STRUCTURE AND STEREOCHEMISTRY OF GALBANIC ACID

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On the basis of the $^1$H NMR spectrum at 300 MHz and the results of chemical degradation, the structure of 7-[6-(β-carboxyethyl)-5-isopropylidene-1,2-dimethylcyclohexylmethoxy]coumarin has been proposed for galbanic acid.

Galbanic acid, which was first isolated from galbanum resin [1] and then from a number of species of Ferula [2-6], was ascribed structure (I) [2, 3] and then, on the basis of PMR and mass spectra, structure (II) [6]. The greater informativeness of the $^1$H NMR spectrum obtained on a spectrometer with a working frequency of 300 MHz and also the results of the degradation of the substance now permit structure (III) to be suggested for galbanic acid.

As has been established previously [6], the terpenoid moiety of galbanic acid contains a six-membered cyclohexane ring, a carboxy group, two methyl groups at a double bond, a CH$_3$-CH group, and one methyl group attached to a quarternary carbon atom. However, the oxidative degradation of galbanic acid shows that its structure includes an isopropylidene group. The epoxidation of galbanic acid gives an epoxide C$_2$H$_3$O$_2$ in the $^1$H NMR spectrum of which the CH$_2$-C$_1$1 and CH$_3$-C$_1$2 signals have been shifted upfield (1.32 ppm, s 6 H) in comparison with the initial compound (1.43 and 1.63, s, 3 H each); the opening of the epoxide ring in an acid medium and periodic acid oxidation lead to acetone, identified in the form of the 2,4-dinitrophenylhydrazone. Figure 1 shows a fragment of the $^1$H NMR spectrum of galbanic acid at a working frequency of 300 MHz (CDCl$_3$: O -- TMS). The assignment of the signals was made with the aid of double resonance. When the signals of the H$_2$, H$_{a}$, and 2H$_7$ protons, which have the same chemical shift (1.89 ppm), were irradiated, the signals of the H$_{a}$ (2.96 ppm), H$_{4}$ (2.05 ppm), CH$_3$-11 (1.45 ppm) and CH$_3$-15 (0.91 ppm, d, J = 7.0 Hz) protons were converted into singlets and those of the 2H$_8$ protons (2.20 ppm) into an AB quartet (ARAB = 10 Hz, J = 16.0 Hz). It follows from this that the aliphatic chain has the structure $-CH_2-CH_2-COOH$ and not $-CH_2-CH-COOH$, as was previously assumed [6]. The fact that the HOOC--

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carbon atom (C₁) attached to which are a methyl and an aryloxymethyl group. The position of
the secondary methyl group follows from an analysis of the shape of the signals of the pro-
tons of this group and of the H₄e proton (2.50 ppm). The chemical shifts of the H₃ methine
proton and the H₄a proton practically coincide. If the methine proton were present in posi-
tion 3, the relation J₃,₄a > Δν₃,₄a would exist between the difference in the chemical shifts
of the H₃ and H₄a protons (Δν₃,₄a) and the coupling constant J₃,₄a. In this case, additional
lines should appear in the spectrum of the signal of the methyl group [7], the conse-
quence of which would be broadening or fusion of the components of the signal of the methyl
group. The shape of the signal of the H₄e proton would change on passing from the 100-MHz spectrum
to the 300-MHz spectrum which does not in fact take place. Furthermore, the components of
the doublet signal of the methyl group would not be broadened even on passing to the 60 MHz
spectrum. Since these phenomena are not observed, the methyl group is present in position 2,
since there is practically no spin-spin coupling between the H₄a and H₃ protons.

The orientation of the aliphatic chain can be established from an analysis of the coup-
ling constants of the protons present in the homoallyl position in relation to one another
[7]. The coupling constants of the H₄a and H₄e protons with the protons of the methyl groups
of the isopropylidene fragment are different (JCH₃,₄a ≈ 2 Hz; JCH₃,₄e < 1 Hz). The upfield
shift of the signal of the methyl group to 1.45 ppm from its usual position permits this sig-
nal to be assigned to a methyl group oriented in the direction of the aliphatic chain. Con-
sequently, the constant of 2 Hz is due to the interaction of the H₄a proton and the methyl
group located on the other side of the plane perpendicular to the plane of the double bond
and passing through the C₇-C₉ atoms. The absence of such a coupling constant between the
H₄ proton and the other methyl group indicated the equatorial position of the H₄ proton. In
the case of the axial orientation of the substituent at C₆, the substituent at C₂ should be
present in the equatorial position, since the axial position is energetically unfavorable
because of 1,3-interaction of the substituents at C₂ and C₆ [8]. In favor of the axial ori-
entation of the -CH₃-O-Ar grouping is the downfield shift by 0.02 ppm of the signal of one
of the protons of one of the methylene groups in the spectrum of the epoxy derivative of gal-
banic acid. Such a shift is, in all probability, due to the descreening influence of the
epoxide ring when the oxygen atom of the epoxide ring and the protons of the methylene group
are oriented on the same side of the plane of the cyclohexane ring.

EXPERIMENTAL

Epoxidation. Galbanic acid (1.7 g) was dissolved in 34 ml of purified chloroform, and
1.7 g of p-methoxycarbonylperbenzoic acid was added. The reaction mixture was heated in the
water bath for 90 min and it was then filtered and evaporated. The oily residue was crys-
tallized from ethyl acetate. This gave a compound with the composition C₂₄H₃₀O₆, M⁺ 414, mp
131-132°C. ¹H NMR spectrum (CDCl₃, 0 - TMS, Varian HA-100 D): 0.96 ppm, 3 H, d, J = 7.0 Hz
(-CH₂-CH₃), 1.23 ppm, 3H, s, (-CH₃ CH₃), 1.32 ppm, 6H, s, \( \left( \begin{array}{c}
O \\
\text{C} \\
\text{C} \\
\text{CH₃}
\end{array} \right) \); 3.86 ppm, 2H, m
(-CH₂-O-); 6.20-7.68 ppm, 5H (signals of the protons of the 7-hydroxycoumarin nucleus).

Degradation of the epoxide. The epoxy derivative of galbanic acid was dissolved in 4 ml
of purified dioxane and 4 ml of water, 0.25 g of NaIO₄, and concentrated H₂SO₄ to pH 1.0 were
added. The reaction mixture was heated at 80-100°C for 15-20 min, and the acetone formed was
distilled off into a receiving flask containing 3 ml of 2,4-dinitrophenylhydrazine solution.
A yellow crystalline precipitate of acetone 2,4-dinitrophenylhydrazone C₁₀H₁₂O₆N₄O₂ formed
with M⁺ 238, mp 124-126°C. ¹H NMR spectrum: 2.07 and 2.14 ppm, s, 6H [(CH₃)₂-C=O]; 7.93 ppm, 1H,
d, J = 10 Hz (6-H); 8.31 ppm, 1 H, q, Jmeta = 3.0 Hz, Jortho = 10 Hz (5-H); 9.1 ppm, 1 H, d, J = 3.0 Hz (3-H); 11.0 ppm, 1H, m (N-H).