THE STRUCTURE OF BRITANNIN – A SESQUITERPENE LACTONE FROM Inula britannica

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Inula britannica L. (British inula) is widely used in folk medicine as a rapid-healing and diuretic agent [1]. From the epigeal part of this plant we have isolated [2] a new sesquiterpene lactone – britannin (I), $C_{19}H_{26}O_7$, mp 192-194°C (from ethanol), $[\alpha]_D^{20} -26°$ (c 5.0; chloroform). The IR spectrum of britannin (Fig. 1) has absorption bands at (cm^{-1}) 3540 (OH), 1758 (γ-lactone carbonyl), 1735, 1720, 1270-1240 ($OCOCH_3$), and 1668 (C=C).

The NMR spectrum has the signals of secondary and tertiary methyls (doublet at 0.95 ppm and singlet at 1.00 ppm), of two acetoxy groups (singlets at 2.03 and 2.22 ppm), and of an exocyclic methylene conjugated with the lactone carbonyl (doublets at 5.41 and 6.14 ppm, J=3 Hz) [3].

The dehydrogenation of britannin over selenium at 300-360°C for 30 min gave guaiazulene (XI). The presence in the NMR spectrum of britannin of a methyl singlet at 1.00 ppm (angular methyl), and the formation of guaiazulene on dehydrogenation permit britannin to be assigned to the sesquiterpene lactones of the ambrosane (isoguaiazulene) type.

The hydrogenation of britannin over a Pt catalyst (from PtO_2) took place with the consumption of 1 mole of hydrogen and the formation of dihydrobritannin (V), $C_{19}H_{28}O_7$, mp 222-224°C (from ethanol). The NMR spectrum of (V) has no signals of vinyl protons.

On being heated with acetic anhydride in pyridine, britannin gave an acetyl derivative (II), $C_{21}H_{28}O_8$, in the form of an amorphous white powder the IR spectrum of which lacked the absorption band of an OH group.

Britannin was not oxidized by CrO_3 in pyridine but was oxidized in acetic acid to dehydrobritannin (III), $C_{19}H_{24}O_7$. Its IR spectrum has an additional band at 1750 cm^{-1} (cyclopentanone). Substance (III) gives a positive Zimmerman reaction ($CO-CH_2$). Consequently, the OH group in britannin is secondary and is located in a five-membered ring, and there is a CH_2 group adjacent to the OH group. This is also confirmed by the results of the acetylation and oxidation of dihydrobritannin: acetyldihydrobritannin (VI), $C_{21}H_{30}O_8$, and dehydrodihydrobritannin (VII), $C_{19}H_{26}O_7$.

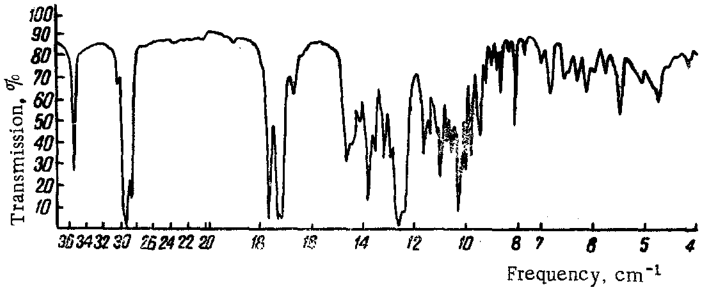

Fig. 1. IR spectrum of britannin (taken on a UR-10 spectrophotometer in Vaseline oil).

