# STEREOCHEMISTRY OF GUAIANOLIDES OF *Ferula oopoda*

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The stereochemistries of badkhyzin, isobadkhyzin, ferulidin, and ferulin, guaianolides from *Ferula oopoda* (Boiss. et Buhse) Boiss. have been established. The stereochemistries of badkhyzin and of 8-hydroxyachillin (at C-5, C-6, C-7, C-8, C-11) are identical. When the lactone ring is opened with alkalis, badkhyzin isomerizes only at the C-6 center.

Certain aspects of the stereochemistry of badkhyzin and isobadkhyzin have been reported previously [1]. On the basis of the spin–spin coupling constants (SSCCs), isobadkhyzin was assigned to the isomerization products of badkhyzin. It differs from the latter by the stereochemistry of the C-6 and C-8 asymmetric centers. Ferulin [2] and ferulidin [3] have also been isolated from the resin of the roots of *Ferula oopoda* (Boiss. et Buhse) Boiss. It is possible to isolate them only from roots that have become moldy on storage. Simultaneously, the amount of badkhyzin and other lactones in the moldy roots decreases sharply. On the basis of these facts it may be assumed that ferulin and ferulidin are transformation products of badkhyzin. This is also shown by the results of the saponification of badkhyzin: a substance was obtained (in small amount) with the formula $C_{15}H_{16}O_3$, mp 184-186°C, the IR spectrum of which showed the maxima of the lactone ring (1780 $cm^{-1}$) of a cyclopentenone (1690 $cm^{-1}$), and of conjugated double bonds (1630, 1600 $cm^{-1}$). The UV spectrum also confirmed the presence of a conjugated system ($\lambda$ 310, 258, and 244 nm; log $\varepsilon$ 3.83, 4.35, and 4.32, respectively). A comparison of the IR and UV spectra of the substance obtained and those of ferulin [4] showed their identity.

On the other hand, on acetylation ferulidin formed ferulin. Consequently, the stereochemistries of ferulin, ferulidin, and badkhyzin at C-6, C-7, and C-11 are identical.

On brief treatment with alkalis, badkhyzin is converted into isobadkhyzin [1] in which the stereochemistries at C-6 and C-8 have changed. This conclusion was made on the basis of the NMR spectrum of isobadkhyzin recorded in deuterated chloroform solution, where the signals of the protons of the lactone ring and of those at the ester groups were superposed, and therefore it is impossible to consider the structure of each signal separately. However, when the spectrum was taken in benzene solution, they diverged at 4.33 ppm (H-6) and 4.80 ppm (H-8). The latter signal appeared in the form of a multiplet the SSCCs ($J_1 = 4, J_2 = J_3 = 9$ Hz) of which differ only slightly from those for H-8 of badkhyzin ($J_1 = 4$, $J_2 = J_3 = 10$ Hz). This means that on treatment with alkali badkhyzin isomerizes only at the C-6 center.

The correctness of this point of view is also confirmed by the nature of the splitting and the SSCC of the lactone proton of isobadkhyzin, which gives a signal in the form of a quartet with constants of 2 and 4 Hz as compared with 7.5 and 10 Hz in badkhyzin. Furthermore, the signal of the lactone proton (H-8) in the NMR spectra of ferulin [2] and ferulidin [3] appears in the form of a sextet ($J_1 = 4, J_2 = J_3 = 10$ Hz) and its substructure resembles that of the signal caused by hydrogen at C-8 of badkhyzin [5] and isobadkhyzin. This shows that the lactone ring in the ferulin and ferulidin molecules is also oriented in the same way as the ester group in badkhyzin and isobadkhyzin. This is supported by the formation (on the saponification of grossmisin) of anhydrogrossmisin [6] with the composition $C_{15}H_{16}O_3$, mp 184-186°C, the physicochemical properties of which resemble those of ferulin [2]. The UV and NMR spectra of ferulin and of anhydrogrossmisin coincide completely:

