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A REVISED STRUCTURE FOR THE DITERPENE ROSMANOL

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Key Word Index—*Salvia canariensis*; *Rosmarinus officinalis*; Labiatae; diterpenes; rosmanol; galdosol.

Abstract—The diterpene rosmanol, previously isolated from *Rosmarinus officinalis*, has been isolated from the flowers of *Salvia canariensis* and its structure revised as 7α,11,12-trihydroxyabieta-8,11,13-trien-20-oic acid 20,6-lactone, on the basis of chemical evidence and an X-ray diffraction analysis.

Continuing with the study on *Salvia canariensis* L. [1, 2] we have isolated from the flowers of this plant an aromatic diterpene, $C_{20}H_{26}O_5$, to which structure **1** was assigned on the basis of the following evidence. Its IR spectrum has bands characteristic of the aliphatic and aromatic hydroxyls, and of the γ-lactonic group. The ^{1}H NMR spectrum shows the signals of the two angular methyl groups (δ0.92 and 1.02), of the isopropyl group (1.22, 6H, *d*, J = 7 Hz; 3.15, 1H, *m*), of the geminal protons to the lactone (4.56, *d*, J = 3 Hz) and to the alcohol group (4.75, *d*, J = 3 Hz) and the hydrogens at C-5 (2.22, *s*) and C-14 (6.90, *s*).

Compound **1** forms a triacetate **2** and a dimethyl ether **3**. The oxidation of **3** with pyridinium dichromate gave the dimethyl ether of galdosol (**5**), identical with the substance obtained by methylation of galdosol with dimethyl sulphate.

With these results only the stereochemistry of the alcoholic group at C-7 remained undetermined. The reduction of the diacetate of galdosol (**6**) [1] with sodium borohydride and acetylation of the alcohol formed gave **8**, different from the triacetate of the natural compound (**2**). Thus **8** and **2** must be epimers. The coupling constant between H-6 and H-7 is the same for both compounds, but the chemical shifts of these protons are different.

Wenkert *et al.* [3] postulated that in this type of diterpene with the lactone on the β-face, the reduction of a ketone at C-7 must occur from the α-face forming the alcohol with the β-configuration. In our hands, reduction of galdosol dimethyl ether **5** with the bulky reagent, potassium *sec*-butylborohydride gave **9**, identical to the product obtained by Wenkert *et al.* [3] using sodium borohydride. We concluded that **9** had a 7β-hydroxyl group, and hence that **3** and **1** had 7α-hydroxyl groups.

In contrast however, Brieskorn [4] concluded on the basis of ^{1}H NMR evidence that reduction of **5** by sodium borohydride gave a product with the 7α-configuration. Inatani *et al.* [5] recently reported structure **7** for rosmanol, an anti-oxidative phenolic diterpene isolated from *Rosmarinus officinalis*. The Japanese authors assigned the β-configuration to the hydroxyl group at C-7 using NOE effects, which we considered to be inconclusive. Rosmanol proved identical to our compound **1**, so the stereochemistry at C-7 was in dispute.

To resolve the controversy we subjected rosmanol triacetate to X-ray crystallographic analysis. The resulting structure **2** confirmed our conclusions that rosmanol and its derivatives have a 7α-hydroxyl group. Thus both Brieskorn [4] and Inatani *et al.* [5] were in error.

Figure 1 shows the X-ray model molecule. Ring A has a chair conformation, but it reveals some distortion in which it deviates from the perfect chair. This is due to the junction with ring B. Ring B has an envelope conformation with the flap at C-5 and the C-7, C-8 and C-9 atoms nearly in a plane.

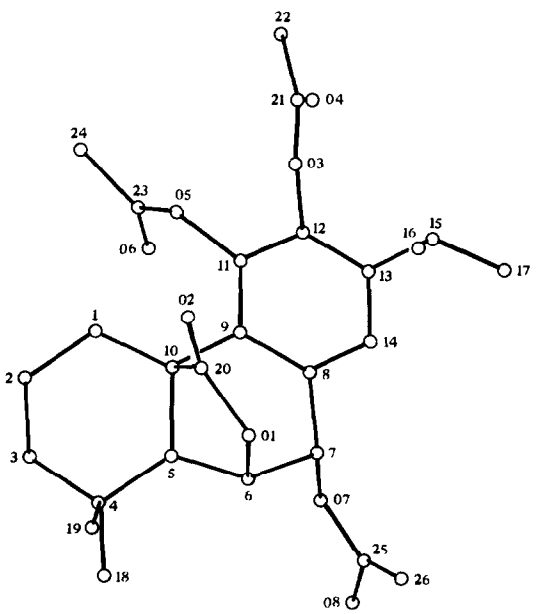
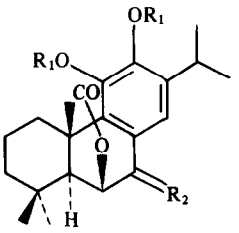


Fig. 1. The X-ray molecular model of rosmanol triacetate (**2**).



1 R_1 = H R_2 = α − OH
2 R_1 = Ac R_2 = α − OAc
3 R_1 = Me R_2 = α − OH
4 R_1 = H R_2 = O
5 R_1 = Me R_2 = O
6 R_1 = Ac R_2 = O
7 R_1 = H R_2 = β − OH
8 R_1 = Ac R_2 = β − OAc
9 R_1 = Me R_2 = β − OH

EXPERIMENTAL

Melting points are uncorr. ^{1}H NMR spectra were obtained using $CDCl_3$ as solvent and TMS as an internal standard. IR spectra were obtained in $CHCl_3$.

