids with their characteristic γ-hydroxy-α,β-enone group, catalytic hydrogenation does not lead to obtaining the target products due to the occurrence of a number of side reactions [3,4].

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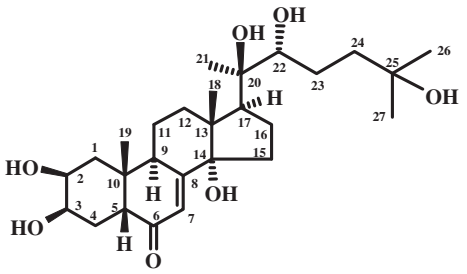


Fig. 1. Structure of a typical ecdysteroid (20-hydroxyecdysone).

Catalytic hydrogenation is extensively used in steroid chemistry. Hydrogenation of isolated and conjugated double bonds and functional groups in steroids has been considered in review [5]. However, catalytic hydrogenation of ecdysteroids has almost not been studied. To a considerable extent, this result from the fact that the double bond of the Δ^7-6-keto moiety was believed incapable to hydrogenation due to steric hindrance [3]. In fact, catalytic hydrogenation (Pd-C, Ni-Ra) under standard conditions does not give 7,8-dihydro ecdysteroids. Rather than being hydrogenated, the Δ^7 bond is shifted along the steroid frame; furthermore, dehydration of the 14α-hydroxy group occurs to give a complex mixture of compounds, including the original ecdysteroid [4]. Hydrogenation of 20-hydroxyecdysone diacetonide **1** or 20,22-acetonide **2** in chloroform over Pd/C gave podecdysone B 20,22-acetonide **3**, which was hydrolyzed to a phytoecdysteroid podecdysone B **4** (Scheme 1) [6].

Hydrogenation of allyl alcohols (6α-**5**) and (6β-**6**) obtained by reduction of diacetonide **1** with complex hydrides of alkaline metals [7] over Raney nickel involves hydrogenolysis of 14a-hydroxyl group with the shift of the Δ^7-bond to 8,14 position (Scheme 2).

The structure of compounds **7** and **8** was established on the basis of the data of 1D and 2D ^{1}H and ^{13}C NMR spectra. According to the data of ROESY spectrum, proton H(6) in 6α-epimer alcohol **7** is axial and has β-configuration, which is confirmed by the NEE of this proton with the protons of Me (19) group. Accordingly, the hydroxyl group at C(6) atom has α-orientation. The large value of $J_{5,6}$ constant (11 Hz) is an evidence of the axial-axial *trans*-position of protons H(5) and H(6) in cycle B and α-orientation of H(5), hence, *trans*-coupling of cycles A and B in compound **7**. In the ROESY spectrum of 6β-alcohol **8**, there is no correlation of proton H(6) with the protons of Me(19), which is the evidence of α-configuration of H(6) and therefore β-orientation of group OH at atom C(6). The correlation peaks of H(5) with Me(19) confirm β-configuration of atom H(5) and *cis*-coupling of cycles A and B in compound **8** [8].

2. Hydride reduction Δ^7-bond and hydrogenation of ω-double bonds in the ecdysteroid derivatives

It is known that the interaction of α,β-unsaturated ketones with complex hydrides of alkaline metals may involve competitive reactions of 1,2- and 1,4-reduction and the formation of allyl alcohols or saturated ketones, respectively. We demonstrated that the interaction of diacetonide of 20-ecdysterone **1** and its ω-anhydro derivative **9** (obtained from compound **1** according to [11]) with $LiAlH_4$ leads to the formation of both 7,8-dihydro analogues **10** and **11** (yields 24% and 25%, respectively), and the products of reduction of 6-keto group – a mixture of epimeric 6-alcohols **5, 6** and **12** (yields 72% and 54%, respectively) (Scheme 3) [9,10].

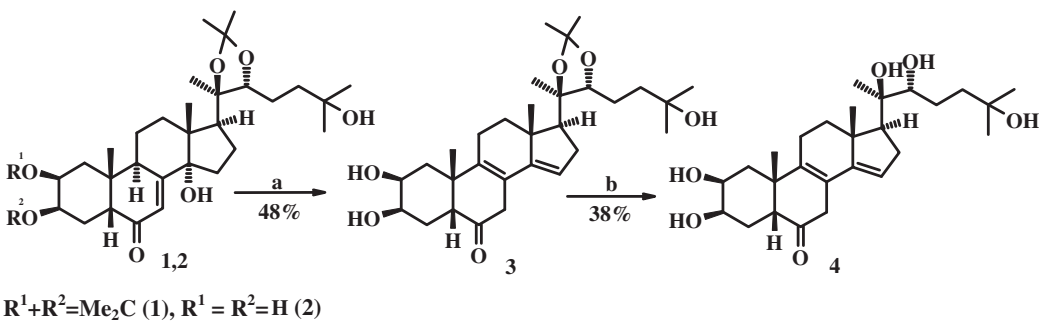
The structure of 7,8-dihydro analogues **10** and **11** was established using 1D and 2D ^{1}H and ^{13}C NMR procedures. The NEE observed in ROESY experiments between the protons of β-oriented Me (19) group and H(5) of ketone **10** provides evidence of the *cis*-conjugation of rings A and B and β-configuration of H(5). The occurrence of the NEE between H(8) and α-HOC(14) confirms α-configuration of the proton at C(8) atom.

Hydrogenation of Δ^{24}/Δ^{25}-alkenes **10** over Raney nickel gave ponasterone A diacetonide **13** [11], whereas hydrogenation of the diacetonide of the 7,8-dihydro analogue of ω-alkenes **11** under similar conditions resulted in reduction of double bonds of the sterine chain along with stereoselective reduction of the 6-ketone to 6α-alcohol **14** [12] (Scheme 3). Hydrogenation of ω-alkene **11** over Pd/C resulted in both saturation of the side chain and dehydration on the 14α-hydroxy group and removal of 2,3-acetonide protection to eventually give compound **15** [10]. The structures of compounds **10–15** were confirmed by ^{1}H and ^{13}C homo- and heteronuclear correlation experiments [10–12].

3. Catalytic hydrogenation of ecdysteroids and their analogues in the alkaline methanol

Recently, it was reported [13] that the selective catalytic hydrogenation of Δ7–6-ketosteroids above the palladium catalyst in the presence of sodium nitrite was carried out and resulted in the formation of the corresponding 7,8-dehydro derivatives. However, we did not succeed in obtaining the required compounds from 20-hydroxyecdysone or its derivatives with the help of this method. On the other hand, we found that selective hydrogenation of the Δ^7-bond in ecdysteroids smoothly occurred over palladium in methanol in the presence of sodium methoxide [14]. Using this method, 20-hydroxyecdysone **16** and its diacetonides **1**, **9** were converted to 7,8α-dihydro analogues **17** and **10, 11**, respectively, in over 90% yields (Scheme 4).

The catalytic hydrogenation of ecdysteroids in alkaline methanol proved to be efficient in the hydrogenation of 7,14-diene



$R^1+R^2=Me_2C$ (1), $R^1 = R^2=H$ (2)

Scheme 1. Reagents and conditions: (a) H_2/Pd–C, $CHCl_3$, 25 °C, 168 h; (b) 70%AcOH/$ZnCl_2$, 4 h, 25 °C.