THE STRUCTURE OF PEREGRININ

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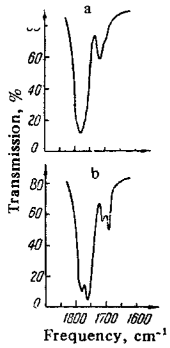
It has been reported previously [1] that a new diterpenoid peregrinin, a furan ketolactone related to marrubiin, has been isolated from Marrubium peregrinum L. On the basis of NMR and mass spectrometry and some chemical reactions, in particular the ready decarboxylation of the acid obtained from the lactone, it has been shown that peregrinin is 3-oxomarrubiin (I) [2].

Simultaneously, Italian chemists [3] isolated 3-oxomarrubiin from another species of horehound, Marrubium incanum. We have compared peregrinin with a sample of 3-oxomarrubiin kindly sent to us by Prof. L. Canonica (Milan, Italy). The IR spectra of the substance in KBr differ substantially in the carbonyl region (figure). The difference disappears when the spectra are recorded in chloroform solution.



In this paper we give a detailed proof of the structure and stereochemistry of peregrinin and also of a substance accompanying it, the new diterpenoid 3-oxotetrahydromarrubiin.

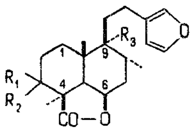
It can be seen from a comparison of the mass spectra of peregrinin and marrubiin (II) [4] that the fragments either coincide in mass and in intensity or each fragment of marrubiin corresponds to a peregrinin peak of equal intensity but differing from it by 14 m/e, i. e., by one carbonyl group.

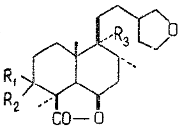
The position of the keto group in ring A in the molecule of peregrinin was established by comparing the peak a of highest intensity in the middle region of the spectrum of I, with m/e 123 (35%), with the corresponding peak a – 14 having m/e 109 (80%) in marrubiin and arising, as is known, by the cleavage of its molecule at the 5–6, 9–10, and 4–9 bonds.

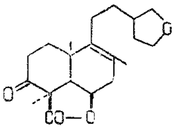
A confirmation of this statement is that the dehydration of peregrinin does not form an α,β-unsaturated ketone and, consequently, the carbonyl group cannot be at $C_{(7)}$ or $C_{(11)}$, the only possible positions outside ring A.

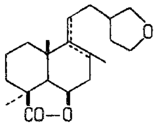
Peregrinin is an unstable compound readily decomposing in solutions in the air. Consequently, we studied its tetrahydro derivative (III), obtained by the hydrogenation of I in ethyl acetate over palladium.

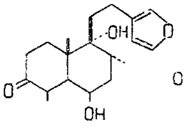
The identity of the carbon skeletons of tetrahydroperegrinin (THP) and tetrahydromarrubiin (THM) and also the identical arrangement of the lactone rings in their molecules was shown by the reduction of THP with amalgamated zinc by Clemmensen's method. Under the conditions of this reaction an intermediate product of the first stage is the unsaturated ketone IV, with mp 176° C. Further reduction leads to a mixture of isomers (V) with IR spectra different from that of dehydrated THM. However, the hydrogenation of all these products gave identical substances VI. Although boiling THM with hydrochloric acid in the absence of amalgamated zinc also took place with dehydration, a product with mp 124° C was formed the IR spectrum of which differed from that of IV only in the 1000–1100 cm^{-1} region.

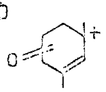

I, II


III, VI-IX


IV


V


X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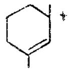
a -14

I. $R_1+R_2=O$, $R_3=OH$. II. $R_1=R_2=H$, $R_3=OH$. III. $R_1+R_2=O$, $R_3=OH$. VI. $R_1=R_2=R_3=H$. VII. $R_1=H$. $R_2=R_3=OH$. VIII. $R_1=H$, Δ^2 –, $R_3=OH$. IX. $R_1=R_2=H$, $R_3=OH$.

It is obvious that the splitting off of a tertiary hydroxyl group under the same conditions takes place with the formation of double bonds in different positions, and possibly with the formation of a three-membered ring through the elimination of hydrogen from the $C_{(5)}$ position.