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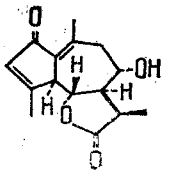
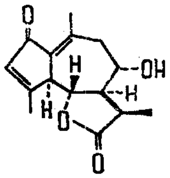
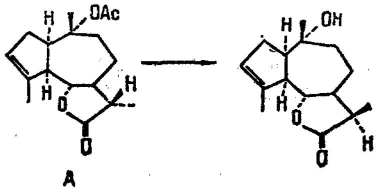
| Compound | $CH_3-CH\langle$ | $CH_3C=$ | –CH–O– (lactone) | –CH= at C-2 | –CH= at C-5 | UV spectrum |
|---|---|---|---|---|---|---|
| Ferulin | d 1,41, J=6Hz | s 2,18, s 2,47 | m 4,43 | s 6,18 | d 5,92 | 244 nm, log ε 4,32; 258 nm, log ε 4,35 |
| Anhydrogrossmisin | d 1,40, J=6Hz | s 2,16, s 2,47 | m 4,40 | s 6,15 | d 5,89 | 243 nm, log ε 4,279; 258 nm, log ε 4,273 |

In view of the identity of anhydrogrossmisin and ferulin, the stereochemistries at C-7, C-8, and C-11 have been established. Grossmisin [6] and austricin [7] are stereoisomers and differ only in the position of the methyl group at C-11: in austricin it has the α orientation and in grossmisin, just as in achillicin [8], the β orientation.

Nevertheless, the composition, melting point, $[\alpha]_D$ value and structure of grossmisin and its acetyl derivative agree with those of 8-hydroxyachillin and its acetate (see below), and the spectral characteristics of the materials compared are also identical [6, 9].

| Compound | Composition | mp, °C | $[\alpha]_D$, deg | Structure | Literature |
|---|---|---|---|---|---|
| Grossmisin | $C_{15}H_{18}O_4$ | 156–158 | +115,26 |  | 6 |
| Grossmisin acetate | $C_{17}H_{20}O_5$ | 190–191,5 | +97,9 | | |
| 8-Hydroxyachillin | $C_{15}H_{18}O_4$ | 161–162 | +110 | | |
| 8-Hydroxyachillin acetate | $C_{17}H_{20}O_5$ | 193–194 | +116 |  | 8 |

Thus, it may be concluded that grossmisin is identical with 8-hydroxyachillin. As is known, on passing from badkhyzin to ferulin the position of the lactone ring changes. Consequently, the probability of a change in the stereochemistry of the methyl group at C-11 is not excluded; furthermore, in the synthesis of achillin [8] by boiling olefin A in butanolic KOH solution for 2 h in an atmosphere of nitrogen, isomerization of the methyl group attached to the lactone ring takes place.



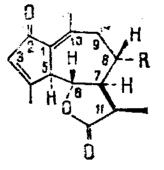
However, apparently, when highly conjugated systems such as badkhyzin [5], 8-hydroxyachillin [9], and austricin [7, 10], etc., are heated, in spite of the change in the position of the lactone ring, the stereoposition of the $CH_3$ group at C-11 remains as before. This is shown by the following facts: austricin, like 8-hydroxyachillin (grossmisin) forms an anhydro derivative. Anhydroaustricin (mp 207-208°C) differs from anhydrogrossmisin (mp 184-186°C). As stated by Konovalova et al. [6], their NMR spectra differ only by the position of the signal of the secondary methyl group. Furthermore, although in anhydroaustricin and in anhydrogrossmisin the posititions of the lactone rings have changed, the stereochemistry of the C-11 methyl group has remained unchanged. Otherwise it would be possible to effect a transition from austricin to 8-hydroxyachillin via anhydro derivatives. Another example: On treatment with 0.2 N methanolic NaOH solution, achillin forms an acid [8] with three double bonds conjugated with a ketone group, the third double bond arising through the dehydration of the hydroxy group obtained on the opening of the lactone ring. However, the methyl at C-11 retains it stereoposition.

As shown previously [5], the saponification of the di- and tetrahydro derivatives of badkhyzin forms a ketodiene lactone with the composition $C_{15}H_{18}O_3$, mp 148-149°C. In the NMR spectrum of the latter, in addition to two doublets of secondary methyl groups (1.33 ppm, J = 7 Hz, $CH_3-$ at C-11; and 1.19 ppm, J = 6 Hz, $CH_3-$ at C-4), the singlet of a vinylmethyl group (2.24 ppm, $CH_3-C=$ at C-10), and the signal of vinyl protons with an area of two proton units (6.3 ppm), the lactone proton appears in the form of a quartet (at 4.86 ppm) with SSCCs of 10 and 7 Hz, which shows the transposition (as in badkhyzin) of the protons at C-5, C-6, and C-7 relative to one another. The Adams hydrogenation of the ketodiene lactone led to a ketolactone with the composition $C_{15}H_{22}O_3$, mp 145-147°C (from aqueous ethanol, $\nu_{max}$ 1770 and 1730 $cm^{-1}$), identified by its IR spectrum and melting point as tetrahydroachillin [9].

