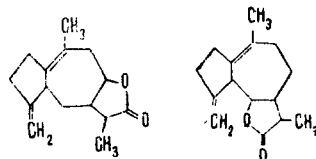


THE STRUCTURE OF GRILACTONE

N. P. Kir'yalov, T. V. Bukreeva,
and V. A. Gindin

UDC 547.913.5 + 547.473.2

From the roots of the giant fennel *Ferula grigorjevii* B. Fedtsch. we have previously isolated grilactone (I), $C_{15}H_{20}O_2$, mp 79.5–81°C, $[\alpha]_D -125^\circ C$, for which the probable structural formulas A and B were proposed.



In both formulas for grilactone the presence of a tertiary–tertiary double bond was assumed, since the oxidation of the dihydroxy dihydrolactone with chromium trioxide gave a ketone with a five-membered ring (band at 1743 cm^{-1} in the IR spectrum). The absence from the oxidation product of an oxo group in an aliphatic chain was explained by the assumption that instead of this an oxide ring arose (anomalous oxidation). It was found later that on oxidation with potassium permanganate grilactone forms, in addition to a tetrahydroxy lactone (II), $C_{15}H_{24}O_6$, mp $245^\circ C$, a monohydroxy derivative (III) with the composition $C_{15}H_{20}O_4$, mp $212\text{--}213^\circ C$, mol. wt. 264 (mass spectrometry). In the NMR spectrum of this substance it is easy to detect a triplet signal with $\delta\ 4.1$ ppm corresponding to a geminal proton associated with a hydroxyl (Table 1 and Fig. 1b). In the acetate of this substance (see Table 1 and Fig. 1c), the corresponding signal has shifted downfield and appears at $\delta\ 5.25$ ppm. This shows that in the monohydroxy derivative of grilactone the OH group is secondary and, consequently, in grilactone there is no tertiary–tertiary double bond. In view of the facts that one of the methyl groups of grilactone is present at a double bond and that the oxidation product contains a secondary OH group, we assumed that in addition to a primary–tertiary double bond grilactone also has a secondary–tertiary double bond. This was shown to be correct and was subsequently confirmed repeatedly by experiment. The position of the secondary–tertiary double bond is most probably in the five-membered ring since the monohydroxy derivative of grilactone gave on oxidation with chromium trioxide an oxo derivative $C_{15}H_{18}O_4$ with mp $208^\circ C$ in the IR spectrum of which an absorption maximum appeared at 1745 cm^{-1} , which is characteristic for an oxo group in a five-membered ring. On oxidation with chromium trioxide, the hydroxy derivative of the dihydrolactone formed an oxo derivative $C_{15}H_{24}O_4$ with mp $218^\circ C$ showing a maximum (Fig. 2) at 1743 cm^{-1} in the IR spectrum. Thus, the secondary–tertiary double bond is located in the five-membered ring at $C_1\text{--}C_2$. It follows from this that the ring methylene group is not located in the five-membered ring but in the seven-membered ring, at C_4 .

The absence from the hydroxy derivatives of a second free hydroxyl (just as in their monoacetates and monoketones) or of a hydroxyl difficult to detect because it is involved in a strong hydrogen bond makes it possible to suggest that the fourth O atom is an oxide atom. A mass-spectrometric determination of the molecular weight of the oxo compound $C_{15}H_{20}O_4$ with mp $218^\circ C$, mol. wt. 264, and of other products confirms the reliability of the interpretation according to which the permanganate oxidation of the guaianolides studied forms oxides.

A comparison of the NMR spectra of grilactone, isogrilactone and dihydrogrilactone with the corre-

V. L. Komarov Botanical Institute, Academy of Sciences of the USSR. Translated from *Khimiya Prirodnikh Soedinenii*, No. 4, pp. 446–451, July–August, 1972. Original article submitted December 11, 1971.

© 1974 Consultants Bureau, a division of Plenum Publishing Corporation, 227 West 17th Street, New York, N. Y. 10011. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without written permission of the publisher. A copy of this article is available from the publisher for \$15.00.

