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THE STRUCTURE OF VULGAROL – A NEW DITERPENOID FROM *Marrubium vulgare*

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UDC 547.913

We have previously [1] reported the isolation from the plant mentioned in the title (family Labiatae) of a new minor diterpene glycol $C_{20}H_{36}O_2$, which was called vulgarol. In the present paper we give results which enable us to establish structure (I) for this compound.

According to IR and mass spectrometry, vulgarol contains one trisubstituted double bond and two hydroxy groups.

On reaction with acetic hydride in pyridine, it readily forms a monoacetate, $C_{22}H_{38}O_3$ (II), and oxidation with active manganese dioxide converts it into an aldehyde (III), which shows the presence in the molecule of one primary allyl alcohol group.

The great similarity of its IR and mass spectra to the spectra of labd-13-ene-8α, 15-diol (IV), and also the presence in its NMR spectrum of the signals of five methyl groups characteristic for the labdane skeleton, give grounds for considering that vulgarol must have the labdane carbon skeleton (without taking stereochemistry into account).

The hydrogenation of vulgarol on platinum in ethyl acetate led, as also in the case of the diol (IV) [2], to two dihydro derivatives (V) and (VI) and a hydrogenolysis product (VII). The latter has similar IR spectra and identical R_f values to 13(RS)-tetrahydroabienol (VIII). However, these substances differ by their specific rotations, and a mixture of them gave a depression of the melting point.

Thionyl chloride dehydration of the monoacetate (II) yielded a diene (IX) with an exocyclic double bond; the IR spectra of this compound and of the acetate (X) are identical in the 800-1800 cm^{-1} region and differ only in the region of C–H vibrations (2800-3000, 700-800 cm^{-1}). However, the specific rotations of these substances are opposite in sign (Table 1).

The hydroxylation of vulgarol with osmium tetraoxide gave a tetrol (XI), which was converted by oxidation with periodic acid and potassium permanganate into a lactone (XII) differing from norambreinolide both in its constants and in the sign of the smooth ORD curves.

Finally, dehydration of the hydrogenolysis products (VII) with thionyl chloride led to a hydrocarbon (XIII) with an 8(20) double bond and a specific rotation opposite in sign to the rotation of labd-8(20)-ene (XIV) (Table 1).

A mass-spectrometric analysis of vulgarol performed in comparison with that of labd-13-one-8α,15-diol confirmed the relationship of these two substances. Thus, the mass spectrum of vulgarol (Fig. 1) is characterized by the presence of a weak peak of the molecular ion, the fragmentation of which shows the presence of two hydroxy groups. Two molecules of water are eliminated in two directions: M – (18 +15 +18) [m/e $308 \to 290 \to 275 \xrightarrow{*} 257$] and M–(18 +18 +15) [m/e $308 \to 290 \to 272 \to 257$]. The $275 \to 257$ transition is confirmed by a metastable peak with m/e 240.5 (calculated, 240.2). Similar fragmentation is observed in the spectrum of labdene-8α, 15-diol (IV). Moreover, in the region of mass numbers relating to the fragmentation of the bicyclic

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TABLE 1. Specific Rotations of Derivatives of Vulgarol and of Labdene-8α, 15-diol

Vulgarol derivatives	$[\alpha]_D^{20}$	Labdene-8α, 15-diol derivatives	$[\alpha]_D^{20}$
Vulgarol (I)	±0	Labdene-8α,15-diol	−5,0
Acetate (IX)	−24,6	Acetate (X)	+26,0
Hydrocarbon (XIII)	−27,0	Labd-8(20)-ene	+32,0
Alcohol (VII)	− 9,4	Tetrahydroabienol (VIII)	−3,0
Lactone (XII)	−32,0	Norambreinolide	+49,0