From the flowers of *Salvia canariensis* (1 kg) an ethanolic extract (32 g) was obtained. After chromatography on silica gel, the diterpenes rosmanol (**1**, 1.8 g) [5] and galdosol (**4**, 0.9 g) [1] and the triterpenes 2α-hydroxyursolic acid (120 mg) [6, 7] and the mixture of ursolic and oleanolic acids (300 mg) were isolated. These compounds were identified by their ^{1}H NMR spectra, being identical with those reported in the literature cited. In the case of rosmanol, its triacetate (**2**) and dimethyl ether (**3**) were prepared, their physical and spectroscopic data being identical with those published [5]

Oxidation of dimethyl rosmanol (**3**). Compound **3** (48 mg) in dry DMF (3 ml) was treated with pyridinium dichromate (140 mg) at room temp for 1 hr. The soln was poured into H_2O and extracted with Et_2O as usual. In this way compound **5** was obtained, mp 117–118° (from MeOH) (lit. [5] 120–121°). $[M]^+$ at 372.1913. (Calc. for $C_{22}H_{28}O_5$ 372 1937). ^{1}H NMR (90 MHz): δ0.99 and 1.04 (each 3H, *s*), 1.22 (6H, *d*, *J* = 7 Hz), 2.42 (1H, *s*), 3.30 (1H, *m*), 3.82 and 3.91 (each 3H, *s*), 4.83 (1H, *s*), 7 81 (1H, *s*). EIMS *m/z*: 372 $[M]^+$, 328, 317, 273, 258, 244. This product was identical to the compound obtained by methylation of galdosol (**4**).

Triacetate **8**. The diacetate of galdosol (**6**, 82 mg) in MeOH (20 ml) was treated with $NaBH_4$ (100 mg) at room temp. for 1 hr The soln was acidified, the solvent was evaporated under red. pres. and the residue extracted with EtOAc in the usual way. The residue obtained was acetylated with Ac_2O and pyridine giving the triacetate **8**, mp 78–80° (from MeOH), IR ν_{max} cm^{-1}: 3025, 2925, 2850, 1775, 1730, 1460, 1365. ^{1}H NMR (60 MHz): δ0.92 (3H, *s*), 1.01 (3H, *s*), 1.18 (6H, *d*, *J* = 7 Hz), 2.19 (3H, *s*), 2.26 (3H, *s*), 2.31 (3H, *s*), 4.88 (1H, *d*, *J* = 3 Hz), 6.00 (1H, *d*, *J* = 3 Hz), 7 00 (1H, *s*). EIMS *m/z*. 472 $[M]^+$, 444, 402, 388, 328, 300, 284, 215, 149.

Reduction of dimethyl galdosol (**5**). To a soln of **5** (70 mg) in THF (20 ml) potassium tri-*sec*-butyl borohydride (K-Selectride) and KH_2PO_4 (160 mg) at 0° were added. The reaction was left at 0° with stirring and under N_2 for 2 hr. The mixture was treated with aq. H_3PO_4 (10%) to adjust the pH to ~ 3 and then extracted with CH_2Cl_2. In this way compound **9** was obtained. ^{1}H NMR (60 MHz): δ0.95 (3H, *s*), 0.99 (3H, *s*), 1.19 (6H, *d*, *J* = 7 Hz), 1.93 (1H, *s*), 3.15 (1H, *m*), 3.77 (3H, *s*), 3.81 (3H, *s*), 4.75 (2H, *br s*), 7.23 (1H, *s*). EIMS *m/z*: 374 $[M]^+$, 328, 315, 301, 284, 243, 215, 149.

Crystal data of rosmanol triacetate (**2**). Crystals of **2** are monoclinic, $C_{26}H_{32}O_8$, space group P21, with *Z* = 2, in a cell of *a* = 10.587(1)Å, *b* = 10.853(1)Å, *c* = 11.513(1)Å and β = 110.073(3)°, V = 1242.52(31) Å^3. A crystal of paralepipedic shape of 0.3 × 0.3 × 0.2 mm was selected to measure the 2218 independent reflexions for θ > 65°, using graphite monochromated CuKα radiation. No intensity decay was observed during the data collection on an automatic four-circle diffractometer. The structure was solved by MULTAN [8] with the greatest 250 E's. After the anisotropic full-matrix least-squares refinement [9]. A weighting schema [10] was selected to have no dependence of $\langle w\Delta^2 F\rangle$ vs. $\langle Fo\rangle$ and vs. $\langle \sin\theta/\lambda\rangle$. A weighted full-matrix least-squares anisotropic refinement using 2026 observed pairs, with $I > 2\sigma(I)$ converged to $R = 7.2\%$ and $R_w = 8.7\%$, respectively. The absolute configuration of rosmanol triacetate was determined comparing the 45 Bijvoet pairs with Δ Fc > 0.075 for which the averaged Bijvoet difference was 0.973 for the right enantiomer vs. 1.046 for the wrong one [11]. The X-ray data has been deposited at Cambridge Crystallographic Data Centre, U.K.

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