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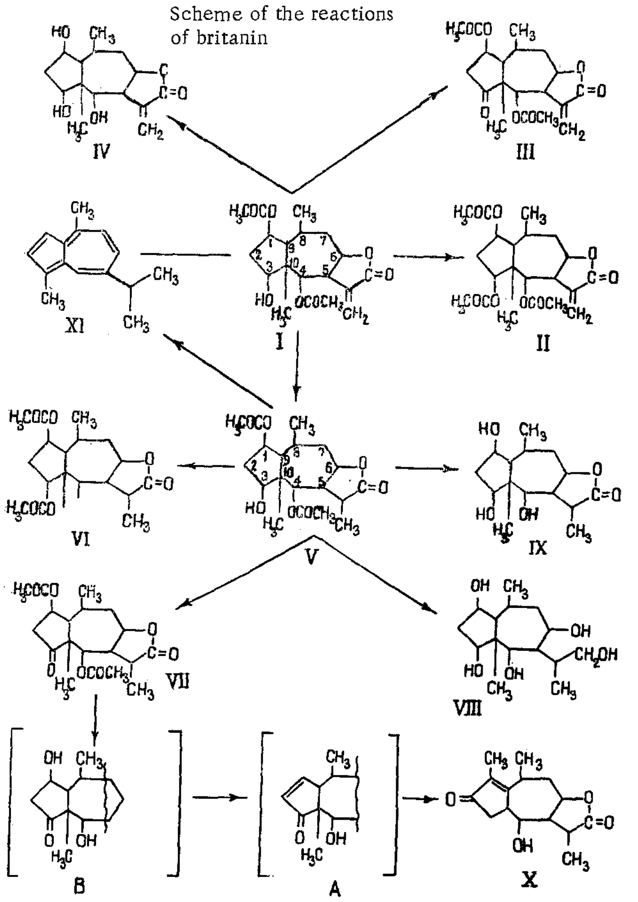
Britannin contains two acetoxy groups, one of them being readily saponified and the other less readily. The product of the complete hydrolysis of britannin,(IV), $C_{15}H_{22}O_5$, has mp 172-173°C (from ether); dihydrobritannin (IX), $C_{15}H_{24}O_5$, has mp 210-214°C (decomp.).

The lactone ring and the ester groups are reduced by lithium tetrahydroaluminate with the formation of a pentaol (VIII), $C_{15}H_{28}O_5$.

The signal of the lactone proton in the NMR spectrum of britannin (Fig. 2) forms a sextet at 4.55 ppm ($\Sigma J = 25$ Hz), and this suggests that the lactone ring is located at C_5-C_6 [3].

In the NMR spectrum of britannin, a doublet at 5.10 ppm ($\Sigma J = 10$ Hz) and a multiplet at 4.90 ppm are the signals of hemiester protons; in bisdesacetylbritannin (IV) these signals are shifted upfield (as was to be expected)(3.78 and 4.09 ppm). The nature of the signal (doublet of the hemi proton of one acetoxy group in I shows that it is located at C_4. To the latter proton attached to oxygen – a hemihydroxy proton – a signal with a center at 4.18 ppm corresponds; in the oxidation products (III) and (IV), as was assumed, this signal is absent.

The hydrolysis of dehydrodihydrobritannin (VII) gave a substance with the composition $C_{15}H_{20}O_4$ (X); ν_{max} 3300 cm^{-1} (OH), 1770 cm^{-1} (γ-lactone), 1685 cm^{-1} (α,β-unsaturated ketone), and 1630 cm^{-1} (C=C); λ_{max} 240 nm, ε 8035. The NMR spectrum has no signal of an angular methyl and in the place of this a new signal of a $CH_3-C=C$ group appears (singlet at 1.75 ppm). Consequently, in the hydrolysis of (VII) in an alkaline medium a rearrangement took place. A similar phenomenon has been observed repeatedly when ambrosanolides containing the grouping A are heated with alkalis; under the action of the alkali the angular methyl migrates to C_1, and the positions of the double bond and of the carbonyl also change [see (X)]. The rearrangement products have been given the name of neo compounds [4, 5]. The formation of neo compounds in the saponification of (VII) probably takes place in the following way: first the dihydroxy keto compound B is formed which readily dehydrates to A, this being possible when the OH is in the β position with respect to carbonyl; the product formed rearranges as described above. The formation of (X) from (VII) can take place only when the hydroxy group in (I) is located at C_3 and the acetoxy group at C_1. Thus, britannin has the structure (I).


