UDC 547.92+547.926.5+542.91+542.941

Molecular Rearrangements under Chemical Transformations of Ecdysteroids

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Abstract

It was established that 9α,14α-epoxy-14α-deoxyecdysteroids (oxetanoecdysteroids) formed from the corresponding ecdysteroids in the solutions of alkaline metals in liquid ammonia undergo molecular rearrangements catalyzed by acids. As the result of these rearrangements, 9α,13α-epoxy-14β-methyl-13β-demethyl-14α-deoxyecdysteroids and 9α-hydroxystachisterone B are formed. The reduction of oxetanoecdysteroids by sodium borohydride results not only in the reduction of 6-keto group but also in the rearrangement of the oxetane cycle. The oxetane molecular rearrangement takes place also in the course of the catalytic hydration of Δ^7 bond in oxetanoecdysteroids.

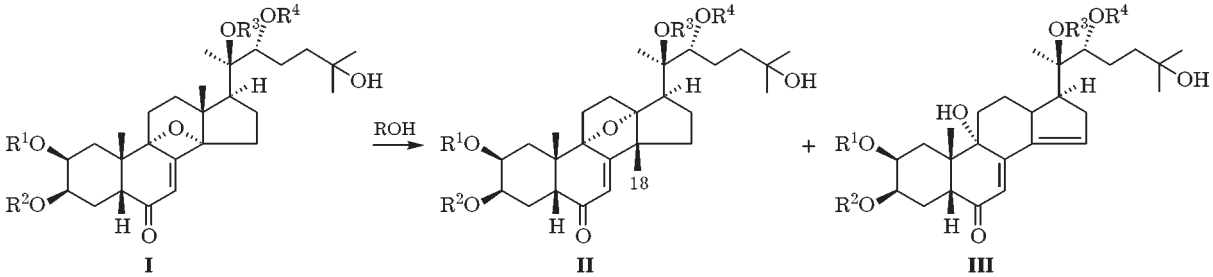
Key words: ecdysteroids, 9α,14α-epoxy-14α-deoxyecdysteroids, molecular rearrangements, 9α,13α-epoxy-14β-methyl-13β-demethyl-14α-deoxyecdysteroids, hydride reduction, catalytic hydrogenation

INTRODUCTION

Ecdysteroids represent the ecdysis, metamorphosis and diapause hormones of insects and crustaceans isolated and identified in 1954. A decade later, ecdysteroids were also found in plants, being in the concentrations many times much higher than in the case mentioned above. Ecdysteroids isolated from plants became available for the investigation of their biophysical properties and for performing their chemical transformations to produce less common in nature (minor) ecdysteroids, as well as for the synthesis of structural analogs with new types of biological activity [1].

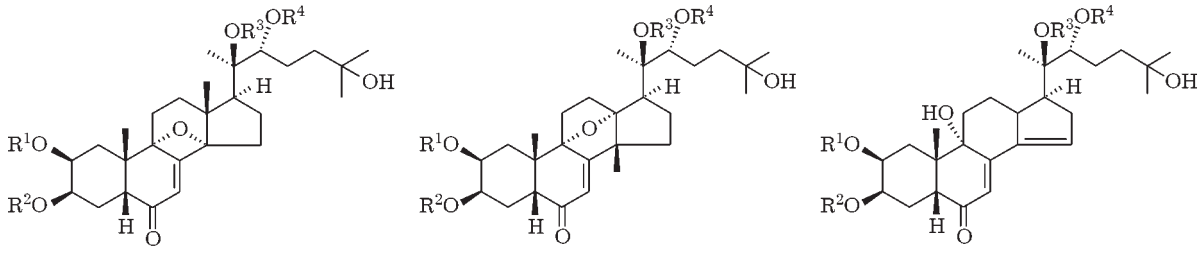
In the course of studying the interaction of 20-hydroxyecdysone and acetonides with alkali metals in liquid ammonia, we found that instead of the expected 7,8-dihydro analogues [2, 3] there is the formation of 9α,14α-epoxy-14α-deoxyecdysteroids with the oxetane cycle in the steroid skeleton (oxetanoecdysteroids) [4, 5].

