THE STRUCTURE OF PEREGRINOL, A DITERPENOID FROM MARRUBIUM PEREGRINUM. II

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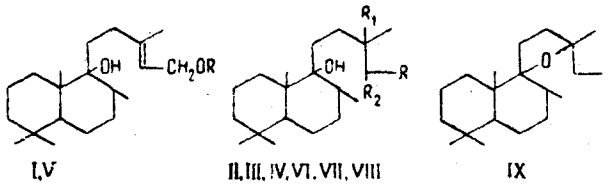
We have previously [1] described a diterpenoid isolated from M. peregrinum L., peregrinol $C_{20}H_{36}O_2$, a bicyclic diterpene diol with a trisubstituted double bond.

In the present communication we give information permitting structure (I) to be assigned to peregrinol.

The hydrogenation of substance (I) in acetic acid on platinum took place with the absorption of 1.8 mole of hydrogen and with the formation of dihydroperegrinol $C_{20}H_{38}O_2$ (II) and a hydrogenolysis product of peregrinol $C_{20}H_{38}O$ (III). When (I) was hydrogenated in alcohol in the presence of palladium on strontium carbonate, less of the peregrinol underwent hydrogenolysis (1.2 mole of hydrogen was absorbed) and the main reaction product was dihydroperegrinol.

The ease of hydrogenolysis of peregrinol makes it possible to assume that its molecule contains at least one allyl hydroxy group:

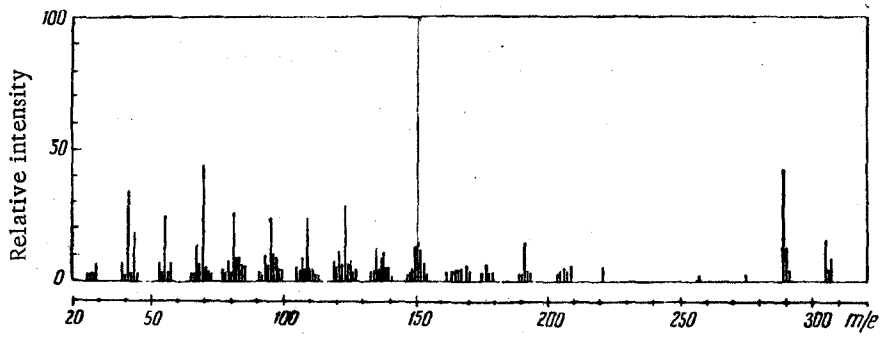


I, V II, III, IV, VI, VII, VIII IX

I R=H; II R=CH_2OH, R_1=R_2=H; III R=CH_3, R_1=R_2=H; IV R=CH_2OH, R_1=R_2=OH; V R=$COCH_3$; VI R=COOH, R_1=R_2=H; VII R=$COOCH_3$, R_1=R_2=H; VIII R=CH_2OTs, R_1=R_2=H.

The hydroxylation of peregrinol with osmic acid gave a tetrol (IV), which consumed two equivalents of periodic acid on oxidation. This means that only one of the two hydroxy groups is present in the allyl position.

The reaction of (I) with acetic anhydride in pyridine gave a monoacetate $C_{22}H_{38}O_3$ (V). The oxidation of dihydroperegrinol with chromic acid [2, 3] led to a hydroxy acid $C_{20}H_{36}O_3$ (VI) with the same number of carbon atoms. The methylation of the latter with diazomethane gave the methyl ester (VII). It can be seen from these facts that one hydroxy group in peregrinol is primary and the other is tertiary.



Mass spectrum of peregrinol.

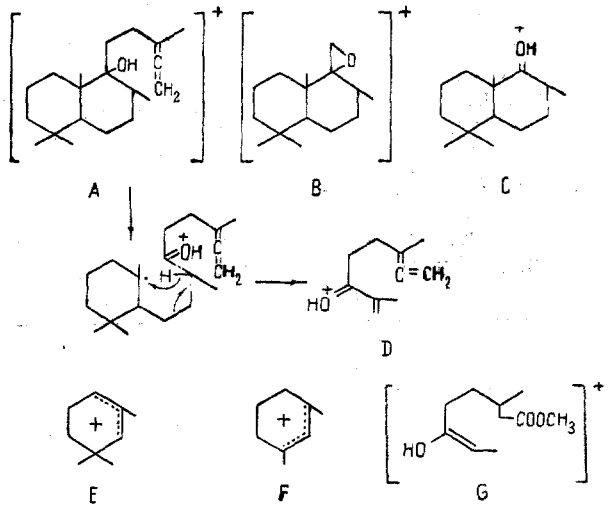
Since the tosylation of dihydroperegrinol and subsequent reduction of the tosylate (VIII) with lithium aluminum hydride gave the hydrogenolysis product of peregrinol (III), it may be assumed that the allyl hydroxyl is primary.

The structure of peregrinol (I) was confirmed by a study of the mass spectra taken on a MKh-1305 instrument with an ionization energy of 90 eV and an ionization temperature in the chamber of 150° C.