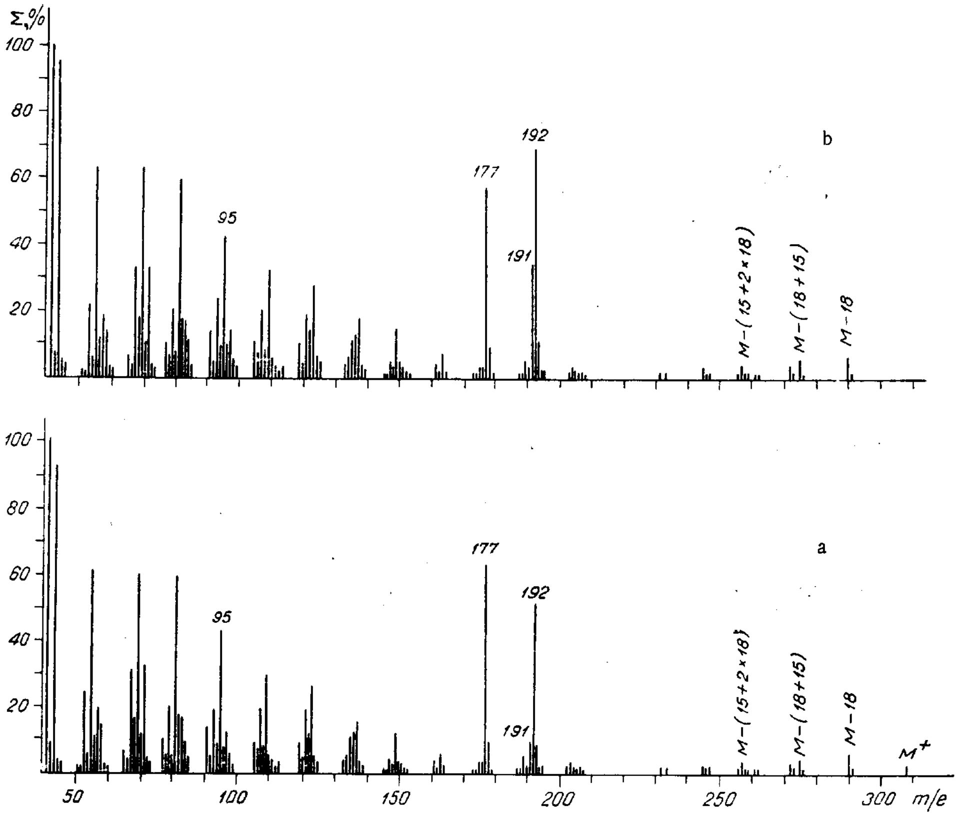


Fig. 1. Mass spectra of vulgarol (a) and of labdene-8α, 15-diol (b).

nucleus (m/e < 177), the mass spectra of these two compounds are identical. In a higher region there are several differences connected with features of the structures of these substances. Thus, labdene-8α,15-diol (IV) does not give the peak of the molecular ion, while the mass spectrum of vulgarol does contain M^+ (1.7%). In the spectrum of compound (IV) there are peaks with m/e 192 (70%) ("a"), 191 (35%) ("b"), and 177 (58%) ("a" − 15), the intensities of which in the spectrum of vulgarol are 52, 10, and 65%, respectively.

The different relative intensities of the peaks with m/e 192 and 191 in the spectra of the compounds considered show that the process of dehydration through the C_8 hydroxyl and the subsequent cleavage of the C_9-C_{11} bond in vulgarol take place with the predominant participation of the protons of the side chain, while in the case of the diol (IV) one of the protons of the bicyclic system of the molecule, most probably detached from the C_9 position, also participates in this process [3]. This, like all the facts mentioned above, gave grounds for assuming that vulgarol is not the antipode of the diol (IV), but differs from the latter by the stereochemistry of the linkage of the A/B rings, which is also responsible for the direction of dehydration. Confirmation of this was given by the results of a study of the ORD of the ketone (XV) obtained by the hydroxylation of the hydrocarbon (XIII) followed by periodate oxidation of the intermediate diol.

A comparison of the forms, amplitudes, and signs of the Cotton effects of the ORD curve of the ketone (XV) with that of the ketone (XVI) obtained from the known labdene (XIV) (Fig. 2), and also a comparison of these curves with the ORD curves of oxosteroids of the cholestane and coprostane series [4] and of cis-decalones [5] enabled compound (XV) and consequently, vulgarol as well to the bicyclic diterpenoids with the cis linkage of the A/B rings.

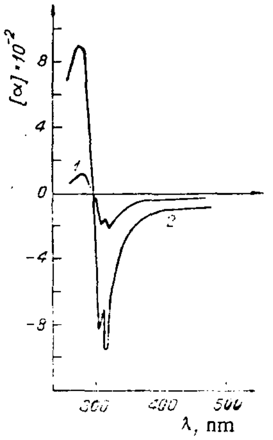


Fig. 2. ORD curves of the ketone (XV) (1) and of the ketone (XVI) (2).