TABLE 1

| Substance | mp, °C | C ₁ -CH ₃ | C ₂ -H | Acetate CH ₃ | C ₄ -CH ₃ | C ₁ -CH ₂ | C ₂ -H | C ₃ -H | C ₄ -H | C ₅ -CH ₃ |
|----------------------------------|---------|---------------------------------|---|-------------------------|---------------------------------|---------------------------------|-------------------|---|---|---------------------------------|
| Grilactone | 80 | d 1.84 (3H) J=2 Hz | br. s 5.45 (1H) | | br. s 4.75 (2H) | | | q 4.35 (1H) J ₁ =6; J ₂ =10 Hz | | d 1.14 (3H) J=7 Hz |
| Hydroxygrilactone | 212-213 | s 1.5 (3H) | t 4.1 (1H) J=8 Hz | | br. s 4.83 (2H) | | | d 4.27 (1H) J=8 Hz | | d 1.15 (3H) J=7 Hz |
| Hydroxygrilactone acetate | 185 | s 1.45 (3H) | t 5.2 (1H) J=8.5 Hz | s 2.1 (3H) | d 4.85 (2H) J=4 Hz | | | d 4.25 (1H) J=5 Hz | d 3.3 (1H) J=7 Hz | d 1.10 (3H) J=7 Hz |
| Dihydrogrilactone | 135 | d 1.66 (3H) J=3 Hz | d 5.44 (1H) J=12 Hz | | | | | t 4.7 (1H) J=4 Hz | | d 1.19 (3H) J=7 Hz |
| Hydroxydihydrogrilactone | 210-211 | s 1.45 (3H) | t 4.1 (1H) J=7 Hz | | | | | d 4.3 (1H) J=8 Hz | | d 1.20 (3H) J=7 Hz |
| Hydroxydihydrogrilactone acetate | 165 | s 1.45 (3H) | t 5.07 (1H) J=8 Hz | s 2.1 (3H) | | | | d 4.3 (1H) J=6 Hz | | d 1.10 (3H) J=7 Hz |
| Oxodihydrogrilactone | 218 | s 1.5 (3H) | | | | | | d 4.35 (1H) J=6 Hz | | d 1.25 (3H) J=7 Hz |
| Isogrilactone | 110 | s 1.75 (3H) | br. s 5.45 (1H) | | d 4.85 (2H) J=12 Hz | | | J ₁ =8; J ₂ =11.5 Hz | | d 1.20 (3H) J=7 Hz |
| Hydroxyisogrilactone | 169-170 | s 1.50 (3H) | q 4.1 (1H) J ₁ =6; J ₂ =8 Hz | | s 4.9 (2H) | | | d 4.6 (1H) J=8 Hz | q 3.2 (1H) J ₁ =5; J ₂ =9 Hz | d 1.20 (3H) J=7 Hz |
| Hydroxyisogrilactone acetate | 172-173 | s 1.45 (3H) | 5.2 (1H) J=7.5 Hz | s 2.1 (3H) | d 4.9 (2H) J=4 Hz | | | d 4.5 (1H) J=9 Hz | q 3.3 (1H) J ₁ =4; J ₂ =9 Hz | d 1.20 (3H) J=7 Hz |

Note. s - singlet; br.s - broadened singlet; d - doublet; t - triplet; q - quartet.

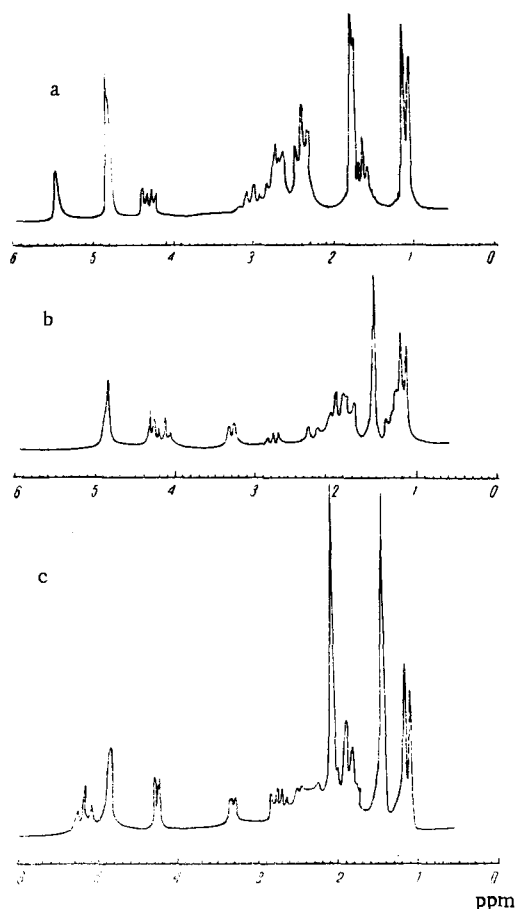
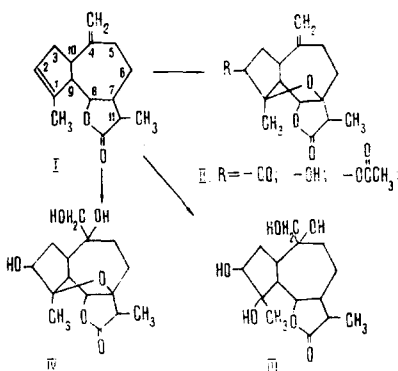