The position of the tertiary hydroxyl group and the stereochemistry of peregrinin remained unclear. This was shown by the conversion of THP into THM by the reduction of the former with $NaBH_4$ to the alcohol VII, the splitting out of the resulting secondary hydroxyl group by boiling the tosylate in pyridine, and subsequent hydrogenation of the unsaturated compound VIII [3]. The compound obtained in this way was identical with respect to its IR spectrum, specific rotation, and behavior on TLC with substance IX, the structure and stereochemistry of which are known [5, 6]; a mixture of these substances gave no depression of the melting point.

The position of the keto group in ring A was determined in the following way. In the NMR spectrum of peregrinin, kindly recorded for us by Dr. Z. Samek (Prague, Czechoslovakia), the methyl group at $C_{(4)}$ is represented by a signal at 1.47 ppm, shifted considerably in the weak-field direction as compared with the same signal of marrubiin (1.30 ppm) [5], which is explained by the presence of a keto group in the α-position with respect to the methyl group.

In addition, the action of ethanolic alkali on peregrinin gave as the main product the nor- derivative $C_{19}H_{28}O_4$(X). This is possible only if peregrininic acid, obtained by the cleavage of the lactone ring of the diterpenoid I, is a β-oxoacid.

Having analyzed the features of the optical rotatory dispersion and compared the molecular rotation of peregrinin at the extreme points with the values for 5α-chlestanones [7] and oxomannoyl oxides [8] we confirmed the conclusion that peregrinin is a 3-oxo derivative.

In a study of secondary substances from the same plant we isolated another new diterpenoid with mp 173° C, $[\alpha]_D^{18}$ +36°. The IR spectrum, TLC behavior, and absence of a depression in mixtures with THP obtained by the hydrogenation of I showed that this substance is natural 3-oxotetrahydromarrubiin (III).

EXPERIMENTAL

The IR spectra were recorded on a UR-10 spectrometer, the NMR spectra on a HA-Varian-100 instrument in $CDCl_3$ solution (working frequency 100 MHz, the signal of tetramethylsilane takes as 0), and the mass spectra on a MKh-1303 instrument at 153° C with an ionization energy of 90 eV. The optical rotatory dispersion of peregrinin was determined on a Japan Spectroscopic Co. Ltd. ORD/UV-5 polarimeter, the specific rotations for all the other compounds were determined in chloroform at 18° C, and the melting points of the substances on a Kofler block. The adsorbent for TLC was a mixture of silica gel and gypsum in a fixed layer.

Peregrinin. Mp 176° C (from benzene), NMR spectrum, ppm: 0.90 (3H, singlet, methyl at $C_{(10)}$), 1.04 (3H, doublet, J = 6 Hz, methyl at $C_{(8)}$), 1.47 (3H, singlet, methyl at $C_{(4)}$), 2.86 (1H, doublet, J = 5 Hz, proton at $C_{(5)}$), 4.14 (1H, singlet, proton of a hydroxyl), 4.70 (1H, resolved triplet, J = 5 Hz, proton at $C_{(6)}$), 6.32 (1H, β-H of furan), 7.36 and 7.48 (1H each, α- and α'-protons of furan). Mass spectrum (main peaks, m/e): 346 M^+, 328, 251, 223, 179, 165, 152, 149, 135, 123, 109, 95, 81, 67, 55, 53, 41. Optical rotatory dispersion curve in methanol (c 0.48), 27° C:

$[\alpha]_{589}$ +43.4°, $[\alpha]_{400}$ +141°, $[\alpha]_{340}$ +353°, $[\alpha]_{328}$ +530°, $[\alpha]_{316}$ +760°, $[\alpha]_{275}$ −495°, $[\alpha]_{265}$ −424°.

Hydrogenation of peregrinin. One gram of the substance was dissolved in acetic acid with heating and was hydrogenated in the presence of $Pd/BaSO_4$. Two equivalents of hydrogen were absorbed. The usual working up yielded white crystalline tetrahydroperegrinin (THP), (III), with mp 153° C, giving a single spot on TLC. After repeated recrystallization from methanol, the mp of the substance was 200–202° C, $[\alpha]_D$ +37° (c 6.86). IR spectrum, cm^{-1}: 1780 (lactone), 1710 (ketone), 3400 (OH).

Found, %: C 68.48, 68.36; H 8.59, 8.71. Calculated for $C_{20}H_{30}O_5$, %: C 68.54; H 8.63.

