*Chemistry of Natural Compounds, Vol. 30, No. 1, 1994*

# SYNTHESIS OF LAGOHIRSIN BY THE DEHYDROGENATION OF LAGOCHILIN AND OF 3,18-O-ISOPROPYLIDENELAGOCHILIN

**Y. N. Zainutdinov, Kh. Khaitboev, M. A. Safaev,**
**R. Islanov, and Kh. A. Aslanov**

UDC 547.914.6+547.996.02

*A method is proposed for the synthesis of lagochilin by the dehydrogenation of lagohirsin and 3,18-O-isopropylidene lagochilin with an activated Raney nickel catalyst, and a method is given for obtaining 3,18-O-isopropylidenelagochilin by ketalization with acetone.*

The diterpene lactone lagohirsin, isolated from various species of plants of the genus *Lagochilus*, serves as a source of a material for obtaining new physiologically active compounds. The low content of lagohirsin in these plants (0.1-0.3%) and their limited stocks are making it necessary to search for more effective ways of obtaining this compound. We have developed a method for obtaining lagohirsin by the dehydrogenation of lagochilin - a diterpenoid present in a number of species of the genus *Lagochilus* in considerable amounts [1, 2].

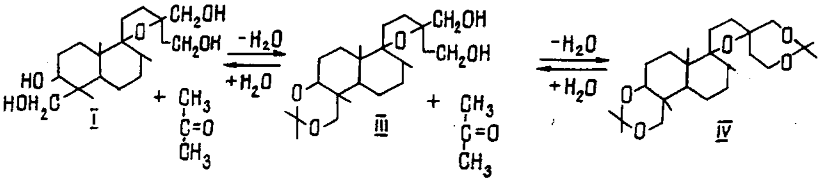
The formation of lagohirsin (II) from lagochilin (I) is achieved by the selective elimination of four hydrogen atoms from two hydroxymethyl groups (C-15 and C-16) of lagochilin with the formation of a $\gamma$-lactone. The hydroxy groups at C-3 and C-18 remain unchanged.

It is known that compounds having alcohol groups in the 1,4-position (1,4-diols) form lactones in high yields on dehydrogenation under the action of activated Raney nickel [3]. In view of this, we investigated the dehydrogenation of lagochilin with a skeletal nickel catalyst. The yield of (II) was 10-12%.

To increase the yield we used the following weight ratios of lagochilin to Raney nickel catalyst: 1:1, 1:2, 1:3, 1:4. and 1:5. The solvents used were acetone, benzene, and toluene. The reaction time was from 1 to 13 h. The highest yield of (II) (27%) was achieved at a weight ratio of lagochilin to Raney nickel to toluene of 1:3:100 with a reaction time of 6 h at the boiling point of the toluene.

Low yield of (II) is explained by the fact that not only the alcoholic groups of the lagochilin molecule at $C_{15}$ and $C_{16}$ but also those at $C_3$ and $C_{18}$ take part in the dehydrogenation reaction. Consequently, it is necessary to protect the alcohol groups at $C_3$ and $C_{18}$ from unintended dehydrogenation by obtaining suitable acetal and ketal derivatives with subsequent elimination of the protective groups. However, the results of a study of the formation of lagochilin derivatives at the alcohol groups show that a mixture of mono- and di- derivatives is always formed, in ratios depending on reaction conditions and the initial reactants. The most suitable derivatives for protecting C3 and C18 alcoholic groups is 3,18-O-isopropylidenela-gochilin (III).

A method of obtaining (III) is described in the literature, but its isolation was difficult and the yield was only 27% [4]. We have developed a method for obtaining (III) from (I). The ketalization of (I) with acetone takes place in an acid medium in two stages and is reversible:

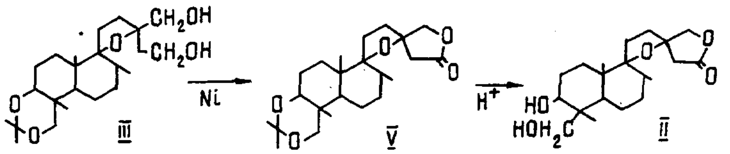


The first stage comprises the formation of (III). In the second stage, the (III) reacts with acetone to form di-O-isopropylidenelagochilin (IV). The elimination of (III) from the reaction mixture with cyclohexane in the presence of an excess of water suppresses the formation of (IV), and the ketalization of (I) with acetone stops at the first stage.