In the spectrum of peregrinol (figure), the molecular ion at mass 308 has a low intensity. The ionized molecule very readily loses a molecule of water forming an ion with mass 290 m/e. If it is assumed that in the elimination of water the hydroxy group is split off from position 15 (cf. the appearance of ion D below), structure A (scheme 2) may be assigned to this particle with mass 290. Ion B with mass 222 evidently arises by the splitting of the molecule in the allyl position of the 11,12 carbon–carbon bond with the transfer of a hydrogen atom. The fragment with mass 209 denoted by C in the scheme splits off a molecule of water (metastable transition at 174.5) and is converted into the ion C – 18 with mass 191.

The main peak in the spectrum is formed by ion D with mass 151, which (metastable transition at 78.7) arises from ion A by the elimination of a particle with mass 139. This is analogous to the fragmentation of grindelane (IX) [5] which also forms the ion M – 139 as the main peak in the mass spectrum.

Ion D, in contrast to fragment C, does not lose a molecule of water; the conjugation of an oxonium ion with a secondary double bond evidently promotes the stabilization of ion D. The ions with masses 123 and 109 may be represented by structures E and F [4, 5].



The mass-spectroscopic fragmentation of the ester (VII) is similar to that of peregrinol (I). Here the molecular ion is represented by a comparatively intense peak at mass 338. In the spectrum of the ester, the M – 18 ion has a very low intensity, which once again confirms the presence of a tertiary hydroxy group in position 9 in ion A.

Ion B is not found in the spectrum of the ester, since in this case there is no double bond. On the other hand, the fragments C, C –18, and E with masses 209, 291, and 123 are preserved. Very intense peaks in the central part of the spectrum are due to fragments of types D (199 m/e) and D –32 (167 m/e).

The loss of methanol by ion D shows the presence of a metastable transition at 140.2. Structure G may be assigned to the fragment with mass 186. Although there is no metastable transition in the spectrum, it can be stated with confidence that the ion G loses a molecule of methanol to form the ion G – 32 with mass 154. Similarly, the ion G in the spectrum of peregrinol has mass 138.

The mass spectra of peregrinane (from peregrinol) and of sclarane (from sclareol) are also similar. Their molecular peak is at 278 m/e, and they have characteristic peaks at M – 15, 123 m/e (E) and 109 m/e.

Thus, the mass-spectrometric fragmentation of peregrinol and the ester (VII) confirm the structure (I), including the position of the tertiary hydroxy group on C – 9. The latter is further confirmed by the results of the NMR spectra (taken in a Varian-100 instrument in $CDCl_3$ solution), according to which the molecule of peregrinol contains one secondary methyl group (doublet at 0.91 ppm, J = 6 Hz) and four tertiary methyl groups (three singlets at 0.97, 0.90, and 0.88 ppm and a singlet at 1.68 ppm due to a methyl group on a double bond).

If one takes into account the fact that the IR spectra of peregrinol and its derivatives are very similar to the spectra of some sclareol derivatives, peregrinol may with confidence be assigned the structure 13-labdene-9, 15-diol(I). At the moment we are carrying out a correlation of peregrinol with sclareol. This part of the investigation, and also the chemical proof of the position of the tertiary hydroxy group, will be published in a subsequent paper.

Experimental

Hydrogenation of peregrinol. A. A solution of 205.2 mg of peregrinol in 15 ml of glacial acetic acid was saturated with hydrogen in the presence of 21 mg of platinum oxide (Adams). At 19° C and 738 mm, 26.6 ml of hydrogen were absorbed, which corresponds to 1.8 equivalents. Then the solution was diluted with water (120 ml), and extracted with ether (4 × 25 ml). The ethereal extracts were washed with sodium bicarbonate solution and water, dried with sodium sulfate, and distilled.

Crystallization of the resulting oily residue from petroleum ether gave 45 mg of dihydroperegrinol (II) with mp 106.5°–108.5° C, $[\alpha]_D^{20}$ +3.1° (c 7.8; chloroform).

Found, %: C 77.47; H 12.28; H_{act} 0.63. Calculated for $C_{20}H_{38}O_2$, %: C 77.36; H 12.34; $2H_{act}$ 0.64.

The mother liquor remaining after the crystallization of the dihydroperegrinol was chromatographed on 10 g of silica gel. Petroleum ether–benzene (1:1) eluted 150 mg of (III) in the form of a liquid with bp 112°–115° C at 0.03 mm, $[\alpha]_D^{20}$ +6.4 (c 12.6; chloroform).

Found, %: C 82.01; H 13.13. Calculated for $C_{20}H_{38}O$, %: C 81.56; H 13.01.

B. A solution of 106 mg of peregrinol in 15 ml of ethanol (or ethyl acetate) was hydrogenated in the presence of 32 mg of 5% Pd/$SrCO_3$. At 21° C and 734 mm, the substance absorbed 9.2 ml of hydrogen or 1.2 equivalents. After the usual working up and crystallization from petroleum ether, 96 mg of (II) identical with the product described above, and traces of the hydrogenolysis product (III) were obtained.

