THE STRUCTURE AND STEREOCHEMISTRY OF TEUCRIN A

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To confirm the structure of teucrin A (I) proposed previously [1] and to study the stereochemistry of this diterpenoid, we have investigated a number of its derivatives and have performed an analysis of their NMR spectra.

The NMR spectrum of the acetate (II) was considered previously only in connection with the position of the hydroxyl in the molecule of teucrin A. The present paper gives the results of an analysis of the signals of the protons which enables additional information to be obtained on the structure of (I). This relates mainly to the protons of rings A and B.

In the spectrum of the acetate (II), in addition to the H_7 signal there is another one-proton signal at 4.82 ppm, which is also present in the spectrum of teucrin A (Table 1). It belongs to the proton of an unsaturated γ-lactone (H_6) present in the vicinal position to H_7, as was confirmed by experiments using the double-resonance precedure. When the H_7 signal was saturated with a strong radiofrequency field, the H_6 signal contracted and, conversely, a saturation of the latter led to the conversion of the H_7 signal into a doublet (J = 2.5 Hz) due to vicinal coupling with H_8. The form of the H_6 signal is, in our opinion, a consequence of long-range coupling with the H_3 protons (J = 1–1.5 Hz). A broad signal in the 2.8-ppm region can be assigned to H_{10} coupling both with the neighboring H_1 protons and also with H_3. These results are satisfactorily explained by the mutual location of the oxygen functions and the double bond in the molecule.

The signals of the protons of the pentaacetate (IV), obtained by acetylating the pentaol (III) show the positions of the lactone rings in the molecule of teucrin A.

In addition to the signals of five acetate methyl groups in the 2-ppm region, the furan protons, and the H_{12} signal (see Table 1), the NMR spectrum of compound (IV) (Fig. 1a) clearly shows two groups of signals (4.70 and 4.11 ppm) forming a system of the AB type. They are due to the methylene groups at C_{19} and C_{17}, respectively, formed from the lactone carbonyls on the reduction of (I) and are located on quaternary carbon atoms, since otherwise they would appear in the form of multiplets instead of the actual AB quartets [2]. In a system of the kolavane type, taking into account the facts given previously [1], such carbon atoms can only be C_4 and C_9. The presence of one $-CH_2-OAc$ group at the unsaturated C_4 atom (4.7 ppm) is confirmed by the oxidation of the pentaol (III) with manganese dioxide to the lactone (V), which is not oxidized by sodium periodate. This is possible only if the hydroxy group is present in the allyl position to the double bond.

The enol-lactone (VI) obtained by the dehydration of teucrin undergoes hydrogenation over a catalyst to form a lactone acid [methyl ester (VII)] [1]. The absence of hydrogenolysis in the hydrogenation of the enol-lactone, which is generally observed in such cases [3], induced us to confirm the structures of these substances by a more detailed study of their NMR spectra. The spectrum of the product of the dehydration of (VI) lacks a H_6 signal (see Table 1), and, in addition to the signals of the furan and methyl protons and of a H_{12} triplet, the doublet of the H_7 olefinic proton is found at 5.23 ppm. In the spectrum of the product of the hydrogenation of (VII), this signal has disappeared and has been replaced by the multiplet of the H_6 proton at 4.68 ppm entering into spin-spin coupling with the two hydrogen atoms at H_7 and the protons on C_3.

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TABLE 1. Chemical Shifts and Spin-Spin Coupling Constants in the NMR Spectra of Derivatives of Teucrin A

Compound	H_6	H_7	H_{10}	$H_{11}'H_{11}''$	H_{12}	H_{14}	H_{15}	H_{16}	H_{17}	H_{18}	H_{20}	Other protons
I*	5,12 m $J_{6,7}=4,5$	4,21 dd $J_{7,8}=2,5$	3,00 m	2,66 d $J_{11,12}=8,5$	5,75 t	6,53	7,61	7,83	—	—	1,20 d J=7,0	
II	4,82 m $J_{6,7}=5,0$	5,50 dd $J_{7,8}=2,5$	2,80 m	2,62d† 2,64d	5,40 t	6,36	7,38	7,42	—	—	1,04 d J=7,0	
IV	5,25 m	5,11dd	—	—	5,89 dd J+J'=12	6,28	7,27	7,35	4,27/3,92 AB J=12,5	4,76/4,6 AB J=12,0	1,08d J=7,0	15H, 1, 90—2,00 Acetate CH_3 groups
VI	—	5,23 d $J_{7,8}=2,5$	2,85 m	2,53d† 2,57d	5,36 t	6,35	7,37	7,41	—	—	1,19 d J=7,5	H_8, 2,75
VII‡	4,68 m	—	2,62 m	—	—	—	3,10 - —3,90	3,10— —3,90	—	—	0,89 d J=6,0	3 55 Ester CH_3
IX**	7,17s	5,16 d J=3,0	2,80 m	—	4 80 dd J+J'=16	6,45	7,37	7,41	4,00/3,69 AB J=12,5	7,17 s	1,05 J=7,0	
X**	4,85 m	4,58d J=2,0	2,76 m	—	—	—	3,10— —3,95	3,10— —3,95	—	—	1,10 d J=7,0	
XI	4,92 m	4,54 d J=2,0	2,87 m	—	—	6,23	7,20	7,30	—	—	1,12 d J=7,0	

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* Spectrum taken in deuteropyridine.

