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Constituents of Umbelliferous Plants

IX.* The Configuration of (+)-Oxypeucedanin Hydrate and Related Coumarins

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The configuration of the coumarin (+)-oxypeucedanin hydrate is shown to be (*R*) by degradation of the diacetate (II) to 2(*S*)-2,3-diacetoxy-3-methylbutyric acid (III).

On the basis of a stereospecific synthesis of (*S*)-(−)-oxypeucedanin (V) from (*R*)-(+)-oxypeucedanin hydrate (I), the configuration of the naturally occurring coumarin (+)-oxypeucedanin (VI) is shown to be (*R*).

The configuration of ostruthol (VII) is concluded to be (*R*) from the relationship with (*R*)-(+)-oxypeucedanin hydrate (I).[1]

The configurations of the coumarins heraclenin (VIII), heraclenol (IX), byakangelicin (X), and byakangelicol (XI) are determined tentatively by optical comparison.

The constitution of ostruthol (VII) is confirmed by PMR-spectroscopy.

In previous papers [2,3] the isolation and identification of the coumarins (+)-oxypeucedanin hydrate (I), (+)-oxypeucedanin (VI), and ostruthol (VII) have been reported. This paper presents the results of the investigation of the stereochemistry of these coumarins.

The diacetate (II) of (+)-oxypeucedanin hydrate upon ozonolysis yielded (+)-1-hydroxy-2,3-diacetoxy-3-methylbutane (XIII) and an acid (III) which was characterized as its *p*-phenylphenacylester. This ester was shown to be (*S*)-(+)-2,3-diacetoxy-3-methylbutyric acid *p*-phenylphenacylester by comparison with the synthetic enantiomer.[4] Accordingly, (II) and (+)-oxypeucedanin hydrate (I) both possess the configuration (*R*).

Tosylation of (*R*)-(+)-oxypeucedanin hydrate (I) and subsequent treatment of the tosylate with triethylamine yielded (−)-oxypeucedanin (V) possessing the (*S*) configuration. This is concluded on basis of the well-established inversion accompanying ring-closure reactions of the present type,

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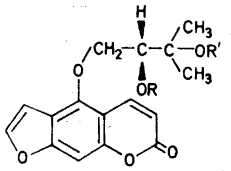
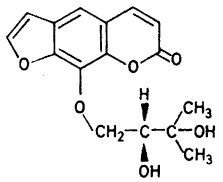
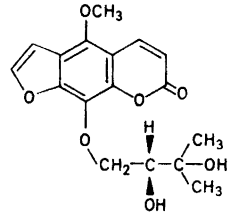


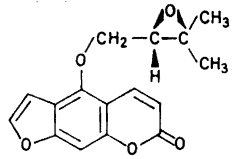
I. R=R'=H
(R)-(+)- oxypeucedanin hydrate
II. R=R'= acetyl
IV. R'=H, R= tosyl
VII. R'=H, R= angeloyl



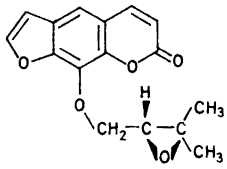
IX. (R)-(+)-heraclenol



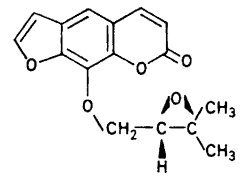
X. (R)-(+)-byakangelicin



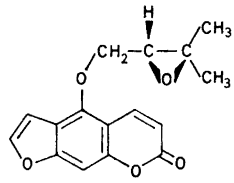
V. (S)-(−)-oxypeucedanin



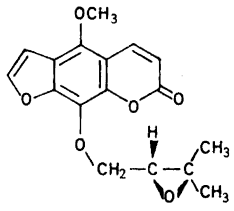
VIII. (R)-(+)-heraclenin



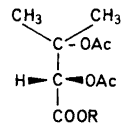
XII. (S)-(−)-heraclenin



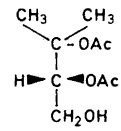
VI. (R)-(+)-oxypeucedanin



XI. (R)-(+)-byakangelicol



III. R=H
(S)-2,3-diacetoxy-3-methylbutyric acid
XIV. R= p-phenylphenacyl



XIII. (R)-(+)-1-hydroxy-2,3-diacetoxy-3-methylbutane

induced through nucleophilic displacement. Accordingly the naturally occurring coumarin (+)-oxypeucedanin (VI) possesses the configuration (*R*).