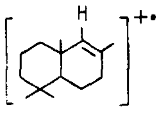
On the basis of octant diagrams [6] and also of a consideration of the molecular models of the ketone (XV), it has been concluded that of the four possible conformations of cis-linked bicyclic systems [7], two of them are possible in this case; steroid-like (XVa) and nonsteroid (XVb). The other two conformations were rejected since curves with positive Cotton effects were predicted for them.

The choice between conformations (XVa) and (XVb) in favor of the former was made after comparing the values of Δε calculated from the molecular amplitude (Δε = [A]/4018) [8] of the curve of the ketone (XV) with literature information for substances present in corresponding conformations. Thus, a value of Δε of −0.25 for the ketone (XV) coincides with Δε for a 2-oxo-5α,10α-steroid (−0.28) and differs considerably from Δε for 6β, 7β-isopropylidene-10β-methyl-cis-2-decalone (−0.06) [7], which shows the steroid-like conformation of the vulgarol molecule.

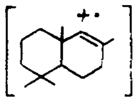
The hydroxy group at C_8 must be α-oriented (equatorial), since the dehydration of compounds (II) and (VII) with thionyl chloride, taking place by a trans-elimination mechanism, forms only 8(20) olefin.

It follows from a consideration of octant diagrams of the ketone (XV) that the side chain at C_9 must be equatorially oriented, as in all known bicyclic diterpenoids. Otherwise (if this position were axial), a positive Cotton effect would be expected for compound (XV).

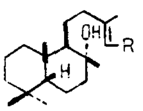
Summarizing all that has been said, the structure and stereochemistry of vulgarol can be represented by formula (I).



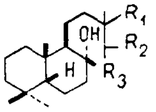
a



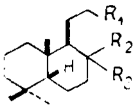
b



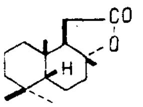
I, II, III



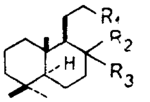
V, VI, VII, XI



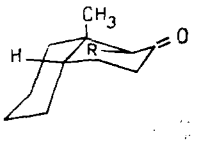
IX, XIII, XV



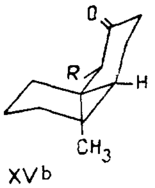
XII



IV, VIII, X, XIV, XVI



XVa



XVb

I. R = CH_2OH. II. R = CH_2OAc. II. R = CHO. IV. R_1 = $C(CH_3) = CH-CH_2OH$, R_2 = α−OH, R_3 = CH_3. V. R_1 = α−H, R_2 = CH_2OH, R_3 = H_2. VI. R_1 = β−H, R_2 = CH_2OH, R_3 = H_2. VII. R_1 = H, R_2 = CH_3, R_3 = H_2. VIII. R_1 =

$C(CH_3)-C_2H_5$, $R_2 = \alpha-OH$, $R_3 = CH_3$. IX. $R_1 = C(CH_3) = CH-CH_2OAc$, $R_2 + R_3 = CH_2$. X. $R_1 = C(CH_3) = CH-CH_2OAc$, $R_2 + R_3 = CH_2$. XI. $R_1 = R_3 = OH$, $R_2 = CH_2OH$. XIII. $R_1 = CH(CH_3)-C_2H_5$, $R_2 + R_3 = CH_2$. XIV. $R_1 = CH(CH_3)-C_2H_5$, $R_2 + R_3 = CH_2$. XV. $R_1 = C(CH_3)-C_2H_5$, $R_2 + R_3 = O$. XVa. $R = C_6H_{13}$. XVb. $R = C_6H_{13}$. XVI. $R_1 = CH(CH_3)-C_2H_5$, $R_2 + R_3 = O$.

EXPERIMENTAL

The IR spectra were taken on a UR-10 spectrometer, the NMR spectra on a HA-Varian-100 instrument (internal standard: tetramethylsilane), and the mass spectra on an MKh-1303 instrument fitted with a system for the direct introduction of the sample into the ion source. The ORD curves were obtained on a Spectropol instrument by V. A. Raldugin (Institute of Organic Chemistry, Novosibirsk). The melting points of the substances were determined on a Kofler block and the specific rotations in chloroform solution.