Earlier we reported the reduction of ecdysteroid derivatives by complex hydrides of alkali metals [6, 7] and the catalytic hydrogenation [8, 9] resulting in the formation of 6-hydroxy derivatives and 7,8-dihydro analogues of ecdysteroids. The presence of the oxetane cycle could cause some of the features of the hydrogenation and reduction reactions of ecdysteroids.



$R^1 = R^2 = R^3 = R^4 = H$ or $R^1 + R^2 = R^3 + R^4 = Me_2C$; R = Me, Et

Scheme 1.



1, **2** **3**, **5**, **7** **4**, **6**, **8**

$R^1 = R^2 = R^3 = R^4 = H$ (**1**, **3**, **4**); $R^1 + R^2 = R^3 + R^4 = Me_2C$ (**2**, **5**, **6**); $R^1 = R^2 = H$, $R^3 + R^4 = Me_2C$ (**7**, **8**)

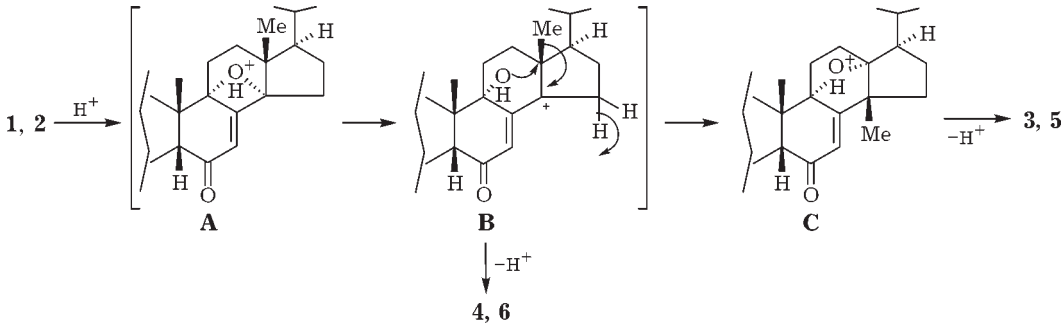
Scheme 2.

We have found that oxetanoecdysteroids **I** in alcohols (MeOH, EtOH) are slowly rearranged to form 9α,13α-epoxy-14β-methyl-13β-demethyl-14α-deoxyecdysteroids **II** *i. e.* ecdysteroids with the 18-methyl group displaced from the position 13 to position 14 (similar to stachysterone, the only naturally occurring C_{27} steroid with the migrated methyl group [10]) and the derivatives of 9α-hydroxystachysterone B **III** [5] (Scheme 1).

ACID-CATALYZED MOLECULAR REARRANGEMENTS OF OXETANOECDYSTEROIDS

It should be expected that acids would accelerate the above mentioned transformation of oxetanes. Indeed, the rearrangement slowly running at a room temperature in alcohols (24 h for 20-hydroxyecdysone **1** in MeOH, 240 h for 20-hydroxyecdysone diacetonide **2** in EtOH [5]) is abruptly accelerated in the presence of BF3 etherate, thus the formation of compounds **3** and **4** or **5** and **6**, respectively, is completed during 5 min in MeOH, EtOH, *t*-BuOH or THF. Under the same conditions in methylene chloride or benzene solution, the process was complicated by the deprotection of 2,3-hydroxyl groups in diacetonide **2**, thus alongside with compounds **5** and **6** there are compound **7** and **8** formed (Scheme 2). The rearrangement of oxetane **1** into compounds **3** and **4** was completed during 10 min at a room temperature in THF solution in the presence of 5 % HCl, whereas in the presence of cationite DOWEX the oxetane **1** at 50 °C during 1.5 h was converted into the only product **4**.