---

Tashkent State University, fax 462472. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 38-40, January-February, 1994. Original article submitted July 13, 1993.

Thus, repeated extraction with cyclohexane enables (III) to be isolated with 65-70% yield. Compound (III) was dehydrogenated with activated Raney nickel under the same conditions as (I). The highest yield of (II) (74%) was achieved at a weight ratio of 3,18-O-isopropylidenelagochilin, activated Raney nickel, and toluene of 1:4:15, respectively, with a reaction time of 3 h at the boiling point of the toluene.



## EXPERIMENTAL

The compositions of the mixtures of substances and the individuality of the compounds were monitored in a fixed layer of type L 5/40 silica gel with 13% of gypsum in the solvent systems: 1) ether–acetone (15:1); and 2) chloroform–acetone (4:1). The chromatograms were revealed in a 10% solution of sufuric acid in alcohol. The Raney nickel catalyst was activated by a standard method [5].

PMR spectra were taken on a Varian XL-100-15 spectrophotometer with a working frequency of 100 Hz. Hexamethyldisiloxane (HMDS) was used as internal standard.

**Dehydrogenation of (I).** A solution of 1 g of (I) in 100 ml of toluene was treated with 3 g of activated Raney nickel. The reaction mixture was boiled for 6 h, the course of the reaction being monitored by TLC. After the end of the reaction, the catalyst was filtered off, and the (II) was extracted from the combined filtrate with a 5% solution of caustic soda. By-products of the reaction were eliminated from the alkaline solution by washing it with chloroform. The purified alkaline solution was acidified with 20% sulfuric acid, and the resulting (II) was extracted with ether. The ethereal solution was washed with 0.5% solution of sodium hydrogen carbonate and then with distilled water. After the ether had been distilled off, the (II) was recrystallized from ether. mp 142-143°C. According to its spectral characteristics and melting point, the compound (II) that had been obtained was identical with a natural sample.

**Preparation of (III).** A solution of 2 g of (I) in 50 ml of acetone and 30 ml of distilled water was treated with 5-6 drops of concentrated sulfuric acid. The mixture was stirred vigorously for 10 min and was then extracted with cyclohexane (6 × 300 ml). The cyclohexane extracts were washed with 5% sodium hydrogen carbonate solution, and the cyclohexane was distilled off. The residue, after being washed with 10 ml of a 15: 1 mixture of petroleum ether and acetone and recrystallization from ether, consisted of a white powder of (III) with mp 165-166°C. Yield 70%.

**Dehydrogenation of (III).** A solution of 2.5 g of (III) in 40 ml of toluene was treated with 10 g of activated Raney nickel, and the reaction mixture was boiled for 3 h, the course of the reaction being monitored by TLC. After the end of the reaction the Raney nickel was filtered off, and the toluene was distilled off under vacuum. The residue was dissolved in 30 ml of isopropyl alcohol, and 50 ml of a 1% solution of sulfuric acid was added to it. The resulting acid solution was made alkaline with 10 ml of 10% sodium hydroxide solution, and the by-products were extracted with chloroform. The further treatment was then as in the dehydrogenation of (I). Yield 74%, mp 141-143°C.

## REFERENCES

1. M. M. Abramov, Zh. Prikl. Khim., **30**, No. 4, 653 (1957).
2. Z. I. Mavlyankulova, U. N. Zainutdinov, and Kh. A. Aslanov, Khim. Prir. Soedin., No. 1, 46 (1977).
3. J. A. Berson and W. M. Jones, J. Org. Chem., **21**, No. 11, 1325 (1956).
4. O. S. Chizhov, A. V. Kessennikh, I. P. Yakovlev, B. M. Zolotarev, and V. A. Petukhov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 9, 1983 (1970).
5. N. B. Dobroserdova and A. B. Anisimov, Practical Handbook on Petrochemical Synthesis [in Russian], Moscow State University, Moscow (1981), p. 109.