Scheme of the reactions of britanin

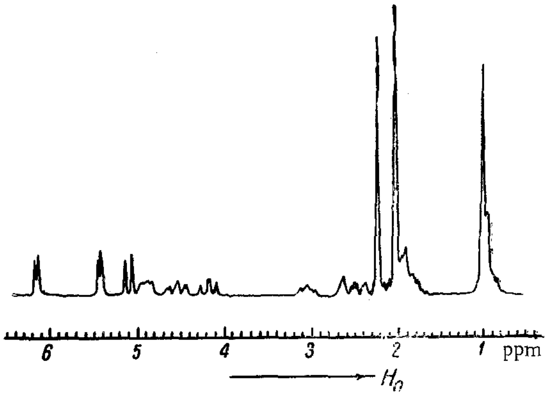


Fig. 2. NMR spectrum of britannin in $CDCl_3$ (taken on a JNM-4H-100 instrument, 100 MHz).

EXPERIMENTAL

Britannin (I). After three recrystallizations from ethanol, mp of (I) 192-194°C, $[\alpha]^{20}_{D}-26°$ (c 5.0; chloroform).

Found %: C 62.13, 62.20; H 7.07, 7.13. Mol. wt. 363 (cryoscopically). H_{mobile} 1.2. $C_{19}H_{26}O_7$. Calculated %; C 62.28; H 7.15. Mol. wt. 366.

Britannin was also isolated from British inula collected in the Caucasus and in the Moscow oblast.

Acetylbritannin (II). A mixture of 0.3 g of britannin, 6 ml of pyridine, and 3 ml of acetic anhydride was heated in the water bath for 1 h and was then diluted with water and extracted with chloroform six times; the chloroform extract was washed three times with 10% HCl and then with water to neutrality. Removal of the solvent by distillation gave a syrupy liquid (containing two substances according to TLC), which was chromatographed on Al_2O_3 (activity grade IV). Ether eluted two fractions: I – viscous transparent liquid (0.2 g); and II – crystals of unchanged britannin. After drying, fraction I was converted into a white amorphous powder, $C_{21}H_{28}O_8$.

The analytical results for acetylbritannin and all the derivatives obtained corresponded to the calculated figures. IR spectrum, ν_{max}, cm^{-1}: 1770 (γ-lactone), 1750 and 1745, 1260-1240 ($OCOCH_3$), 1660 (C=C); there was no absorption band of an OH group.

Dehydrobritannin (III). A mixture of 0.5 g of britannin, 20 ml of 90% acetic acid, and 0.5 g of CrO_3 was left at 0°C for 15 h and was then diluted with water and was extracted with chloroform six times; the chloroform extracts were then washed with 5% $NaHCO_3$ and with water. After the solvent had been distilled off, 0.44 g of a faintly colored crystalline product with the composition $C_{19}H_{24}O_7$, mp 187-188°C (from ethanol) was obtained.

IR spectrum, ν_{max}, cm^{-1}: 1762 (γ-lactone), 1750-1740 ($OCOCH_3$ and C=O); no absorption band of an OH group. When an attempt was made to oxidize britannin in pyridine, the starting material was recovered unchanged.

Bisdesacetylbritannin (IV). A mixture of 1.0 g of britannin and 50 ml of 4% KOH was left at room temperature for two days and was then acidified with 10% H_2SO_4 to pH 1.0 and extracted ten times with ethyl acetate. The ethyl acetate extract was washed with 5% $NaHCO_3$ and with water, and the solvent was driven off. This gave a colorless vitreous mass which was converted by the addition of diethyl ether into small crystals of (IV), $C_{15}H_{22}O_5$, mp 172-173°C (Kofler).

IR spectrum, ν_{max}, cm^{-1}: 3480, 3430, 3300 (OH group), 1740, 1660 (α-methylene of a γ-lactone).

Dihydrobritannin (V). In the presence of 0.3 g of PtO_2 (according to Adams), 10 g of britannin was hydrogenated in 300 ml of ethanol; 1 mole of hydrogen was absorbed, after which hydrogenation ceased. The platinum and the solvent were removed, giving colorless crystals of (V), $C_{19}H_{28}O_7$, mp 222-224°C (from ethanol).

