A SESQUITERPENE LACTONE BADKHYSININ FROM THE ROOTS OF FERULA OOPODA

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We have previously [1] reported that the sesquiterpene lactone badkhysin $C_{20}H_{24}O_5$, mp 139°-140° C, is easily isolated from a cooled ethereal extract of the resin of the roots of Ferula oopoda Boiss.

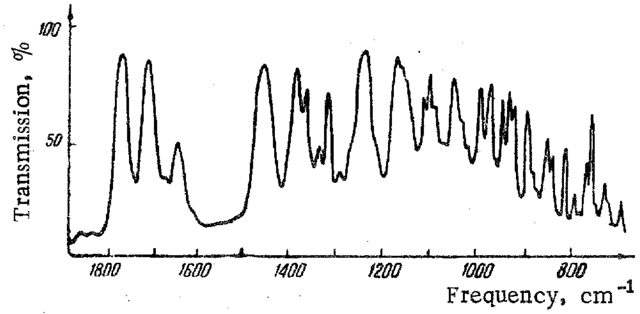
In addition to badkhysin, the resin contains several other lactones of which, by chromatography on alumina (activity grades III and IV), we have isolated an optically active substance with the composition $C_{20}H_{24}O_5$, mp 104°-105° C, which we have called badkhysinin.

From the data of the IR spectrum (figure), badkhysinin contains a lactone group (band at 1765 cm^{-1}), an ester group (maximum at 1708 cm^{-1}), and double bonds (bands at 1668, 1640, 919, 892, and 818 cm^{-1}). The IR spectrum has one maximum at λ 214 mμ (log ε 3.63), which is characteristic for an α, β-unsaturated lactone.

From a study of the IR and UV spectra of badkhysinin we assumed that the fifth oxygen atom which it contains is in the form of an oxide. This was confirmed by the subsequent chemical study of the substance.

The nature of the ester group in badkhysinin was elucidated by its saponification. This gave angelic acid and a crystalline product $C_{15}H_{18-20}O_4$ with mp 185°-186° C.

In the first stage of the investigation, we assumed that badkhysinin had a 10-membered ring, since the dehydration of badkhysinin itself or its saponification product with mp 185°-186° C gave no aromatic or azulenic substances.



IR spectrum of badkhysinin.

However, further experiments showed that a bicyclic hydroazulene system was more probable for this substance hydrogenated under various conditions. By chromatography on alumina of the oil obtained from the products of the exhaustive hydrogenation of badkhysinin in the presence of platinum oxide in ethanol, we obtained liquid substances and a crystalline compound $C_{20}H_{30}O_5$ with mp 201° -202° C. Three moles of hydrogen was consumed in the hydrogenation, which corresponds formally to three hydrogenatable double bonds. From the results of the IR spectrum, the substance of composition $C_{20}H_{30}O_5$ has an OH group (strong band at 3450 cm^{-1}), an α,β-unsaturated lactone group (1748 cm^{-1}), an ester group (1727 cm^{-1}) and a double bond in the lactone ring (1681 cm^{-1}). The latter band is not present in the IR spectrum of badkhysinin. In our opinion this is due to the fact that in the compound under consideration one double bond is that of a methylene group attached to the lactone ring; on hydrogenation this bond migrates into the lactone ring and, thus, from being a primary-tertiary substituted bond becomes a tetra-substituted bond. This phenomenon, which has been observed repeatedly, is characteristic not only for badkhysinin but also for some other lactones [2-5].

The presence of a hydroxyl group in the substance of composition $C_{20}H_{30}O_5$ can be explained only by the rupture of an oxide ring, it being important to nice that the hydroxyl group that appears, which is undoubtedly secondary, is present in a five-membered ring. This was established by the oxidation of the substance concerned with chromic anhydride in acetone. This yielded us a substance $C_{20}H_{28}O_5$ with mp 124°-125° C, whose IR spectrum had maxima at 1743 cm^{-1} (combined band, of increased intensity, of a CO group of an unsaturated lactone and a CO group of a ketone with a five-membered ring), 1733 cm^{-1} (CO group of an ester), and 1681 cm^{-1} (tetra-substituted double bond in a lactone ring). This substance contained no OH group. The UV spectrum of the substance had maxima at λ 286 (log ε 1.7) and 224 mμ (log ε 4.38), which confirms the presence of a ketone CO group.