The acid-catalyzed conversion of oxetanes **1** and **2** into compounds **3**, **4** or **5**, **6**, respectively, occurs, to all appearance, via Wagner–Meerwein type rearrangement (Scheme 3). The oxonium ion resulting from adding a proton to oxygen A isomerizes to form carbenium ion B due to the transition of an electron pair from the C^{14}–O. Its stabilization *via* the elimination of a proton from C-15 results in the formation of 9α-hydroxystachysterons **4** and **6**. On the other hand, the migration of 18-methyl group from position 13 to carbenium atom C-14 and the attack of the hydroxyl group at C-13 atom



Scheme 3.

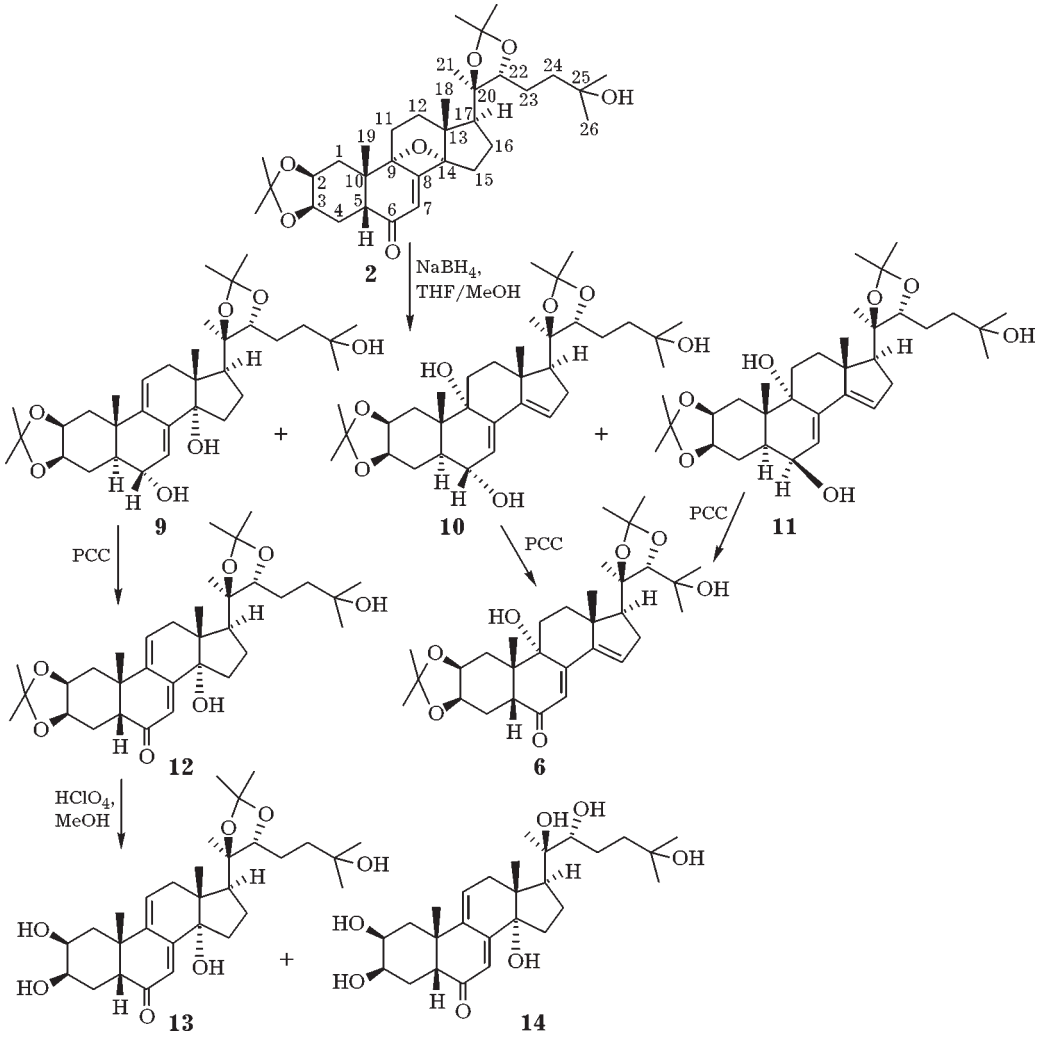
result in obtaining oxonium ion C from tetrahydrofuran cycle (much more stable than the oxetane). The subsequent proton cleavage results in 18-methyl rearranged compounds **3** and **5**. The β-configuration of the CH3 group at C^{14} atom and the α-configuration of C^{9}–O and C^{13}–O bonds, confirmed by XRD structural analysis [5] indicate that the migration of 18-methyl group occurs on the β-side of the steroid skeleton, whereas the attack of OH group to the C^{13} carbene centre is directed from the α-side.