Clemmensen reduction of THP. Concentrated HCl and 1 g of freshly-amalgamated zinc were added to a solution of 100 mg of substance III in ethanol, and the mixture was boiled for 20 hr. After the usual working up and chromatography on silica gel in the benzene–ether (4 : 1) system, two products were isolated. The first was crystalline IV with mp 176° C (from ether); IR spectrum (CCl_4), cm^{-1}: 1780 (lactone), 1705 (C=O), 1040, 1060, 1080, 1100; no OH or double bonds.

Found, %: C 72.00, 71.86; H 8.40, 8.37. Calculated for $C_{20}H_{28}O_4$, %: C 72.26; H 8.49.

The second product (V) was liquid. Its IR spectrum (film) had absorption bands at, cm^{-1}: 1760 (lactone), 1650, 3050 (double bonds); no bands for C=O and OH.

The subsequent Clemmensen reduction of the purified ketone IV led to product V.

Hydrogenation of V. The mixture of liquid isomers (V) obtained from THP (0.1 g) was dissolved in acetic acid and hydrogenated in the presence of PtO_2. The amount of hydrogen absorbed was 1 mole. Dehydrated liquid THM was hydrogenated under the same conditions. In both cases the liquid product VI was obtained. The IR spectra of the substances obtained were identical.

Dehydration of THP with hydrochloric for acid. With heating, 0.6 g of substance III was dissolved in methanol, conc. HCl was added, and the mixture was boiled for 4 hr. A white crystalline substance with mp 124° C (from ether) was isolated. IR spectrum (KBr) cm^{-1}: 1780 (lactone), 1705 (C=O), 1050, 1080, 1100; no OH group or double bonds.

Found, %: 72.30, 72.52; H 8.32, 8.42. Calculated for $C_{20}H_{28}O_4$, %: C 72.26; H 8.49.

Reduction of THP with $NaBH_4$. Over 1 hr, 1 g of $NaBH_4$ was added to a solution of 0.5 g of the substance in 15 ml of aqueous methanol. Crystals of VII with mp 138° C were isolated. IR spectrum (chloroform , cm^{-1}: 1750 (lactone); no C=O. Found, %: C 68.49, 68.79; H 9.23, 9.30. Calculated for $C_{20}H_{32}O_5$, %: C 68.15; H 9.15.

Preparation of THM from the diol VII. A solution of 0.2 g of the substance in 5 ml of dry pyridine was treated with 0.25 g of p-toluenesulfonyl chloride and the mixture was left for a day. The crystalline precipitate with mp 154–156° C that separated out was boiled in pyridine for 12 hr, giving 0.2 g of the unsaturated product VIII, which was hydrogenated over PtO_2, and a crystalline product with mp 135° C. A mixture with THM (mp 123° C) melted at 127° C. The slightly higher melting point of the new compound as compared with THM from I is obviously due to the formation of a mixture of isomers of $C_{(13)}$ with a somewhat different composition from that in the hydrogenation of I. The IR spectra were identical. $[\alpha]_D$ +24.4° (c 4.83).

Reaction of peregrinin with alkali. A solution of 0.4 g of peregrinin in 5 ml of ethanol was treated with 1 g of KOH and the mixture was boiled for 6 hr. The reaction products, isolated by the usual methods, were methylated with diazomethane and were then chromatographed on silica gel. A mixture of benzene and ether (3 : 1) eluted 0.2 g of substance X with mp 145–147° C. IR spectrum (chloroform), cm^{-1}: 1705 (C=O); no lactone; 3400, 3600 (OH).

Found, C 71.11, 70.84; H 8.73, 8.65. Calculated for $C_{19}H_{28}O_4$, %: C 71.22; H 8.81.

Isolation of natural THP. After the chromatographic separation of peregrinin on Al_2O_3 or SiO_2, the more polar fractions were found to contain a crystalline product with mp 173° C, $[\alpha]_D$ +36° (c 7.26), the IR spectrum of which was identical with that of III. A mixture with III gave no depression of the melting point.

Found, %: C 68.37, 68.25; H 8.60, 8.57. Calculated for $C_{20}H_{30}O_5$, %: C 68.54; H 8.63.

CONCLUSIONS

1. The structure and stereochemistry of peregrinin, a diterpenoid isolated from *Marrubium peregrinum* L., have been shown.

2. The same plant has yielded a new diterpenoid identical with the tetrahydroperegrinin obtained by the hydrogenation of peregrinin.

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