IR spectrum, ν_{max}, cm^{-1}: 3527, 3497 (OH), 1777 (γ-lactone), 1737, 1700 and 1250-1260 ($OCOCH_3$).

Acetyldihydrobritannin (VI). Dihydrobritannin (0.5 g) was acetylated in the same way as for acetylbritannin. After the solvent had been distilled off, a vitreous product was obtained (consisting of two substances according to TLC), which was then chromatographed on Al_2O_3 (activity grade IV), being eluted with diethyl ether. The first fraction deposited colorless crystals (0.3 g) of (VI), with the composition $C_{21}H_{30}O_8$, mp 134.5-136°C (ether).

IR spectrum, ν_{max}, cm^{-1}: 1780, 1750-1735 and 1240-1270.

Dehydrodihydrobritannin (VII). Dihydrobritannin (0.5 g) was oxidized with CrO_3 in 90% acetic acid as described for britannin. When the solvent was distilled off, a slightly colored crystalline product was obtained – (VII) (0.47 g) with the composition $C_{19}H_{26}O_7$, mp 207-208°C (from ethanol, decomp.).

IR spectrum, ν_{max}, cm^{-1}: 1770, 1758, 1750.

Production of the Pentaol (VIII). A solution of 0.5 g of dihydrobritannin in 10 ml of dioxane was added dropwise to a solution of 0.3 g of $LiAlH_4$ in 50 ml of dioxane, and the mixture was boiled for 10 min; then a solution of 1.0 g of $LiAlH_4$ in 150 ml of dioxane was added and the mixture was boiled for 6 h. The excess of lithium tetrahydroaluminate was carefully destroyed with water, and the mixture was filtered, and the solvent was driven off. This gave a crystalline precipitate of (VIII), $C_{15}H_{28}O_5$, mp 248.5-250.5°C (from ethanol). IR spectrum, ν_{max}, cm^{-1}: 3450-3250 (OH group); there were no absorption bands of a γ-lactone or of $C=O$ groups.

Bisdesacetyldihydrobritannin (IX). A mixture of 1.0 g of dihydrobritannin and 50 ml of 4% KOH was left for 2 days (by which time the crystals had dissolved completely) and was then treated as described for the hydrolysis of britannin. This led to the deposition of 0.03 g of colorless crystals of (IX) with mp 210-214°C (decomp.).

IR spectrum, ν_{max}, cm^{-1}: 3480, 3350 (OH), 1750 (γ-lactone).

Desacetyldehydrodihydroneobritannin (X). A mixture of 1.6 g of (VII) and 80 ml of 4% KOH solution was left for two days and was then acidified with 10% H_2SO_4 to pH 1.0 and was extracted 15 times with ethyl acetate, the extract being washed with 5% $NaHCO_3$ solution and with water. Distillation of the ethyl acetate yielded 0.6 g of a slightly colored product (X), $C_{15}H_{20}O_4$, mp 244-247°C (from ethyl acetate). IR spectrum, ν_{max}, cm^{-1}: 3300 (OH), 1770 (γ-lactone), 1685 (α,β-unsaturated ketone), and 1630 ($C=C$). UV spectrum: λ_{max} 240 nm, ε 8035.

Dehydrogenation of Britannin. A mixture of 2.0 g of britannin and 2.0 g of selenium was heated at 300-360°C for 40 min. The reaction product was extracted with petroleum ether and chromatographed on Al_2O_3. The blue-violet liquid obtained (10 mg) was identified as guaiazulene (XI) by TLC with a marker.

A somewhat greater yield was obtained in the dehydrogenation of dihydrobritannin under similar conditions.

SUMMARY

From the epigeal part of Inula britannica L. a new sesquiterpene lactone has been obtained – britannin, with the composition $C_{19}H_{26}O_7$, mp 192-194°C (from ethanol). $[\alpha]_D^{20} -26°$ (c 5.0; chloroform). Structure (I) has been proposed for it.

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