†$J_{11',12}=J_{11'',12}=8.5$ Hz (continued by double resonance).

‡In CCl_4.

**At a frequency of 60 MHz. For more accurate assignment of the signals, the spectra of compounds (II), (IV), and (VI) were taken at frequencies of 60 and 100 MHz; s – singlet; d – doublet; t – triplet; dd – doublet of doublets; m – multiplet. The spin-spin coupling constants are given in Hz.

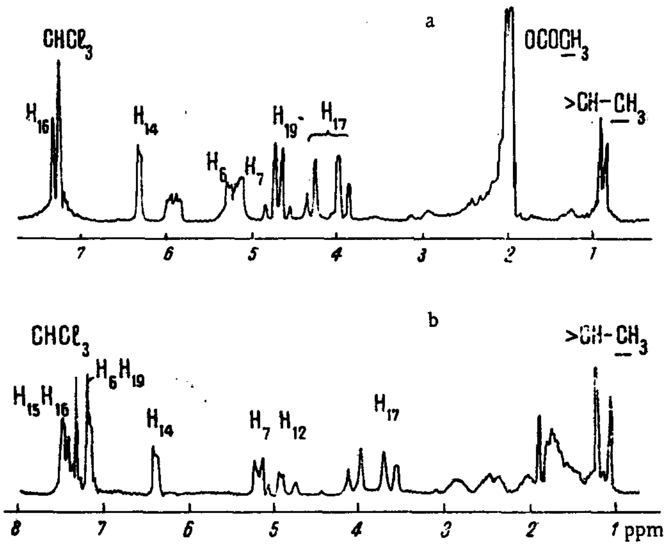


Fig. 1. NMR spectra of the pentaacetate (100 MHz) (a) and of compound (IX) (60 MHz) (b).

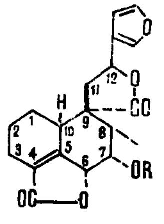
In the 2.6-3.0-ppm region in compound (VI) in addition to a one-proton multiplet which is present in the spectra of the other compounds (see Table 1), an additional signal is found which can be assigned to the H_8 allyl proton interacting with the methyl group (J = 7 Hz) and with the H_7 proton (J = 2.5 Hz). Thus, the dehydration of teucrin A takes place with the formation of a Δ^6 bond, from which it follows that the structure of the compound obtained must be represented by formula (VI).

Additional information was obtained also for the structure of the product of the periodate oxidation of the pentaol (III). It undergoes oxidation with the formation of the acetal (VIII), which does not contain a carbonyl group. Compound (VIII) is unstable even in the cold. It changes into a hydroxyl-free derivative (IX) containing one more furan ring. In its NMR spectrum (Fig. 1, b), as compared with the spectra of the other derivatives with a furan ring described above, there is an additional two-proton broadened singlet at 7.17 ppm due to the H_6 and H_{19} protons of the new furan ring. This is explained by the splitting out of the elements of water from the hemiacetal group of compound (VIII) with the formation of a more stable furan derivative, as is observed in the marrubiin series [4, 5]. In addition to this, in the NMR spectrum of (IX) a one-proton signal can be seen at 4.9 ppm which is characteristic for H_{12} and which is shifted upfield as compared with the signal of the same proton in the lactone. The doublet at 5.17 ppm is formed as the result of the interaction of the H_7 proton, deshielded by the two acetal oxygen atoms, with the H_8 proton. Another proof of the presence of an acetal grouping is the existence of an AB system with its center at 3.8 ppm due to the two protons at C_{17}. This unambiguously confirms the structure of substance (IX) and, consequently, also the correctness of the explanation given of the periodate oxidation of the pentaol (III).

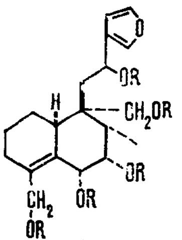
On the basis of the chemical and spectral results obtained, we drew the conclusions given below which permit teucrin A to be assigned the configuration expressed by formula (I) or its mirror image.

It follows from a consideration of Stuart–Briegleb models of the possible configurations for teucrin A that the most probable are those in which the C_9-C_{10} bond is equatorial and the hydrogen at C_{10} occupies the axial position with ring B in the chair conformation. In the opposite case (axial bond or boat conformation for ring B) ring B would be highly strained and translactonization during the hydrogenation process with the formation of compound (X) would be impossible, since the hydroxy group at C_7 and the carbonyl at C_{17} would be very remote from one another (see scheme following page).