Fig. 1. NMR spectra of grilactone (a), of monohydroxygrilactone with mp 212-213°C (b), and of monohydroxygrilactone acetate with mp 184-185°C (c).

sponding spectra of their hydroxy derivatives also confirmed the oxide nature of the fourth oxygen atom in all the monohydroxy derivatives obtained and answered the question of the position of this oxide. The quartet signal with δ 4.3-4.5 ppm in the NMR spectra of grilactone, isogrilactone, and dihydrogrilactone is due to the proton at C_8 , which is connected with the oxygen atom of the lactone ring and with the protons at C_7 and C_9 . This explains the fact that the signal of the protons at C_8 can appear in the δ 4-5 ppm region in the form of a triplet or a quartet. However, in all the monohydroxy derivatives of these compounds and also their acetyl and oxo derivatives we observed in the δ 4.3-4.6 ppm region not a quartet or a triplet but a clear doublet signal (1 H). The different nature of the splitting of the signal is explained by the assumption that in the neighborhood of the protons at C_8 in the monohydroxy derivatives studied there is one vicinal proton, and not two, as in the initial substances for oxidation. The doublet nature of the signal at C_8 can be explained by the formation of an α - or a γ -oxide ring. We tend to consider that a γ -oxide is formed, since these substances are readily produced and are fairly stable to acid reagents. Furthermore, in the monohydroxy derivatives of the guaianolides studied there is a doublet or quartet signal in the δ 3.2-4 ppm region which may be ascribed to a proton at C_9 . Consequently, the proton at C_9 does not participate in the formation of the oxide ring. This can mean that a γ -oxide is formed, and the proton at C_7 plays an important part in its appearance. It may be assumed that other guaianolides, including those having several functional groups, may also form γ -oxides on oxidation.



EXPERIMENTAL

The IR spectra of the substances were taken on a UR-10 spectrometer (paraffin oil) and the NMR spectra on a Varian HA-100-D-15 spectrometer (deuteriochloroform) with HMDS as the internal standard (see Table 1).

The properties of the grilactone used for the investigation were identical with those of the sample investigated previously [1] (see Table 1).

Oxidation of Grilactone. A solution of 1 g of the substance in 60 ml of acetone was gradually treated at room temperature with 3 g of $KMnO_4$ in 60 ml of water. After decoloration, the solution was filtered, and the filtrate was evaporated to small volume. The precipitate that deposited was extracted with chloroform, and the insoluble part was recrystallized from ethanol, mp 245°C. The yields varied between 20 and

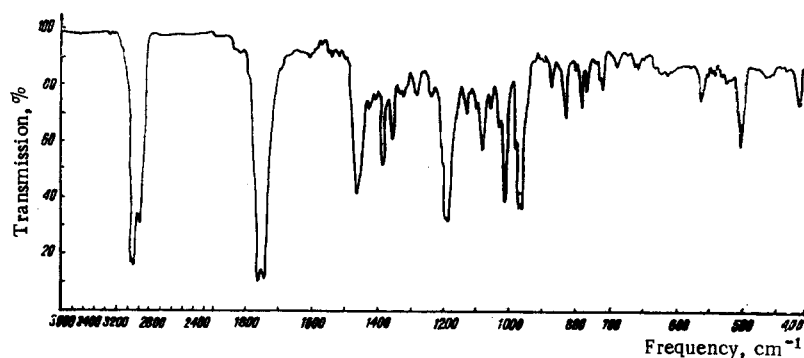


Fig. 2. IR spectrum of the oxo dihydrolactone with mp 218°C.

50%. The product was almost insoluble in CHCl_3 and ether. IR spectrum, cm^{-1} : 3450, 3300, 3250 (OH group), 1750 (lactone CO); no maxima in the 3100–3000, 1700–1600, and 900–800 cm^{-1} regions.

Found %: C 60.31, 60.36; H 7.8, 7.9. $\text{C}_{15}\text{H}_{24}\text{O}_6$. Calculated %: 60.00; H 8. Mol. wt. 300 (mass spectrometry).

The chloroform-soluble part of the oxidation products was chromatographed on Al_2O_3 (inactive) and was washed with chloroform. Crystals deposited in the form of needles with mp 212–213°C (from 80% ethanol). Yield 10–30%. IR spectrum cm^{-1} : 3550 (OH group), 3100 ($\text{CH}_2=$), 1780 (lactone CO), 1650, 900 ($\text{CH}_2=$).