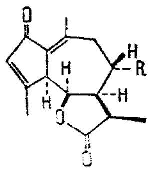
In view of this, the stereochemistries at C-5, C-6, C-7, and C-11 of badkhyzin could be considered as established. In order to exclude the probability of a change in the stereochemistry of the methyl group attached to the lactone ring during the saponification of badkhyzin derivatives, the di- and tetrahydro derivatives of the latter were treated with 5% aqueous KOH solution. After acidification, they were recovered unchanged. Their IR spectra and melting points coincided in detail with those of the corresponding initial compounds. Mixtures of the samples being compared gave no depression of the melting points. This means that isomerization had taken place at none of the asymmetric centers.

On the basis of the experimental facts and the results given in the literature, it may be considered that the methyl group at C-11 in the molecules of badkhyzin, isobadkhyzin, ferulidin, and ferulin have the β orientation just as in achillin [8] and 8-hydroxyachillin (Grossmisin [6, 8]). The stereochemistry of ferulidin at C-5, C-6, C-7, and C-8 also coincides with that of badkhyzin. This is shown by the SSCCs of the protons at C-5, C-6, and C-7 [3] and the production from badkhyzin of ferulin, which is formed by the acetylation of ferulidin.

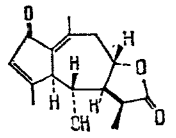
Thus, for the guaianolides of *Ferula copoda* (Boiss. et Buhse) Bois. badkhyzin, isobadkhyzin, ferulidin and ferulin the stereochemistries (I), (II), (III), and (IV), respectively, are proposed.



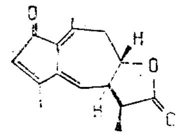
I



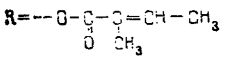
II



III



IV



$R=-O-\underset{\underset{O}{\|}}{C}-\underset{\underset{CH_3}{|}}{C}=CH-CH_3$

## EXPERIMENTAL

IR spectra were taken on a UR 20 spectrophotometer, UV spectra on an SF-4a instrument, and NMR spectra on a Varian HA-100D spectrometer with TMS as internal standard; the chemical shifts are given in the δ scale.

Saponification of Badkhyzin. With heating, 1 g of badkhyzin was dissolved in 500 ml of 0.5% aqueous KOH solution. After it had dissolved, the solution was kept at room temperature for 24 h. Then is was acidified with dilute sulfuric acid and was left to stand for 30 min. The resulting precipitate was filtered off, washed to a neutral reaction with water, dried, dissolved in 10 ml of chloroform, and chromatographed on a column of $Al_2O_3$ (40 × 3.5 cm). The volume of each fraction was 100 ml. Elution was performed with petroleum ether, benzene, and chloroform. The last fraction eluted by benzene yielded a very small amount of a substance with the composition $C_{15}H_{16}O_3$, mp 184-186°C (from aqueous ethanol), which was identified as ferulin by a comparison of IR spectra and from the absence of a depression of the mixed melting point.

Hydrogenation of the Ketodiene Lactone with mp 148-149°C. The hydrogenation of 0.05 g of the substance dissolved in 5 ml of ethanol was carried out with 0.03 g of $PtO_2$. The consumption of hydrogen was 10.5 ml. One double bond requires 4.55 ml of hydrogen. The ethanolic solution was filtered and the ethanol was distilled off. The residue was recrystallized from aqueous ethanol; mp 145-147°C.

Treatment of Di- and Tetrahydrobadkhyzins with Alkali. A solution of 0.08 g of the substance in 5 ml of 5% aqueous KOH was heated in the waterbath for 1 min and was left at room temperature for 3 min. Then it was acidified with dilute hydrochloric acid and extracted with chloroform. The chloroform layer was washed twice with water, dried over $Na_2SO_4$, filtered, and evaporated. The residue was crystallized from aqueous ethanol: mp 167-169 and 198-199°C, respectively.

## SUMMARY

1. The stereochemistries of badkhyzin, isobadkhyzin, ferulidin, and ferulin, guaianolides of *Ferula copoda* (Boiss. et Buhse) Boiss. have been established.

2. It has been established that the stereochemistries of badkhyzin and of 8-hydroxyachillin (at C-5, C-6, C-7, C-8, and C-11) are identical.

3. It has been shown that when the lactone ring is opened with alkalis badkhyzin isomerizes at the C-6 center.

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