Preparation of the tetrol (IV). A solution of 142 mg of peregrinol in 12 ml of absolute ether was treated with 200 mg of OsO_4 in 5 ml of ether and five drops of dry pyridine. The mixture was left at room temperature for 45 hr. Then 20 ml of ether and 30 ml of 10% caustic potash solution containing 3 g of mannitol were added and the mixture was shaken until the ethereal layer was clear. The ethereal layer was washed with water until neutral, dried, and distilled. The residue was chromatographed on 5 g of silica gel. Ether (200 ml) eluted 138 mg of crude (IV) in the form of a brown oil, which was crystallized from petroleum ether and from petroleum ether–ethyl acetate (5:2). Long crystalline fibers with mp 77°–79° C were obtained.

Found, %: C 70.48; H 11.45; H_{act} 1.16. Calculated for $C_{20}H_{38}O_4$, %: C 70.13; H 11.18; $4H_{act}$ 1.16.

The tetrol (IV) was oxidized with periodic acid and the excess was determined polarographically, which showed that the reaction had consumed 2.02 equivalents of HIO_4.

Peregrinol monoacetate (V). A solution of 130 mg of peregrinol in 1 ml of dry pyridine was mixed with 1 ml of acetic anhydride and left at room temperature for 20 hr. Then the mixture was diluted with water and extracted with ether, and the ethereal extract was washed, dried, and distilled. The resulting pale yellow oil was chromatographed on 7 g of silica gel. Benzene (80 ml) eluted 100 mg of (V) and an almost colorless liquid with $[\alpha]_D^{20}$ +12° (c 10; chloroform). IR spectrum (taken on a UR-10 instrument): 1675 (>C=C–), 1735, 1240 (acetate), and 3500 (OH) cm^{-1}.

Found, %: C 75.25; H 10.90. Calculated for $C_{22}H_{38}O_3$, %: C 75.38; H 10.93.

Oxidation of dihydroperegrinol. A. An oxidizing agent prepared from 150 mg of sodium dichromate, 0.1 ml of concentrated sulfuric acid, and water to make 0.7 ml was added to a solution of 70 mg of (II) in 7 ml of ether. The mixture was stirred vigorously at room temperature for 3 hr. Then another 15 ml of ether was added, and the ethereal layer was washed with water and 10% caustic potash. The alkaline solutions were acidified with sulfuric acid and extracted three times with ether. After the usual working up, the ethereal solutions were distilled. The residue was crystallized from petroleum ether. It gave 50 mg of (VI) with mp 115°–116° C. IR spectrum: 1700 (COOH), 2650 (OH of an acid), 3500, 3610 (OH) cm^{-1}.

Found, %: C 73.84; H 11.20. Calculated for $C_{20}H_{36}O_3$, %: C 74.02; 11.18.

B. An oxidizing mixture prepared from 270 mg of chromic anhydride, 0.25 ml of concentrated sulfuric acid, and 1 ml of water was added dropwise to 30 mg of (II) in 2 ml of acetone until a permanent light brown coloration was produced. After 20 min, the excess of oxidizing agent was decomposed with methanol, water was added, and the mixture was extracted with ether. The ether was washed with a solution of alkali. The usual working up of the alkaline solutions gave an acid (25 mg) which was identical with the acid (VI) described above in respect to its melting point, IR spectrum, and R_f value in thin-layer chromatography.

Methyl ester of (VII). A solution of 80 mg of (VI) in 5 ml of ether was added dropwise to an ethereal solution of diazomethane obtained from 200 mg of nitrosomethylurea. The mixture was kept at room temperature for 10 min and the excess of diazomethane was decomposed with acetic acid, after which the ethereal solution was treated in the usual way.

Distillation of the ether gave 64 mg of substance (VII), which was distilled at 160° C (bath temperature) and

0.02 mm, $[\alpha]_D^{22}$ + 2.6° (c 7.7; chloroform). IR spectrum: 1722 (ester CO), 3600 (OH) cm^{-1}.

Found, %: C 74.63; H 11.35. Calculated for $C_{21}H_{38}O_3$, %: C 74.51; H 11.32.

Tosylation of dihydroperegrinol and reduction of the tosylate with $LiAlH_4$. A solution of 40 mg of (II) in 1 ml of dry pyridine was treated with 70 mg of p-toluenesulfonyl chloride and the mixture was allowed to stand at room temperature for 19 hr. Then it was diluted with water and extracted with ether. The ethereal extracts were washed with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water, and were then dried and distilled. The residue was dissolved in 3 ml of tetrahydrofuran, 150 mg of $LiAlH_4$ was added, and the mixture was boiled for 3 hr. The excess of $LiAlH_4$ was decomposed with alcohol, water was added, and the mixture was acidified with sulfuric acid and extracted with ether. The ethereal solutions were treated in the usual way. The residue from the distillation of the ether was chromatographed on 2 g of alumina (activity grade III). Petroleum ether eluted 30 mg of (III), identical (IR spectra and thin-layer chromatography) to the product of the hydrogenolysis of peregrinol.

The IR spectra were taken by S. F. Manol and the analyses were performed by R. S. Shish.

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Summary

On the basis of chemical and spectroscopic data, the diterpene alcohol peregrinol has been assigned the structure 13-labdene-9, 15-diol.

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