STUDY OF NEW REACTIONS OF SOME POLYCYCLIC TERPENIC ALCOHOLS USING REAGENTS BASED ON GLYCOLURIL

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ABSTRACT OF DISSERTATION

Natural triterpene compounds are of great interest due to their availability and a wide range of biological effects. The use of natural compounds as objects of chemical transformations in order to obtain biologically active agents has become one of the actively developing areas of organic synthesis. Currently, considerable attention is paid to the study of the biological activity of triterpenoid derivatives of the lupane series — betulin, which is evidenced by the growth of publications about synthesis of new betulin derivatives and the study of their biological activity.

Betulin is produced from birch bark of various species. The outer part of the bark is richest with extractive substances: their content reaches 40%. The content of betulin in the outer part of the bark varies within 10-35 % depending on the type of birch, the place and conditions of its growth, the age of the tree and other factors. The inner bark contains less than 2% betulin, while in the wood only traces are detected

The high availability of betulin from the bark of birch trees makes it a potentially important raw material as the precursor of biologically more active compounds. Betulin can be converted into many kinds of derivatives by chemical synthesis and biotransformation.

Thus, on the basis of these compounds, a number of pharmacologically promising agents have been obtained, containing various acyl substituents in the C-3 and C-28 positions. A special place among the biologically active triterpenoids occupy betulin derivatives containing different substutituents at C-30 position, promising for the development of antiviral and anticancer drugs. During recent years, several interesting biological properties were found for the oleanane group, more particularly allobetulin (**3**) and its derivatives, which are obtained from the readily available lupane betulin (**1**), form a part of the oleanane group.

The aim of the present work is to study new reactions of some polycyclic terpenic alcohols using reagents based on glycoluril. In addition, prepare some new betulin and allobetulin derived compounds and investigate theirs antioxidant activity.

To accomplish this goal, the work is supposed to solve the following tasks:

1. Search and analysis of literature data on synthesis of betulin derivatives and theirs applications.
2. Isolation of betulin from outer birch bark in good yield and high purity for further uses.
3. Develop a novel method for isolating diacetate betulin directly from outer birch bark (raw material) in sufficiently high yield and purity in order for it to be further used for the synthesis of its derivatives.
4. Acetylation of betulin, allobetulin and cholesterol using TAGU as new acetylating agent.
5. Synthesis of betulin diformate and allobetulin formate using two method.
6. Prepare some new esters of allobetulin using haloacetic acids.
7. Modification of isopropylene fragment in the betulin diacetate through halogenation substitution reaction using tetra haloglycoluril.
8. Confirmation of the structure of the compounds obtained by physicochemical methods of analysis.
9. Evaluate the antioxidant activity of some synthesized derivatives.

The obtained results, and the most important conclusions in this work are given as following:

- A review of the literature data of the history and pharmaceutical uses of betulin and birch bark vegetable raw materials has been carried out. Furthermore, methods for modifying betulin and allobetulin using the acylation reactions and substitution reactions on double bond has been investigated.

- A modified method of producing betulin diacetate with high purity directly from birch bark has been developed by treating birch bark with technical mixture of 36% acetic acid and 64% of its anhydride for 48 hours.
- Synthesis of betulin diformate for the first time in one step directly from outer birch bark without a separate stage of the betulin preparation has been achieved. along with betulin diformate, allobetulin formate also has been obtained separately as byproduct. This study is currently under consideration for patent by "federal'naya sluzhba po intellektual'noy sobstvennosti (rospatent)".
- A new method for preparation of betulin diformate under the action of formic acid has been developped using thioglycoluril as catalyst, which prevent the isomerisation of betulin into allobetulin. therefore betulin diformate was transformed into allobetulin formate by the action of TFA. This latter method is considered as new method for the preparation of allobetulin formate.
- Four new allobetulin esters **70**, **90-92** have been synthesized through acetylation of β-hydroxyl group at C-3 position using different haloacetic acid. The importance of acetyl group at C-3 for antioxidant activity has also been investigated.
- Vinylic and allylic halogenation substitution on C20-C29 vinylidene group of betulin diacetate has been achieved and studied using TBGU and TCGU. The mechanism formation of the obtained product has been proposed.
- Comparative antioxidant activity of betulin, betulin diacetate and betulin diformate was studied using cathodic voltammetry. Betulin diformate has been shown to have the highest antioxidant activity compared to betulin and betulin diacetate. We think that such a pronounced effect of inhibiting oxidation is associated with the presence of active double bonds in the structure of betulin diformate, which undergoes easier oxidation than the similar connection in betulin itself. An argument in favor of this assumption is that in the C-3 and C-28 positions in betulin diformate hydroxyl groups are protected by formyl substituents, which makes it difficult for the oxidation of these positions. Betulin diacetate shows an average antioxidant activity, since, in its structure there is also a protecting groups at the positions C-3 and C-28.

- The evaluation of antioxidant activity of the synthesized allobetulin esters 78, 90-92 has been achieved using voltammetric method. The results showed the effectiveness of introduction of alpha-haloacetyl group on the improvement of the antioxidant of allobetulin which can be interpreted by the comparison of these latter with ascorbic acid since they surpass its antioxidant value. In addition, it may be worthwhile to evaluate them for the antiviral properties against herpes virus, since allobetulin esters has been demonstrated to treat herpes virus.[66] It is possible that an anviral drug could emerge as a result of future studies.
- The modification of betulin with formyl groups at C-3 and C-28 into ester **88** yielded a highly antioxidant derivative that surpass two times the antioxidant activity of ascorbic acid.
- The synthesized compounds were studied by modern methods of physicochemical analysis: IR, ^{1}H NMR and ^{13}C NMR spectroscopy, high performance liquid chromatography, melting point and thin layer chromatography.