Saponification of the liquid substances of badkhysinin hydrogenated in ethanol gave a crystalline compound $C_{15}H_{24}O_4$ with mp 202°–203° C. A study of the latter showed the position of the oxide ring in the molecule of badkhysinin. The IR spectrum of this product has a broad band at 3500–3550 cm^{-1} (OH group) and a narrow band at 1755 cm^{-1} (CO group of a lactone). Oxidation of the substance with chromic anhydride in acetone led to the formation of a substance of composition $C_{15}H_{22}O_4$ with mp 197°–198° C, whose IR spectrum had maxima at 3548 cm^{-1} (OH group), 1765 cm^{-1} (CO group of a lactone), and 1718 cm^{-1} (CO group of a ketone with a seven-membered ring). The UV spectrum had a maximum at λ 296 mμ (log ε 1.33) which is characteristic for a nonconjugated ketone. These results show that the OH group that is esterified with angelic acid in badkhysinin is in the seven-membered ring, and the second hydroxyl, which is apparently tertiary (it is not oxidized by CrO_3), is at the junction of the five- and seven-membered rings or in a methyl group of the five-membered ring (if the arrangement of substituents in badkhysinin is similar to their arrangement in chamazulene or guaiazulene). Thus, the oxide ring on the five-membered ring could be at C_1—C_2 or C_3—C_{10}. The assumption of a bicyclic hydroazulene structure for badkhysinin is confirmed by the results of dehydrogenation with selenium of some products formed from badkhysinin after its hydrogenation and saponification, and also by reduction with $LiAlH_4$. At the end of this series of conversions, we obtained chamazulene, which enables the positions of the substituents on the lactone ring to be deduced.

The hydrogenation of badkhysinin with $PdCl_2/C$ in ethyl acetate leads to the formation of a saturated compound with retention of the oxide ring. The product is a substance with the composition $C_{15}H_{22}O_4$, mp 204°–205° C, whose IR spectrum has bands at 3550 cm^{-1} (OH group) and 1765 cm^{-1} (CO group of a lactone); there are no maxima characteristic for double bonds. Oxidation of the preceding compound with chromic anhydride in acetone gave a crystalline product $C_{15}H_{20}O_4$, with mp 179°–180° C. The IR spectrum of this substance exhibits bands at 1770 and 1714 cm^{-1} characteristic for the CO group of a lactone and the CO group of a seven-membered ring, respectively; there is no OH group. The UV spectrum [maximum 308 mμ (log ε 1.68)] confirms that the substance contains a nonconjugated CO group.

The lactone ring in badkhysinin is attached to the seven-membered ring possibly in the C_6—C_7 or the C_7—C_8 position, since an isopropyl group, which can be present only at C_7, participates in the formation of the lactone. This is shown by the fact that we obtained chamazulene.

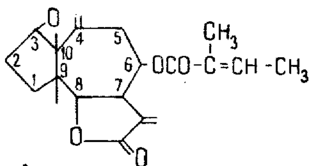
The position of the oxide ring at C_3—C_{10} is preferred in view of the fact that the NMR spectrum of badkhysinin has one singlet corresponding to 9.02 ppm, which may be interpreted as a CH_3 group located at a junction of the 5- and 7-membered rings at C_9 [6]. Thus, the position of the oxide oxygen is determined also by the fact that it is attached to secondary and tertiary carbon atoms, because derivatives with secondary and tertiary hydroxyl groups were obtained.

In view of the observation of the singlet mentioned, the question of the nature and arrangement of all the double bonds in the molecule of badkhysinin can be decided. As was shown previously, one double bond in badkhysinin is in the angelyl group and the second, a primary-tertiary double bond, is in the lactone ring. The third double bond, which is also primary—tertiary, is apparently in the C_4 position of the seven-membered ring, since otherwise the NMR spectrum of badkhysinin would exhibit, besides the singlet, the doublet characteristic for CH_2—CH. In an endeavour to show the position of the two primary—tertiary double bonds in badkhysinin or the product of its saponification by hydrogenation, we used the method of hydrogenation with deactivated Raney nickel.

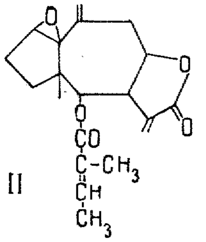
The hydrogenation of one double bond of badkhysinin gave a viscous liquid and a crystalline substance with the composition $C_{20}H_{24}O_5$ having mp 182°–183° C, which proved to be isobadkhysinin, differing from badkhysinin by the position of one double bond. The latter, at the CH_2 group of the lactone ring of badkhysinin, passes into the lactone ring. The presence of a terminal methylene group in isobadkhysinin is confirmed by the maxima at 1648 and 893 cm^{-1}; this showed the presence of two methylene double bonds in badkhysinin.

