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# DITERPENOIDS OF *Pulicaria salviifolia*. III. THE STRUCTURE OF SALVICININ

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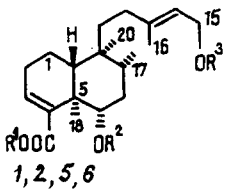
*The new diterpene acid salvicinin has been isolated from the epigeal part of* Pulicaria salviifolia *and its structure has been established as 15-acetoxy-6α-hydroxy-*trans*-cleroda-3,13-dien-19-oic acid. A capacity of salvicinin for undergoing lactonization in the presence of acetic anhydride has been revealed, and the lactone formed has been isolated and chracterized.*

Three diterpenoids of the clerodane series and the flavone pulicarin have previously been isolated from *Pulicaria salviifolia* Bgl in Mem (fam. Asteraceae) ([1-3].

In studying the epigeal part of this plant gathered in the Fergana valley (Uzbekistan) we have isolated a new diterpenoid $C_{22}H_{34}O_5$ (**1**), which has been called salvicinin. Salvicinin is readily soluble in aqueous solutions of sodium bicarbonate and alkalies, which shows its acidic nature. IR spectrum ($cm^{-1}$): 3200-3600 (hydroxy group), 1740 (ester carbonyl), 2380-2680, 1670 (carboxy group). Mass spectrum, m/z: 378 ($M^+$), 360 ($M - H_2O$), 333 ($M - COOH$).

The PMR spectrum was characterized by the following signals: singlets with an intensity of 3H each from tertiary methyl groups at 0.65 and 1.12 ppm; doublet (3H) of a secondary methyl at 0.7 ppm, J = 6.5 Hz; three-proton singlet of a methyl group on double bond at 1.62 ppm; narrow three-proton singlet of the protons of an acetyl group at 1.96 ppm. A one-proton broadened triplet at 7.04 ppm with $^3J$ = 7.0 Hz relates to a proton on a double bond conjugated with carbonyl; and the resonance of an olefinic proton in a side chain gives a signal at 5.2 ppm in the form of a triplet (1H) with $^3J$ = 6.5 Hz. At 3.6 ppm there is the signal of a proton geminal to a hydroxy group, in the form of a one-proton broadened triplet, $^3J$ = 6.25 Hz. A two-proton doublet at 4.42 ppm, J = 6.5 Hz relates to a methylene group linked to an acetoxy group.

The composition of salvicinin and the number and nature of the methyl groups, in combination with the signal of an olefinic proton at 7.04 ppm (t, $^3J$ = 7.0 Hz), permits to be assigned to the diterpenoids of the clerodane type with an aliphatic side chain. In actual fact, the alkaline hydrolysis of (**1**) gave the clerodane acid salvicin (**2**) [2], which was identified by its physicochemical and spectral parameters. The compositions of salvicin and salvicinin differ by one acetyl group, and a comparison of the PMR spectra of (**1**) and (**2**) (Table 1) shows that salvicinin is the monoacetate of salvicin at the C-15 primary hydroxy group, since in the PMR spectrum of salvicinin the signal of the H-15 protons have undergone a paramagnetic shift by Δ 0.32 ppm and, correspondingly, a diamagnetic shift of the signals of H-14 proton by 0.12 ppm is observed. The signal of the H-6 secondary hydroxy group is unchanged. Thus, salvicinin has the structure of 15-acetoxy-6α-hydroxy-*trans*-cleroda-3,13-dien-19-oic acid (**1**).

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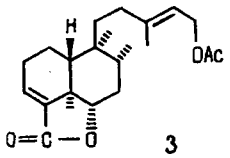


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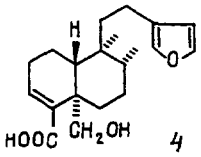


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1. $R^1$=$R^2$=H; $R^3$=Ac
2. $R^1$=$R^2$=$R^3$=H
5. $R^1$=Me; $R^2$=H; $R^3$=Ac
6. $R^1$=Me; $R^2$=$R^3$=Ac

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TABLE 1. CS, Multiplicities, and SSCC of the Protons in the PMR Spectra of Salvicinin and Its Derivatives (0 — HMDS, 100 MHz, $\delta$, ppm, J, Hz)

| Substance and solvent | H-3 | H-6 | H-14 | H-15 | H-16 | H-17 | H-18 | H-20 | $OCH_3$ | OAc |
|---|---|---|---|---|---|---|---|---|---|---|
| Salvicinin (1) ** $CDCl_3$ | 7.04 t 7.0 | 3.6 t 6.25 | 5.2 t 6.5 | 4.42 d 2H 6.5 | 1.62 s 3H | 0.7 d 3H 6.5 | 1.12 s 3H | 0.65 s 3H | – | 1.96 s 3H |
| Salvicin (2) ** $CDCl_3$ | 7.1 t 7.0 | 3.62 t 6.0 | 5.32 t 6.5 | 4.1 d 2H 6.5 | 1.6 s 3H | 0.72 d 3H 6.5 | 1.14 s 3H | 0.65 s 3H | – | – |
| The lactone (3) $CDCl_3$ | 6.4 t 5.6 | 3.64 q 12, 4.0 | 5.26 t 7.0 | 4.45 d 2H 7.0 | 1.62 s 3H | 0.92 d 3H 6.5 | 0.96 s 3H | 0.8 s 3H | – | 2.0 s 3H |
| Methyl ester of salvicinin (5) $C_5D_5N$ | 5.87 t 7.0 | 3.63* m | 5.65 t 6.5 | 4.42 d 2H 6.5 | 1.65 s 3H | 0.59 d 3H 6.5 | 1.4 s 3H | 0.51 s 3H | 3.63 s 3H | 2.0 s 3H |
| Diacetate of the methyl ester of salvicinin (6) $C_5D_5N$ | 5.78 t 6.0 | 4.7 q 10, 5.0 | 5.25 t 6.5 | 4.5 d 2H 6.5 | 1.64 s 3H | 0.77 d 3H 6.5 | 1.32 s 3H | 0.7 s 3H | 3.6 s 3H | 1.92 s 3H 2.0 s 3H |