Thus, oxetanoecdysteroids under catalysis with Lewis or Brönsted acids are characterized by a rapidly occurring molecular rearrangement of Wagner–Meerwein type to form 14β- methylecdysteroids and 9α-hydroxystachysterone and its derivatives.

TRANSFORMATIONS OF OXETANOECDYSTEROIDS UNDER THE ACTION OF SODIUM BOROHYDRIDE

The interaction between oxetanoecdysteroid **2** and sodium borohydride in THF–MeOH mixture (10 : 1) and the subsequent treatment of the reaction mixture with water resulted in obtaining a mixture of 7,9-diene-6α,14α-dihydroxy **9** and 7,14-diene-6α,9α-dihydroxy **10** derivatives and a 6β-epimer of the latter **11** (Scheme 4). Compounds **9**–**11** were separated using a column chromatography technique, the structure of each was determined with the help of ^{1}H and ^{13}C NMR spectroscopic methods in 1D and 2D modes [11].

According to [6], the hydride reduction of the 6-keto group in ecdysteroids results in an epimerization at C(5) atom, *i. e.*, it should be



Scheme 4.

expected that the rings A and B in the compounds **9**–**11** are *trans*-concatenated. This could be evidenced by the fact that there is no correlation between protons and H_3C^{19} and HC^5 in the NOESY spectra of compounds **9**–**11**. In the COSY spectra of compounds **9** and **10**, there were no cross peaks between protons H-5 and H-6 detected, whereas such a cross peak is present in the case of 5αH,6αH-epimer **11**.

The rearrangement of the oxetane cycle occurs, to all appearance, only after reducing the 6-keto group and further treating the reaction mixture with water to result in the formation 9α-hydroxy-$\Delta^{14(15)}$ derivatives **10** and **11** as well as a regioisomeric compound 14α-hydroxy-$\Delta^{9(11)}$ derivative **9**. Such a sequence of oxetane **2** transformation into alcohols **9**–**11** is indicated by the conservation of the oxetane cycle **2** in the alkaline solution of methanol (KOH/MeOH) during 2 days (TLC monitoring).

The oxidation of the dienol **9** resulted in the formation of 25-hydroxydacryhainansterone diacetonide **12** unknown earlier, whose structure was determined according to 1D and 2D NMR spectra ^1H and ^{13}C [11]. The interaction between the proton of HC^5 with the protons of the H_3C^{19} group in the NOESY spectrum indicates its β-configuration and the *cis*-concatenation of rings A and B. Just the same fact is indicated by the correlation between the chemical shift (δ) of the proton H-5 and the concatenation of rings A and B observed for brassinosteroid [12] and confirmed later for ecdysteroids [13]: δ ~ 2.4 ppm corresponds to the *cis*-concatenation of rings A/B, whereas δ ~ 2.2 ppm corresponds to *trans*-concatenation. The chemical shift of H-5 δ = 2.45 ppm indicates *cis*-concatenation A/B in ketone **12**.