The liquid component was hydrogenated in the presence of a platinum oxide and was then saponified. This gave a small amount of a substance $C_{15}H_{22}O_4$ with mp 173°–175° C, whose IR spectrum had the bands of a hydroxyl (3500, 3400 cm^{-1}), a lactone ring (1740, 1728 cm^{-1}), and a tetra-substituted double bond in a lactone ring (1680 cm^{-1}). The substance did not absorb in the UV region. The same substance is readily obtained by hydrogenating the saponification product of badkhysinin (mp 185°–186° C) with deactivated Raney nickel. The process of formation of this substance is complex. In addition to the migration of one methylene double bond into the lactone ring and the hydrogenation of a second double bond, this substance contains a new hydroxyl group which is formed as a consequence of the opening of the oxide ring and is possibly tertiary. This was shown by oxidation of the substance obtained with chromic anhydride in acetone. The oxidation gave a product probably having the composition $C_{15}H_{20}O_4$ with mp 162°–164° C, whose properties, from the features of the UV spectrum [λ_{max} at 334 (log ε 1.7) and 242 mμ (log ε 3.8)] and the IR spectrum (bands at 3430, 1750, 1738, 1678, and 1610 cm^{-1}) show that the product is a hydroxyketolactone with a tertiary OH group (not oxidized by CrO_3) and a conjugated CO group in the seven-membered ring. The formation of a keto group conjugated with a double bond of the lactone ring makes it possible to establish the position of the OH group esterified with angelic acid in badkhysinin as at C_6 or C_8.

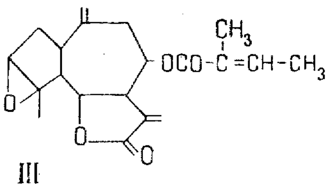
Thus, possible formulas for badkhysinin are (I), (II), (III), and (IV), of which (I) and (II) are the most probable.



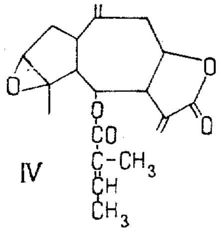
I



II



III



IV

Experimental

Preparation of badkhysinin. After the isolation of badkhysin, the resin (10 g) was dissolved in a mixture of benzene and petroleum ether (1:1) and was then chromatographed on alumina (565 g, activity grade III–IV) in a column 100 cm high. The substances were eluted from the column with petroleum ether, petroleum ether + benzene (1:1), benzene, benzene + ether (1:1), and ether. Fractions of 25–50 ml were collected. Fractions 10–35 were viscous liquids which partially crystallized from solution in a mixture of ether and petroleum ether. This gave 2 g of badkhysinin with mp 104°–105° C (from a mixture of ether and petroleum ether and then from aqueous ethanol), $[\alpha]_D$ −212.4° C (c 2.6; alcohol). UV spectrum: λ_{max} 214 mμ (log ε 3.628); IR spectrum (IKS-14, in paraffin oil): 1765, 1708, 1668, 1640, 919, 892, 818 cm^{-1}. No OH group or ketonic CO groups were present.

Found, %: C 69.59, 69.45; H 7.15, 7.16. Calculated for $C_{20}H_{24}O_5$, %: C 69.75; H 7.02.

Saponification of badkhysinin. A solution of 0.5 g of badkhysinin in 10 ml of methanol was heated with 10 ml of 12% caustic potash for 20–30 min, diluted with water, acidified, and extracted with ether. The ethereal layer was shaken with 1–2% sodium carbonate solution, dried with sodium sulfate, and concentrated. Crystals were deposited in a yield of 20% with mp 185°–186° C. IR spectrum: 3500, 1757, 1665, 1650, 916, 895, 809, 803 cm^{-1}

Found, %: C 68.18, 68.33; H 7.23, 7.12. Calculated for $C_{15}H_{18}O_4$, %: C 68.64; H 6.86.

The sodium carbonate solution was acidified and extracted with ether. The ethereal layer was dried with sodium sulfate and the ether was distilled off. The residue consisted of an oil which crystallized, mp 44°–45° C (from aqueous alcohol or by sublimation). In admixture with angelic acid, the substance gave no depression of the melting point.