Treatments of (*R*)-(+)-oxypeucedanin (VI) with acid and alkali, respectively, have been carried out.

Under acidic conditions, (*R*)-(+)-oxypeucedanin hydrate (I) was obtained. It is most likely [5] that the reaction passes through a transition state in which the tertiary carbon atom carries a partial positive charge stabilized by electron release from the *gem*-dimethyl groups. As the tertiary C atom is not asymmetric the ring opening reaction under acidic conditions is expected to give retention of the configuration at the secondary carbon atom. The result obtained is in accordance with the result obtained from the synthesis of (−)-oxypeucedanin (V) described above.

In the treatment of (VI) with alkali, a nucleophilic attack of hydroxide ions on the epoxide ring is expected to take place at the secondary C-atom, the attack at the tertiary C-atom being sterically hindered.[5] Since this reaction is known to be accompanied by inversion of the configuration, the formation of (*S*)-(−)-oxypeucedanin hydrate was expected. However, optically impure,

slightly dextrorotatory oxypeucedanin hydrate was obtained and accordingly no conclusion concerning the configuration of (VI) can be based on this experiment.

Späth and von Christiani have proposed the structure (VII) for ostruthol.[1] However, the only evidence obtained, as to which of the hydroxyl groups is esterified with angelic acid, was that careful distillation left ostruthol unchanged, whereas a tertiary ester would normally suffer elimination.

PMR-Spectroscopy confirmed the structure (VII). In the PMR-spectrum of a dimethyl sulfoxide solution of ostruthol the hydroxyl group gives rise to a singlet (δ 4.95), which according to Chapman and King [6] is characteristic for tertiary alcohols.

Späth and Christiani have shown that ostruthol on saponification yielded (+)-oxypeucedanin hydrate (I) [1] and accordingly the configuration of ostruthol is (*R*).

Table 1.

Compound	$[\alpha]_D^t$; pyridine	lit.[a]
(+)-Oxypeucedanin (VI)	+26.2°, t = 24.3°	
(+)-Heraclenin (VIII)	+22°, t = 32°	7
(+)-Byakangelicol (XI)	+34.77°, t = 25°	8
(−)-Heraclenin (XII)	−24°, t = 23.5°	9
(+)-Oxypeucedanin hydrate (I)	+18.5°, t = 24.1°	
(+)-Heraclenol (IX)	+16.5°, t = 32°	10
(+)-Byakangelicin (X)	+24.62°, t = 25°	8

[a] If no reference is given the values are obtained by the authors.

In accordance with the optical rotation values in Table 1 the coumarins (+)-heraclenin (VIII), (+)-heraclenol (IX), byakangelicin (X), and byakangelicol (XI) are tentatively assigned the configuration (*R*). (−)-Heraclenin (XII) s the optical antipode of (VIII).[9]

EXPERIMENTAL

Acetylation of (+)-oxypeucedanin hydrate (I). A solution of (+)-oxypeucedanin hydrate (339 mg) and anhydrous sodium acetate (752 mg) in acetic anhydride (15 ml) was refluxed for 3 h. The reaction mixture was filtered, and the residue washed with benzene. The filtrate was evaporated under reduced pressure, 20 ml of a sodium hydrogen carbonate solution (*ca.* 10 %) were added and the mixture extracted with chloroform. The combined chloroform solutions were dried and evaporated to dryness. Recrystallization of the residue from cyclohexane-ether yielded 295 mg of the diacetate (II), m.p. 110.0−112.5°. Further crystallizations from ether gave a diacetate with the m.p. 115.0−115.5°, $[\alpha]_D^{26}$ +13.5° (*c* 0.5, chloroform).