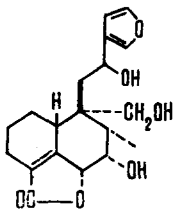
The orientation of the substituents at C_7 and C_9 was shown on the basis of the following considerations. The formation of the lactones (X) and (XI) in the hydrogenation of teucrin is possible only with the mutual cis location of the C_9-C_{17} bond and the hydroxyl at C_7 which, according to NMR spectroscopy, is axial, because the half-width of the signal of the H_7 proton is 9 Hz, which corresponds to an equatorial proton [6]. The axial orientation of the hydroxyl is also shown by the difficulty of its acetylation. Consequently, the C_9-C_{17} bond is axial and the C_9-C_{11} side chain is in the most stable equatorial position, as in all bicyclic diterpenoids. It was shown by the double-resonance method that the coupling constant between the vicinal H_7 and H_8 protons in compounds (X) and (XI) is close to zero, while in the spectrum of teucrin it is 2.5 Hz. This is due to the fact that after translactonization the $H_7-C_7-C_8-H_8$ dihedral angle between these protons



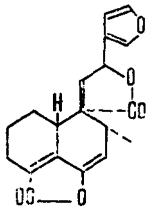
I. R=H II. R=Ac



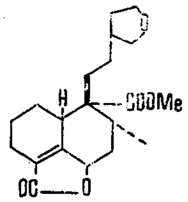
III. R=H IV. R=Ac



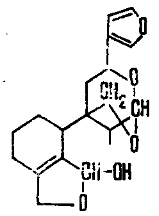
V



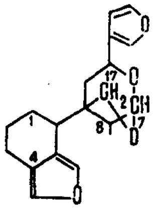
VI



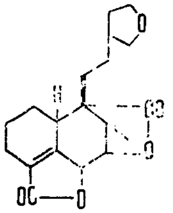
VII



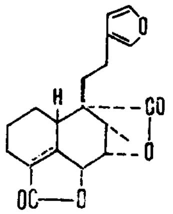
VIII



IX



X



XI

is close or equal to 90°. It was established by a consideration of molecular models that this is possible only if the methyl group is equatorial. With an axial position of the methyl group, this angle would be greater than 90° and, consequently, the coupling constant would differ from zero. The C_6-O bond must also be equatorially directed, since otherwise the formation of a lactone ring would be impossible. Another confirmation of what has been said is the ease of the periodate oxidation of compound (III), which is characteristic for cis-1,2-diols.

Thus, the relative positions of the substituents at all the asymmetric centers of the molecule of teucrin A can be represented by formula (I). Work to establish its absolute configuration is continuing.

EXPERIMENTAL

The IR spectra were taken on a UR-10 spectrometer and the NMR spectra on Varian A-56/60A and Varian HA-100 instruments in deuterochloroform. The internal standard was HMDS, the chemical shift of which in the scale is 0.04 ppm. The double-resonance experiments were performed on the HA-100 spectrometer using a Hewlett-Packard ABR-200 sonic generator with frequency sweep. The elementary analyses of compounds (IV), (V), and (IX) corresponded to the calculated figures.

Production of the Pentaacetate (IV). A solution of 200 mg of the pentaol (III) in 2 ml of pyridine was treated with 1 ml of acetic anhydride and the mixture was left at room temperature for two days. After the usual working up, extraction with ether, and purification by chromatography on silica gel in chloroform, 250 mg of an amorphous substance was obtained. IR spectrum (CCl_4) (cm^{-1}): 1740 (very strong), 1600, 1510, 1370, 1240 (very strong), 1030, 880.

Preparation of the Lactone (V). A mixture of 150 mg of the pentaol (III), 8 ml of dry acetone, and 1.5 g of active manganese dioxide was shaken for 3 h [7]. The solid matter was filtered off and the acetone was distilled off. The residue was chromatographed on silica gel in a mixture of chloroform and 2% of methanol. About 80 mg of the lactone (V) was isolated in the form of a noncrystallizing vitreous mass. IR spectrum (chloroform) (cm^{-1}). 3620, 3400 (OH), 1750, 1690 (α,β-unsaturated lactone), 1600, 1507, 880 (furan). UV spectrum (ethanol): λ_{max} 220 nm (ε 10,150), 209 (8900).

Preparation of Compound (IX). A solution of 200 mg of (VIII) in chloroform was heated at 80-90°C for half an hour. The residue after the evaporation of the solvent was chromatographed on silica gel in chloroform, giving 120 mg of an amorphous substance. IR spectrum (chloroform), cm^{-1}: 1600, 1507, 1030, 980, 890, 880. UV spectrum (ethanol): λ_{max} 212 nm (ε 8500).

SUMMARY

The structure of teucrin A has been confirmed by spectral and chemical methods and the relative configurations at all the asymmetric centers have been shown.

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