Hydrogenation of badkhysinin with PtO_2. A solution of 1.5 g of badkhysinin in 50 ml of ethanol was hydrogenated with PtO_2 (0.2 g). The hydrogenation consumed 290 ml of hydrogen (about 3 moles). The mixture was filtered, and the alcohol was distilled off. The resulting viscous oil was chromatographed on a column of alumina (activity grade II, height of column 50 cm), and was eluted with a mixture of petroleum ether and ether (1:1) and in a ratio of 1:3, 50-ml fractions being collected. Besides liquid substances, a crystalline substance was obtained. This was recrystallized from ether, mp 201°–202° C, $[\alpha]_D$ + 19.29° C (c 1.3; chloroform); IR spectrum: 3450, 1748, 1727, 1681 cm^{-1}.

Found, %: C 68.39, 68.56; H 8.69, 8.68. Calculated for $C_{20}H_{30}O_5$, %: C 68.57; H 8.57.

The liquid substances were saponified with 2.5 g of caustic potash in 20 ml of methanol for 15 min on a water bath. After 20 hr, the mixture was acidified and extracted with chloroform, and the solvent was distilled off. The residue was dissolved in chloroform and was chromatographed through a 5-cm layer of alumina (inactive). From a mixture of ether and petroleum ether, crystals were deposited with mp 202°–203° C (from ether). IR spectrum: 3500–3550 (broad band) and 1755 cm^{-1}. The mother liquor contained a noncrystallizing oil.

Found, %: C 67.02, 67.09; H 9.13, 8.99. Calculated for $C_{15}H_{24}O_4$, %: C 67.16; H 8.96.

Oxidation of the substance with mp 201°–202° C. A solution of 0.3 g of the substance in 5 ml of acetone was mixed with a solution of 0.5 g of chromic anhydride in 2.5 ml of 80% acetone. After 30 min, the mixture was diluted with water and extracted with chloroform, then the chloroform extract was washed with water. Evaporation of the chloroform yielded a viscous oil which crystallized from a mixture of ether and petroleum ether on cooling, mp 124°–125° C. UV spectrum: λ_{max} 224 (log ε 4.38) and 286 mμ (log ε 1.7); IR spectrum: 1743, 1733, and 1681 cm^{-1}. No OH group was present.

Found, %: C 69.10, 68.90; H 8.06, 8.03. Calculated for $C_{20}H_{28}O_5$, %: C 68.94; H 8.10.

Oxidation of the substance with mp 202°–203° C. 0.4 g of chromic anhydride in 0.5 ml of water and 3 ml of acetone was added dropwise to a solution of 0.1 g of the substance in 5 ml of acetone. After 4 hr, the mixture was diluted with water and was evaporated under vacuum without heating; the residue was extracted with chloroform and washed with water, and the extract was evaporated to small bulk and filtered through a 5-cm layer of alumina (inactive). The chloroform was distilled off and the residue was dissolved in a mixture of ether and petroleum ether. On cooling, a crystalline substance with mp 197°–198° C was deposited. UV spectrum: λ_{max} 296 mμ (log ε 1.334); IR spectrum: 3548, 1765, 1718 cm^{-1}.

Found, %: C 68.03, 68.00; H 8.42, 8.32. Calculated for $C_{15}H_{22}O_4$, %: C 67.64; H 8.33.

Hydrogenation of badkhysinin with $PdCl_2/C$. A solution of 0.7 g of badkhysinin in 15 ml of ethyl acetate was hydrogenated with 0.5 g of $PdCl_2$ on carbon (50%). The amount of hydrogen added was 157 ml. The mixture was filtered, the solvent was distilled off, and the residue, a yellow oil, was chromatographed as described above. This gave a small amount of a substance with mp 201°–202° C, identical with that obtained previously. The residue, a viscous oil (0.3 g), was saponified with 0.7 g of caustic potash in 15 ml of 65% methanol for 10 min on a water bath. After 20 hr, the solution was acidified and was extracted with chloroform. The residue from the distillation of the chloroform was dissolved in ether and the solution was filtered through a 5-cm layer of alumina (inactive). A substance with mp 204°–205° C (from ether) crystallized from a mixture of ether and petroleum ether. IR spectrum: 3550, 1765, 888 cm^{-1}.