*Superposition of the H-6 and the $OCH_3$ signals.

**The signal of the proton of the carboxy group is also observed, at 8.9 ppm in the form of a broadened singlet (1H).

On the acetylation of salvicin and salvicinin, a tendency of these substances to undergo lactonization was revealed, and, in the presence of acetic anhydride in pyridine at room temperature both substances yielded the lactone (**3**), $C_{22}H_{32}O_4$, $M^+$ 360,the IR spectrum of which showed clear absorption bands of a $\gamma$-lactone carbonyl at 1780 $cm^{-1}$ and of an ester group at 1745 $cm^{-1}$. The PMR spectrum of lactone (**3**) (see Table 1) revealed diamagnetic shifts of the H-3 and H-18 signals,while the lactone proton resonated at 3.64 ppm in the form of a quartet with SSCC of 12 and 4 Hz. The signals of the aliphatic side chain (H-14, H-15, and H-16) had scarcely changed their character and positions.

A similar tendency of clerodane acids to undergo lactonization has been reported previously for derivatives of hautriwaic acid (**4**) [4-6], in which the acid and hydroxy groups are present at C-4 and C-18, but the capacity for lactonization depends on the spatial propinquity of functional groups capable of undergoing dehydration, as is observed in the cases of salvicin and salvicinin, i.e., cyclization takes place through the C-19 and the C-6 OH groups. It may be assumed that this reaction forms the basis of the biosynthesis of the lactones of salvin and salvinin isolated previously from this plant [1].

It was posible to acetylate the secondary hydroxy group in salvicinin only after the methylation of the carboxy group with diazomethane. The physicochemical and spectral characteristics of salvicinin methyl ester (**5**) and its acetate (**6**) are given in the Experimental part and in Table 1.

## EXPERIMENTAL

The conditions for recording the spectra have been given in [3]. System for TLC: chloroform—ethyl acetate (2:1), Silufol plates (Chemapol). All the substances described gave a claret coloration when revelaed on a chromatogram with a 1% solution of vanillin in concentrated sulfuric acid and were decolorized by an aqueous solution of potassium permanganate [sic].

**Isolation of Salvicinin.** The dried concentrated extract [3] was chromatographed on a column of silica gel (Chemapol) with elution by mixtures of chloroform and ethanol, beginning with a 9:1 ratio. Salvicinin (**1**) was eluted at a ratio of the solvents of 4:1: $C_{22}H_{34}O_5$, mp 78-80°C, $R_f$ 0.2. UV spectrum: $\lambda_{max}$ 220 nm (log $\varepsilon$ 3.95 (in ethanol).

**Hydrolysis of Salvicinin.** Alkaline hydrolysis was carried out with a 5% aqueous alcoholic solution of caustic potash at room temperature. The usual method of working up yielded salvicin (**2**), $C_{20}H_{32}O_4$, $M^+$ 336, mp 157-158°C, $R_f$ 0.13. IR spectrum: $\nu_{max}$ 1680, 2930-2970, 3200-3600.

**The Lactone (3).** A solution of 50 mg of salvicinin in 3 ml of pyridine was treated with 3 ml of acetic anhydride, and the mixture was left at room temperature for 0.5 h. Then it was diluted with water and extracted with ethyl acetate. The reaction product was purified on a column of silica gel, using chloroform as eluent. This gave 30 mg of (**3**), $C_{22}H_{32}O_4$, oily substance, $[\alpha]_D^{20}$ −88° (*c* 5.0; $C_2H_5OH$) $R_f$ 0.35. Compound (**3**) was also formed from salvicin under the same conditions. IR spectrum: $\nu_{max}$ 1780, 1745 $cm^{-1}$.

**Salvicinin Methyl Ester (5).** A solution of 100 mg of salvicinin in ethanol was treated with 5 ml of an ethereal solution of diazomethane, and after 2 h the solvent was distilled off, to give 100 mg of (**5**), $C_{23}H_{36}O_5$, $[\alpha]_D^{22}$ — 44° (s 0.5; $C_2H_5OH$), $R_f$ 0.18.

**Diacetate of Salvicinin Methyl Ester (6).** Compound (**5**) (100 mg) was acetylated with acetic anhydride in pyridine, and after the usual working up, 90 mg of the noncrystalline substance (**6**) was isolated. $C_{25}H_{38}O_6$, $[\alpha]_D^{22}$ — 40° (s 0.5; $C_2H_5OH$), $R_f$ 0.32.

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