The elementary analyses of the compounds coincided with the calculated figures.

Vulgarol was isolated, from an extract of the plant by the method described previously [1]. NMR spectrum (deuterochloroform): 0.74; 0.83, 1.05 ppm (singlets, 3H each, methyl groups at C_4 and C_{10}), 1.42 ppm (singlet, 3H, methyl at C_8), 1.68 ppm (singlet, 3H, methyl at C_{13}), 4.12 (doublet, 2H, J = 7 Hz, methylene protons at C_{15}), and 5.41 ppm (1H at C_{14}).

Acetylation of Vulgarol. A solution of 80 mg of vulgarol in 2 ml of anhydrous pyridine was treated with 1 ml of acetic anhydride and left at room temperature for 12 h. Then it was diluted with water, the product was extracted with ether, and the ethereal layer was washed with 5% hydrochloric acid and with water and was dried with sodium sulfate. After the solvent had been distilled off, 70 mg of a liquid acetate with the composition $C_{22}H_{38}O_3$ (II) was obtained. IR spectrum (film) (cm^{-1}): 3540, 1120 ($-OH$), 1735, 1240 ($-OCOCH_3$).

Preparation of the Aldehyde (III). A mixture of 100 mg of vulgarol in 8 ml of anhydrous acetone and 1.4 g of active manganese dioxide was stirred for 3 h. The precipitate was filtered off and the filtrate was evaporated, giving 90 mg of the aldehyde $C_{20}H_{34}O_2$. IR spectrum (CCl_4) (cm^{-1}): 3580, 1120 ($-OH$), 1725 ($-CHO$).

Hydrogenation of Vulgarol. In the presence of 18 mg of PtO_2, 115 mg of vulgarol in 5 ml of ethyl acetate with the addition of 5 drops of ethanol was saturated with hydrogen. At 23°C and 758 mm Hg, 25 ml of hydrogen was absorbed, which corresponded to 2.3 equivalents. After the usual working up, the product was chromatographed on silica gel (17 g). Benzene eluted 60 mg of a crystalline hydrogenolysis product with the composition $C_{20}H_{38}O$ (VII), mp 48-50°C (methanol), $[\alpha]_D^{20} -9.4°$ (c 8.1). IR spectrum (CCl_4): 3630, 1090 vm^{-1}. A mixture of benzene and 80% of ether eluted 20 mg of the dihydro derivative $C_{20}H_{38}O_2$ (V) in the form of a viscous liquid. IR spectrum (film) (cm^{-1}): 3400, 1090, and 1065. Further elution with the same solvent yielded 20 mg of substance (VI), mp 117-118°C (petroleum ether–benzene). The IR spectrum was identical with that of the dihydro derivative (V).

Preparation of Compound (IX). At 0°C, 0.5 ml of thionyl chloride was added dropwise to a solution of 120 mg of vulgarol acetate (II) in 3 ml of anhydrous pyridine, and the mixture was left at the temperature for 15 min. Then it was diluted with ice water, the product was extracted with ether, and the ethereal layer was washed with 5% hydrochloric acid and with water and was dried with sodium sulfate. The residue (100 mg) after the distillation of the solvent was chromatographed on 9 g of silica gel. A mixture of petroleum ether and 5% of acetone eluted 80 mg of a liquid diene $C_{20}H_{36}O_2$ (IX). IR spectrum (film) (cm^{-1}): 3080, 1645, 895 ($>C=CH_2$), 1740, 1235 ($-OCOCH_3$), 1670, 860 ($>C=CH-$).