Found, %: C 67.55, 67.57; H 8.18, 8.27. Calculated for $C_{15}H_{22}O_4$, %: C 67.67; H 8.27.

Oxidation of the substance with mp 204°–205° C. A solution of 0.3 g of chromic anhydride in 2–3 drops of water and 2 ml of acetone was added to a solution of 0.1 g of the substance in 5 ml of acetone. After 24 hr, the mixture was diluted with water, the acetone was evaporated off under vacuum, the solution was extracted with chloroform, and the extract was washed with water. The solvent was distilled off. The residue in chloroform solution was filtered through a 5-cm layer of inactive alumina. The residue after the removal of the chloroform was crystallized from a mixture of ether and petroleum ether, mp 179°–180° C. UV spectrum: λ_{max} 308 mμ (log ε 1.68). IR spectrum: 1770 and 1714 cm^{-1}. No OH group.

Hydrogenation of badkhysinin with deactivated Raney nickel. 1 g of badkhysinin was dissolved in 10 ml of alcohol and hydrogenated with presence of 0.2 g of freshly-prepared deactivated Raney nickel. Hydrogenation ceased after the addition of 1 mole of hydrogen (72 ml). The filtered solution was evaporated, a few drops of water was added, and the solution was cooled. The precipitate was recrystallized from alcohol. Yield 20%, mp 182°–183° C. IR spectrum: 1754, 1710, 1690, 1648, 890 cm^{-1}. No OH or ketonic CO groups were found.

Found, %: C 69.31, 69.58; H 7.29, 7.30. Calculated for $C_{20}H_{24}O_5$, %: C 69.75; H 7.02.

The liquid substances in alcoholic solution were hydrogenated with in the presence of PtO_2, and were saponified and acidified in the usual way. A substance with mp 173°–175° C (from ether) crystallized from a mixture of ether and petroleum ether. The substance did not absorb in the UV region (224–400 mμ). The IR spectrum exhibited bands at 3500, 3400, 1740, 1728, and 1680 cm^{-1}.

Found, %: 67.95, 67.86; H 8.11, 8.32. Calculated for $C_{15}H_{22}O_4$, %: C 67.95; H 8.33.

The substance with mp 173°–175° C is also formed by the hydrogenation with Raney nickel of the saponification product of badkhysinin (mp 185°–186° C).

Oxidation of the substance with mp 173°–175° C. A solution of 0.3 g of CrO_3 in 3 drops of water and 2 ml of acetone was added to a solution of 0.1 g of the substance in 2 ml of acetone. After 5 min, the mixture was diluted with water and extracted with chloroform. The chloroform layer was washed with water and evaporated. A substance with mp 162°–164° C crystallized from a mixture of ether and petroleum ether. UV spectrum: λ_{max} 334 (log ε 1.794) and 242 mμ (log ε 3.854), and the IR spectrum had bands at 3430, 1750, 1738, 1678, and 1610 cm^{-1}.

Isolation of chamazulene. A solution in 20 ml of dry ether of 0.1 g of a mixture of the substances with mp 202°–203° C and 204°–205° C was treated with 0.1 g of $LiAlH_4$ and heated on a water bath for 6 hr; then moist ether was added, followed by a saturated solution of sodium sulfate. The resulting mixture was extracted with ether, and the extract was dried over sodium sulfate and filtered, and the solvent was distilled off. The residue, a viscous oil, was dehydrogenated with 0.1 g of selenium at 250°–300° C for 10 min, was shaken with petroleum ether, and the solution was filtered through a 10-cm layer of alumina (activity grade II). The blue liquid was evaporated. On chromatography in petroleum ether solution on alumina (activity grade II), the substance obtained had a R_f value (0.75) identical with the R_f value of authentic chamazulene.

The analyses were carried out by E. A. Sokolova. The IR spectra were taken by T. V. Bukreeva; the NMR spectrum of badkhysinin was measured in the Lensovet Technological Institute.

Summary

A sesquiterpene lactone with the composition $C_{20}H_{24}O_5$, mp 104°–105° C, $[\alpha]_D$ −212.4° C (alcohol) has been isolated from the roots of Ferula oopoda Boiss. and has been called badkhysinin. Badkhysinin is an ester of angelic acid and an epoxyhydroxylactone $C_{15}H_{18}O_4$ with mp 185°–186° C apparently related to guaianolide with a hydrocarbon skeleton of irregular structure. A number of possible structural formulas for badkhysinin are given.

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