ABSOLUTE CONFIGURATION OF TEUCRIN-A

D. P. Popa and A. M. Reinbol'd

UDC 547.913

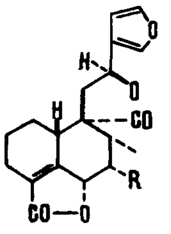
We have shown the structure and relative stereochemistry of teucrin-A – the main terpenoid of Teucrim chamaedrys L. – previously [1, 2]. In the present communication we give information enabling the absolute configuration (I) to be established for this compound.

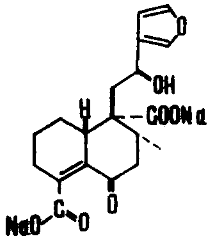
The solution of the problem reduced to determining the absolute configuration of the C_{10} asymmetric center, for which we used the method of circular dichroism (CD) applied to the ketone (III) and its derivative (VIII) obtained for this purpose.

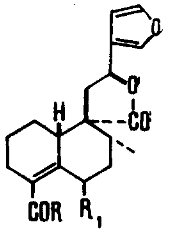
Teucrin-A dissolves in a methanolic solution of alkali with the opening of both lactone rings, as is shown by the IR spectrum of the carboxylate (II) obtained. When the solution is neutralized, the partial lactonization of the acids formed take place, since the product isolated contains, according to its spectra, a γ-lactone group (1770 cm^{-1}) and a carboxy group (1710 cm^{-1}).

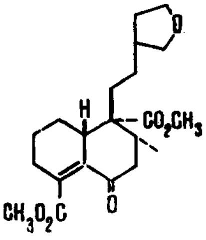
The methylation of the product of the interaction of teucrin-A with alkali by dimethyl sulfate in aqueous solution gave the keto lactone (III) $C_{20}H_{22}O_6$, the structure of which was shown by the following facts. The substance does not contain active hydrogen. Its IR spectrum shows absorption bands for a γ lactone, a methyl ester, and an α,β-unsaturated ketone, and the UV spectrum has two maxima, at 212.5 nm (furan) and 247 nm (unsaturated carbonyl). The saturated γ lactone occupies the same position as in teucrin-A: the hydrogenation of compound (III) also takes place with hydrogenolysis and the formation of the acid (IV).

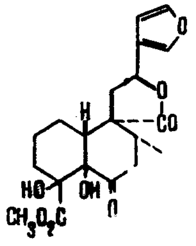
The reduction of the keto lactone (III) with sodium tetrahydroborate gave a crystalline substance (V) readily passing into a dilactone (VI). The IR spectrum of the latter showed, in addition to the furan band characteristic for compound (I) an intense band at 218 nm due to an unsaturated lactone. The IR spectrum showed absorption maxima at 1750 and 1690 cm^{-1} [1].

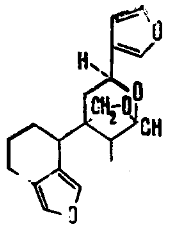

I, VI


II


III, V


IV


VII


VIII

I. R=OH, III. R=OCH_3, R_1=O V. R=OCH_3, R_1=OH VI. R=H

Order of the Red Banner of Labor Institute of Chemistry of the Academy of Sciences of the Moldavian SSR. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 321-324, May-June, 1974. Original article submitted March 13, 1973.

Thus, compound (III) contains ester and ketone groups conjugated with a double bond. Consequently, in the reaction of (I) with alkali, dehydration takes place which, probably through the enolic form, gives a C_6 ketone. The structure of the keto lactone (III) was also confirmed by its NMR spectrum.

Compound (III) shows negative CD coinciding in sign with the Cotton effect of some 6-ketosteroid analogs [3]. On this basis, it could be assumed that in this compound the hydrogen atom at C_{10} had the β orientation. However, the presence of a double bond in it throws doubt on the correctness of this assertion, all the more since there are no examples in the literature for comparison. Consequently, we measured the CD curve of compound (VII), obtained by the hydroxylation of the unsaturated ketone (III) with osmium tetroxide.

It is known [4] that the sign of the CD of 5-hydroxy-6-ketosteroids depends only on the orientation of the substituent at C_{10} and does not depend on the position of the hydroxyl. The latter affects only its amplitude. The maximum of the curve of compound (VII) is in the negative region at 300 nm ($\Delta\varepsilon$ − 1.48), which agrees with the results for 5-hydroxycholestan-6-ones [4]. All this shows the 10β configuration for compounds (VII) and (III) and for teucrin-A.

The configuration at the C_{12}-asymmetric center was established from the NMR spectrum of the derivative (VIII) obtained from teucrin-A by reducing it with lithium tetrahydroaluminate followed by periodate oxidation [1, 2].

In this compound, the C_{12} carbon atom is present in a 6-membered acetal ring. In this ring, the C_{12} proton is in the axial position, since the sum of the spin–spin coupling constants of it with the two H_{11} protons is 16 Hz, which corresponds to the sum of J_{aa} and J_{ae}.

Thus, on the basis of the facts presented, the absolute configuration of teucrin-A can be represented by the formula given above (p. 328).

EXPERIMENTAL

The CD curves were taken on a Spectropol spectropolarimeter (B. A. Babkin, Institute of Organic Chemistry, Novosibirsk), the IR spectra on a UR-10 spectrometer, the UV spectra on a Specord UV-VIS spectrometer, and the NMR spectra on a Varian HA-100 instrument in deuterochloroform (with hexamethyldisiloxane as internal standard). The melting point was determined on a Kofler block. The analyses of all the compounds corresponded to the calculated figures.

