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STRUCTURE AND STEREOCHEMISTRY OF GALBANIC ACID

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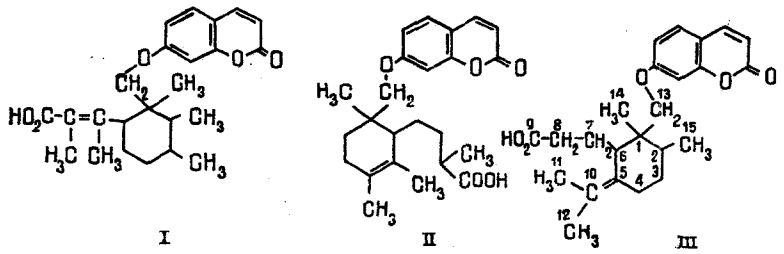
On the basis of the ^{1}H NMR spectrum at 300 MHz and the results of chemical degradation, the structure of 7-[6-(β-carboxyethyl)-5-isopropylidene-1,2-dimethylcyclohexylmethoxy]coumarin has been proposed for galbanic acid.

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.



I II III

As has been established previously [6], the terpenoid moity 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 $C_{24}H_{30}O_6$ in the ^{1}H NMR spectrum of which the CH_3—C_{11} and CH_3—C_{12} 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 the spectrometer of 300 MHz ($CDCl_3$: 0 — TMS). The assignment of the signals was made with the aid of double resonance. When the signals of the H_2, H_4a, and $2H_7$ protons, which have the same chemical shift (1.89 ppm), were irradiated, the signals of the H_6 (2.96 ppm), H_4e (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 ($\Delta\nu_{AB}$ = 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(—CH_3)—COOH, as was previously assumed [6]. The fact that the HOOC—CH_2—CH_2 group is actually present in the α position to the $(CH_3)_2C$= group is shown by the chemical shift and the multiplicity of the signals of the H_6 proton in the spectrum of galbanic acid. The same facts indicate that the other neighboring atom to C_6 is a quaternary

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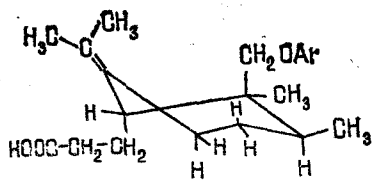
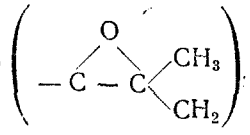
carbon atom (C_1) attached to which are a methyl and an aryloxymethyl group. The position of the secondary methyl group follows from an analysis of the shape of the signals of the protons of this group and of the H_{4e} proton (2.50 ppm). The chemical shifts of the H_2 methine proton and the H_{4a} proton practically coincide. If the methine proton were present in position 3, the relation $J_{3,4a} > \Delta\nu_{3,4a}$ would exist between the difference in the chemical shifts of the H_3 and H_{4a} protons ($\Delta\nu_{3,4a}$) and the coupling constant $J_{3,4a}$. In this case, additional lines should appear in the spectrum of the signal of the methyl group [7], the consequence of which would be broadening or fusion of the components of the signal of the methyl group. The shape of the signal of the H_{4e} 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 H_{4a} and H_2 protons.

The orientation of the aliphatic chain can be established from an analysis of the coupling constants of the protons present in the homoallyl position in relation to one another [7]. The coupling constants of the H_{4a} and H_{4e} protons with the protons of the methyl groups of the isopropylidene fragment are different ($J_{CH_3,H_{4a}} \approx 2$ Hz; $J_{CH_3,H_{4e}} < 1$ Hz). The upfield shift of the signal of the methyl group to 1.45 ppm from its usual position permits this signal to be assigned to a methyl group oriented in the direction of the aliphatic chain. Consequently, the constant of 2 Hz is due to the interaction of the H_{4a} 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 C_5—C_{10} atoms. The absence of such a coupling constant between the H_6 proton and the other methyl group indicated the equatorial position of the H_6 proton. In the case of the axial orientation of the substituent at C_6, the substituent at C_2 should be present in the equatorial position, since the axial position is energetically unfavorable because of 1,3-interaction of the substituents at C_2 and C_6 [8]. In favor of the axial orientation of the —CH_2—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 galbanic 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 crystallized from ethyl acetate. This gave a compound with the composition $C_{24}H_{30}O_6$, M^+ 414, mp 131-132°C. ^{1}H NMR spectrum ($CDCl_3$, O — TMS, Varian HA-100 D): 0.96 ppm, 3 H, d, J = 7.0 Hz (—CH—CH_3), 1.23 ppm, 3H, s, (—C—CH_3), 1.32 ppm, 6H, s,  ; 3.86 ppm, 2H, m (—CH_2—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 $NaIO_4$, and concentrated H_2SO_4 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 $C_9H_{10}N_4O_4$ formed with M^+ 238, mp 124-126°C. ^{1}H NMR spectrum: 2.07 and 2.14 ppm, s, 6H [$(CH_3)_2$—C=O]; 7.93 ppm, 1H, d, J = 10 Hz (6-H); 8.31 ppm, 1 H, q, J_{meta} = 3.0 Hz, J_{ortho} = 10 Hz (5-H); 9.1 ppm, 1 H, d, J = 3.0 Hz (3-H); 11.0 ppm, 1H, m (N—H).

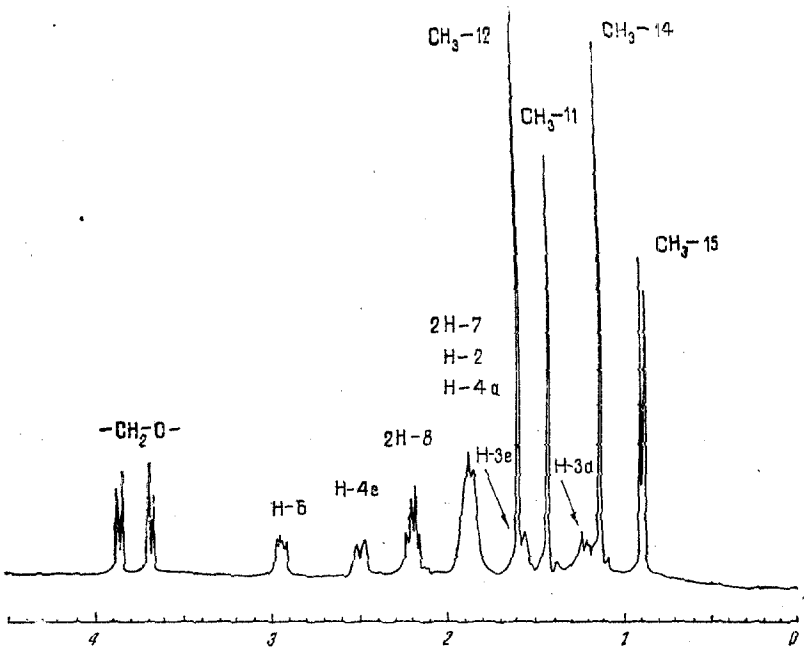


Fig. 1. ^{1}H NMR spectrum of the terpenoid moiety of galbanic acid in $CDCl_3$ (300 mHz).

SUMMARY

The structure of 7-[6-(β-carboxyethyl)-5-isopropylidene-1,2,dimethylcyclohexylmethoxy] courmarin is proposed for galbanic acid.

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