The oxidation of epimeric alcohols **10** and **11** resulted in the formation of the same 6-ketone **6** identical to 9α-hydroxystachysterone B diacetonide (according to m. p., UV, ^1H and ^{13}C NMR spectra), which was described earlier [5].

It could be seen that for the two-stage transformations presented, epimerization occurs with respect to atom C^5, both under the hydride reduction of 6-ketone **2**, and under the oxidation of allyl alcohols **9**–**11**.

The hydrolysis of the diacetonide **12** we obtained 25-hydroxydacryhainansterone **14** and 20,22-acetonide **13** separated by means of column chromatography.

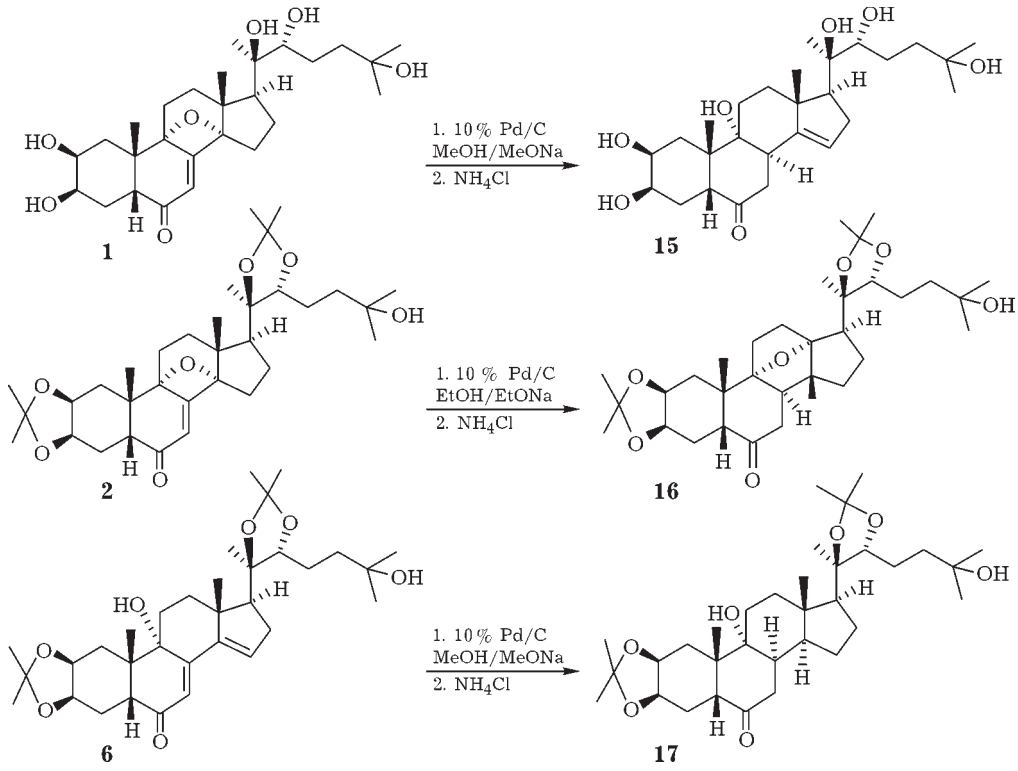
Thus, the hydride reduction of oxetanoecdysteroid **2**, which occurs with respect to 6-keto group and is accompanied by the rearrangement of 9α,14α-oxetane cycle, formed the basis of a three-stage synthesis of 25-hydroxydacryhainansterone obtained earlier by dehydration of turkesterone [14, 15], a minor (content 0.14 %) difficult of access ecdysteroid inherent in plant *Ajuga turkestanica* [16].