Reaction of Teucrin-A with Alkali. With heating, 500 mg of teucrin-A was dissolved in 10 ml of 2% NaOH in methanol. The solution was boiled under reflux for half an hour and was then evaporated in vacuum. The residue was dissolved in 6 ml of water and was methylated with freshly-distilled dimethyl sulfate for 20 h, with the gradual addition of 3 ml of the reagent, the pH being kept at 8-9, and with intensive stirring. The precipitate that deposited was dissolved in chloroform, and the solution was washed with water to neutrality, dried with sodium sulfate, and evaporated in vacuum. The residue (380 mg) was chromatographed on silica gel. Chloroform eluted 290 mg of substance (III). After crystallization from chloroform with ether, mp 148-150°C, $[\alpha]_D + 240°$ (c 0.05; methanol), composition $C_{20}H_{22}O_6$, M^+ 358 (mass spectrometry).

UV spectrum: λ_{max} 212.5 nm (ε 8800), 247 nm (ε 10,000). IR spectrum (chloroform), cm^{-1}: 1770, 1730, 1680, 1640, 1600, 1508, 1170, 1030, 880.

NMR spectrum: 1.10 ppm (3H, doublet, J = 6 Hz, methyl at C_8); 3.53 ppm (3H, singlet − $COOCH_3$); 5.50 (1H, triplet, proton at C_{12}); 6.35 (1H, β −H of furan); 7.40 and 7.44 ppm (1H each, the α and α' protons of furan); CD, λ, nm ($\Delta\varepsilon$): 365 (−0.09), 350 (−0.44), 330 (−1.88), 322 (−2.06), 300 (−1.01), 289 (0), 275, (+1.09) (c 0.047; methanol).

Reduction of Compound (III). To a solution of 70 mg of the substance in 4 ml of methanol were added 0.6 ml of water, 100 mg of boric acid, and, in portions over 3 h, 250 mg of $NaBH_4$. Then the mixture was diluted with water, acidified with hydrochloric acid, and extracted with chloroform. After the usual working up, 60 mg of the crystalline substance (V) was obtained with the composition $C_{19}H_{20}O_5$, M^+ 328 (mass spectrometry), mp 192-195°C (from a mixture of chloroform and ether). UV spectrum: λ_{max} 214 nm (ε 13,600). IR spectrum (chloroform), cm^{-1}: 3500, 3160, 1760, 1730, 1600, 1505, 1170, 880. On standing, it was converted into compound (VI) with mp 207-210°C (chloroform–ether). UV spectrum: 218 nm (ε 15,600); IR spectrum (KBr), cm^{-1}: 3160, 1760, 1750, 1690, 1600, 1500, 880.

Hydrogenation of Substance (III). In 3 ml of acetic acid in the presence of 15 mg of 4% Pd/$BaSO_4$, 90 mg of the substance was hydrogenated. Under normal conditions, 15.8 ml of hydrogen was absorbed, which corresponded to 2.8 equivalents. After the usual working up, 70 mg of an acid was obtained which was methylated with diazomethane. After chromatography on silica gel, 60 mg of (IV) with the composition $C_{21}H_{30}O_6$ in the form of a viscous liquid was isolated. UV spectrum: λ_{max} 207 nm (ε 14,000). IR spectrum (CCl_4), cm^{-1}: 1735, 1680, 1635.

Production of the Diol (VII). A pyridine solution of 110 mg of OsO_4 was added to a solution of 100 mg of the substance in 2 ml of pyridine. After 48 h, the mixture was diluted with water, acidified with hydrochloric acid, and extracted with chloroform. The chloroform solution was saturated with hydrogen sulfide for 10 h. Then it was filtered from the precipitate that had deposited. The filtrate was washed with sodium bicarbonate solution, with ferric chloride, and with water and was dried and evaporated, and the residue was chromatographed on silica gel. Chloroform eluted 40 mg of a hygroscopic osmate. UV spectrum: λ_{max}: 211, 222, 263, 278 nm (ε 9100, 8800, 4500, 4300) [5]. Chloroform containing 2% of methanol eluted 20 mg of the amorphous substance (VII) with the composition $C_{20}H_{24}O_8$. UV spectrum λ_{max}: 210 nm (ε 7500); IR spectrum (KBr): 1750 cm^{-1}, 1730, 1720, 1600, 1505, 880; CD, λ nm (Δε): 400 (+0.21), 380 (+0.42), 350 (+0.64), 330 (+0.63), 320 (0), 300 (−1.48), 280 (−0.85), 260 (0) (c 0.023; methanol).

CONCLUSIONS

The absolute configuration of teucrin-A, a norditerpenoid from Teucrium chamaedrys L. has been shown.

LITERATURE CITED

1. D. P. Popa and A. M. Reinbol'd, Khim. Prirodn. Soedin., 31 (1973).
2. D. P. Popa, A. M. Reinbol'd, and A. I. Rezvukhin, Khim. Prirodn. Soedin., 169 (1973).
3. G. Snatzke, Tetrahedron, 21, 439 (1965).
4. J. R. Bull and P. R. Enslin, Tetrahedron, 26, 1525 (1970).
5. N. A. Milas, J. H. Frepagnier, J. T. Nolan, and M. L. Iliopules, J. Am. Chem. Soc., 81, 4730 (1959).