Found %: C 68.05, 68.14; H 7.63, 7.74. $\text{C}_{15}\text{H}_{20}\text{O}_4$. Calculated %: C 67.8; H 7.57. Mol. wt. 264 (mass spectrometry).

Acetylation of the Substance with mp 212–213°C. In 4 ml of a mixture of pyridine and acetic anhydride (1 : 1), 0.2 g of the substance was heated in the water bath for 1 h, and the mixture was then evaporated and the residue was chromatographed on Al_2O_3 (inactive). The first fractions of eluate deposited colorless needles with mp 184–185°C (from ethanol). IR spectrum cm^{-1} : 3100 ($\text{CH}_2=$), 1785 (lactone CO), 1740 (acetyl CO), 1645, 900 ($\text{CH}_2=$).

Found %: C 66.64, 66.74; H 7.03, 7.24. $\text{C}_{17}\text{H}_{22}\text{O}_5$. Calculated %: C 66.66; H 7.19. Mol. wt. 306 (mass spectrometry).

Oxidation of the Substance with mp 212–213°C. A solution of 100 mg of the substance in 1 ml of CH_3COOH was treated with 100 mg of CrO_3 in 2 ml of 50% CH_3COOH , and the mixture was diluted with water. The precipitate that deposited was filtered off and chromatographed on inactive Al_2O_3 , and the chloroform was evaporated off. This gave needles with mp 208–209°C (from ethanol). IR spectrum, cm^{-1} : 1780 (lactone CO), 1745 (ketone CO in a five-membered ring), 3100, 1660, 900 ($\text{CH}_2=$). No absorption bands of OH groups were found.

Found %: C 68.45, 68.65; H 7.1, 6.95. $\text{C}_{15}\text{H}_{18}\text{O}_4$. Calculated %: C 68.7; H 6.87.

The Dihydrolactone. The dihydrolactone (V), $\text{C}_{15}\text{H}_{22}\text{O}_2$, mp 135°C, used for the oxidation was obtained as described previously [1]. IR spectrum cm^{-1} : 3050, 1770, 1660, 800. There was no absorption band at 900 cm^{-1} .

Oxidation of the Dihydrolactone. The substance (1 g) was oxidized with KMnO_4 as described previously [1]. Needles deposited with mp 210–211°C (from ethanol). IR spectrum cm^{-1} : 3500 (OH group), 1770 (lactone CO group); no absorption bands appeared in the 3000–3100, 1600–1700, and 800–900 cm^{-1} regions of the spectrum.

The acetylation of the substance with mp 210–211°C in a mixture of pyridine and acetic anhydride (1 : 1) gave an acetate $\text{C}_{17}\text{H}_{24}\text{O}_5$ with mp 165°C (from ethanol).

The chromium trioxide oxidation of 0.2 g of the substance with mp 210–212°C, performed in the same way as for the hydroxy derivative of grilactone, gave ketone (VII), $\text{C}_{15}\text{H}_{20}\text{O}_4$, with mp 218°C (from ethanol). Mol. wt. 264 (mass spectrometry). IR spectrum, cm^{-1} : 1765 (lactone CO), 1743 (CO of a ketone with a five-membered ring); no absorption bands were found in the 3100–3000, 1700–1600, and 900–800 cm^{-1} regions of the spectrum.

Oxidation of Isogrilactone. The oxidation of 1 g of the substance with mp 110°C was performed under the same conditions as for grilactone. A chloroform-soluble product was isolated, and it was purified by chromatography on inactive Al_2O_3 , chloroform elution giving the monohydroxy derivative $\text{C}_{15}\text{H}_{20}\text{O}_4$ with mp 169-170°C (from ethanol). Mol. wt. 264 (mass spectrometry). IR spectrum, cm^{-1} : 3550, 3100, 1760, 1640, 920. This substance gave an acetate, $\text{C}_{17}\text{H}_{22}\text{O}_5$, (under the conditions described for grilactone) with mp 172-173°C (from ethanol); IR spectrum, cm^{-1} : 3080 ($\text{CH}_2 =$), 1770 (lactone CO), 1735 (acetyl CO), 1640, 905 ($\text{CH}_2 =$); absorption bands of OH groups were absent.

SUMMARY

The structure of grilactone has been established. It corresponds to guai-1(2),13-dien-12,8-olide.

The permanganate oxidation of grilactone, isogrilactone, and dihydrogrilactone forms, together with the normal oxidation products, monooxides of the guaianolides containing a γ -oxide ring linking carbon atoms 1 and 7.

LITERATURE CITED

1. N. P. Kir'yalov, Zh. Obsheh. Khim., 34, No. 11, 3831 (1964).