TRANSFORMATIONS OF OXETANOECDYSTEROIDS UNDER CATALYTIC HYDROGENATION

The well-known inertness of Δ^7 bond in ecdysteroids [8, 17] under the normal conditions of catalytic hydrogenation is also inherent in oxetanoecdysteroids. The hydrogenation of oxetane **2** above palladium (10 % Pd/C) or nickel (Ni/Ra) catalyst in *t*-butanol does not result in affecting the Δ^7 bond, but there occurs an oxetane rearrangement to form a mixture of compounds **5**, **6** and their 2,3-deblocked derivatives **7** and **8** at a ratio of 15 : 15 : 40 : 30, respectively.

We recently reported [9] a novel efficient method for the catalytic hydrogenation of ecdysteroids in alcohols in the presence of an alkali metal alkoxide. Using this method one could obtain a quantitative yield of the corresponding 7,8α-dihydroecdysteroids. The α-configuration of a newly formed chiral centre C(8) was demonstrated by XRD structural analysis performed for 7,8-dihydro-20-hydroxyecdysone diacetonide. This method appeared generally helpful for different derivatives and analogs of ecdysteroids containing a conjugate 7-ene-6-keto group. The hydrogenation of oxetanoecdysteroids **1** and **2** above Pd/C catalyst in methanol in the presence of sodium methylate results in an easy hydrogenation of Δ^7 bond. At the same time, the oxetane rearrangement also takes place.

It was found that oxetanoecdysteroid **1** is selectively converted into 9α-hydroxy-7,8α-dihydrostachysterone B **15**, whereas diacetonide **2** under the same conditions forms the only 9α,13α-epoxy-14β-methyl-13-demethyl-14-deoxy-7,8α-dihydro-20-hydroxyecdysone diacetonide **16** (Scheme 5). According to ^{13}C NMR spectrometry, compounds **15** and **16** are simi-



Scheme 5.

lar in the structure with respect to 9α-hydroxystachysterone B **4** and 9α,13α-epoxy-14β-methyl-13-demethyl-14-deoxy-20-hydroxyecdysone diacetonide **5** [5], respectively. The absence of signals inherent in $\Delta^{7(8)}$ bond in the ^{13}C NMR spectra of compounds **15** and **16** (δ 133.5 and 163.8 ppm, respectively) and the detection of signals from C(6) in a weaker field (δ 213.0 and 212.5 ppm, respectively) indicates the formation of corresponding 7,8-dihydro derivatives.

It should be noted that, as it is observed for the hydride reduction oxetanoecdysteroids described above, the oxetane rearrangement under the hydrogenation of compounds **1** and **2** takes place after the formation of 7,8-dihydro derivatives and the treatment of the reaction mixture. Confirmation of just this sequence consists in the fact that oxetanes are stable in alkaline media and there is the formation of 9α-hydroxy-7,8α,14α,15-tetrahydrostachysterone B diacetonide **17** under the hydrogenation of 9α-hydroxystachysterone B diacetonide **6**. The 8α,14α-configuration of the newly formed chiral carbon atoms (8) and (14) of compound **17** was confirmed using XRD analysis performed for 7,8α-dihydro-14α-deoxy-20-hydroxyecdysone diacetonide obtained via the hydrogenation of stachysterone diacetonide B [18]. This is also indicated by the formation of compound **15** under the hydrogenation oxetane **1**, whereas in the case if first of all rearrangement occurred to form stachysterone B **4**, the final product of the hydrogenation of oxetane **1** should be presented by 9α-hydroxy-7,8α,14α,15-tetrahydrostachysterone B.

CONCLUSION

Thus, the molecular rearrangements of oxetanoecdysteroids those occur with the transformation 9α,14α-oxetane cycle into 9α,13α-tetrahydrofuran cycle either with displacing the 18-methyl group from C(13) to C (14) atom, or with the formation of 9α-hydroxy derivatives of stachysterone B offer new prospects in the chemistry of ecdysteroids. In this concern, also attractive are the transformations with respect to the Δ^7-6-keto fragment of oxetanoecdysteroids demonstrated by the reactions hydride reduction and catalytic hydrogenation under alkaline conditions.

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