Conversion of Vulgarol into the Lactone (XII). An ethereal solution of 150 mg of OsO_4 was added to a solution of 110 mg of vulgarol in 3 ml of absolute ether in the presence of two drops of pyridine. After 48 h, a solution of 1 g of mannitol in 10 ml of 10% alkali was added, and the mixture was shaken vigorously for 10 h, after which the product was extracted with ethyl acetate. Distillation of the solvent and crystallization from petroleum ether–benzene yielded 80 mg of the tetrol $C_{20}H_{38}O_4$ (XI) with mp 133-134°C. IR spectrum (KBr) (cm^{-1}): 3400, 1095 (hydroxy groups). Substance (XI) was oxidized with periodic acid at room temperature in methanol for 3 h. After the usual working up, the product was isolated, and to a solution of it in 3 ml of acetone was immediately added an aqueous acetonic solution of 200 mg of potassium permanganate. After 24 h, the acetone was separated from the mixture, the residue was washed with sodium bisulfite solution, and the product was extracted with ether. The ether was distilled off and the residue (60 mg) was chromatographed on silica gel (10 g). A mixture of benzene with 1% of acetone eluted 50 mg of the lactone $C_{16}H_{26}O_2$ (XII), mp 132-133°C (petroleum ether). $[\alpha]_D^{20} -32°$(c 5.0). IR spectrum (CCl_4): 1770 cm^{-1} (lactone).

Dehydration of the Hydrogenolysis Product (VII). At 0°C, 0.1 ml of thionyl chloride was added in drops to a solution of 40 mg of the substance in 2 ml of anhydrous pyridine, and the mixture was left at the same temperature for 20 min. The usual working up yielded 30 mg of the liquid hydrocarbon (XIII): $C_{20}H_{36}$, $[\alpha]_D^{20} - 27°$ (c 4.7). IR spectrum (film) (cm^{-1}): 3060, 1645, 890 ($> C = CH_2$).

Preparation of the Ketone (XV). A mixture of 60 mg of the hydrocarbon (XIII) and 100 mg of OsO_4 in 3 ml of absolute ether was left at room temperature for 48 h. Then it was treated as described for vulgarol. The diol isolated (50 mg) was oxidized with periodic acid (150 mg) in methanol at room temperature for 4 h. The product obtained (40 mg) was chromatographed on silica gel (2 g). A mixture of petroleum ether and 2.5% of benzene eluted 15 mg of the ketone $C_{19}H_{34}O$ (XV) in the form of a mobile liquid. IR spectrum (CCl_4): 1715 cm^{-1} ($> C = O$). ORD: $[\alpha]_{500} -23°$, $[\alpha]_{400} -38°$, $[\alpha]_{345} -96°$, $[\alpha]_{323} -233°$, $[\alpha]_{317} -169°$, $[\alpha]_{313} -189°$, $[\alpha]_{305} -65°$, $[\alpha]_{303} -60°$, $[\alpha]_{299}\ 0°$, $[\alpha]_{296} +51°$, $[\alpha]_{294} +57°$, $[\alpha]_{289} +113°$, $[\alpha]_{281} +124°$ (c 0.251, heptane). The ketone (XVI) was obtained from the known hydrocarbon (XIV) in a similar manner. ORD: $[\alpha]_{500} -94°$, $[\alpha]_{370} -169°$, $[\alpha]_{245} -283°$, $[\alpha]_{320} -948°$, $[\alpha]_{314} -712°$, $[\alpha]_{310} -807°$, $[\alpha]_{302} -179°$, $[\alpha]_{300} -141°$, $[\alpha]_{297}\ 0°$, $[\alpha]_{290} +491°$, $[\alpha]_{281} +844°$, $[\alpha]_{273} +901°$ (c 0.212, heptane).

SUMMARY

The structure and stereochemistry of a new minor diterpenoid, vulgarol, isolated from the plant *Marrubium vulgare* L. has been shown. It has been established that it belongs to the bicyclic diterpenoids with the cis (5β, 10β) linkage of the A/B rings.

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TRITERPENE GLYCOSIDES OF Acanthophyllum gypsophiloides

IV. THE STRUCTURE OF ACANTHOPHYLLOSIDES B AND C

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In a preceding paper [1], we reported the structure of the O-glycosidic carbohydrate chains of acanthophyllosides B (I) and C (II). In the present paper we give proof of the structure of the O-acyloside carbohydrate chains of these glycosides. The acyloside carbohydrate chains of the two glycosides are identical and include three molecules of D-xylose, two molecules of O-rhamnose, and one molecule of D-fucose (GLC).

The alkaline saponification of compounds (I) and (II) yielded their progenins, which proved to be identical [1], and the same oligosaccharide. The acid hydrolysis of the oligosaccharide gave D-xylose and L-rhamnose. The absence of D-fucose from the hydrolyzate showed its direct linkage with the carboxy group of the aglycone.

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