The PMR-spectrum was in accordance with the structure (II).

Ozonolysis of the diacetate of (+)-oxypeucedanin hydrate (II). A flow of 2 % ozonized oxygen (50 ml/min) was passed for 15 h through a solution (at 20°) of (+)-oxypeucedanin hydrate diacetate (II) (514 mg) in glacial acetic acid. The reaction mixture was transferred

to a separating funnel containing 250 ml of water and extracted five times with 100 ml of ether. The combined ether phases were extracted with a sodium carbonate solution (pH 8). The water phase was kept in a refrigerator (5°) and worked up later (see below).

The ether layer was washed with a ferrous sulfate solution in order to remove peroxides, dried, and evaporated under reduced pressure. The residue (70 mg) was chromatographed on silica gel (Merck, 15 g) activated at 120° and impregnated with 10 % of water. As eluent was used benzene to which chloroform was added gradually until pure chloroform was obtained. Then chloroform, to which increasing amounts of methanol were added, was used as the eluent. Chloroform containing 0.5 % of methanol eluted 28 mg of (+)-1-hydroxy-2,3-diacetoxy-3-methylbutane (XIII), $[\alpha]_D^{25}$ *ca.* +20° (*c* 1, chloroform).

The PMR-spectrum was concordant with the structure (XIII). However, upon standing the compound (XIII) was not stable, probably due to migration of the acetyl groups, and this compound has not been used in the work on the configuration.

The water phase (pH 8) was left in a refrigerator for 1 month and frequently extracted with ether. The ether extracts were shown (TLC) to contain small amounts of (XIII). The water phase was acidified with 4 N sulfuric acid (pH 2) and extracted with 5 times 100 ml of ether. The combined ether extracts were washed with water (20 ml), saturated sodium chloride solution (20 ml), dried and evaporated under reduced pressure. The PMR-spectrum of the residue (60.8 mg) verified the structure (III). The compound (III) was converted to the *p*-phenylphenacylester according to the method described by Stodola.[11] The reaction mixture was chromatographed on silica gel (Merck, 15 g) activated at 120° and impregnated with 10 % of water. Benzene to which increasing amounts of ethyl acetate were added was used as the eluent. Benzene containing 4 % of ethyl acetate eluted 30.3 mg of 2(*S*)-(+)-2,3-diacetoxy-3-methylbutyric acid *p*-phenylphenacylester (XIV), m.p. 86.5–88.0 (recrystallized from ethanol-water), $[\alpha]_{365}^{25}$ +25° (*c* 0.3, chloroform), XIV was identified by comparison with the synthetic enantiomer.[4] (Ref. 4, m.p. 90.0–91.5°; $[\alpha]_{365}^{23.4}$ −33° (*c* 0.6, chloroform)).

Synthesis of (−)-oxypeucedanin (V). (+)-Oxypeucedanin hydrate (60 mg, m.p. 131.0–131.5°; $[\alpha]_D^{20.4}$ +17.1 (*c* 0.5, acetone)) was dissolved in 1 ml of ice cooled, anhydrous pyridine and 108 mg of 4-toluene sulfonyl chloride were added. The solution was placed in the refrigerator (+5°) for five days. The reaction mixture was poured into 5 ml of ice cooled water and extracted with 5 times 5 ml of methylene chloride. The combined methylene chloride phases were dried with anhydrous sodium sulfate and 500 µl of triethylamine were added. The mixture was left at room temperature for 5 days. The reaction was followed by TLC. The solution was evaporated at room temperature under reduced pressure to dryness. The residue was dissolved in 5 ml of methylene chloride and chromatographed on silica gel (Merck, reinst 13 g). Methylene chloride was used as the eluent. 41.8 mg of (−)-oxypeucedanin (V), m.p. 101.5–102.5°, $[\alpha]_D^{24.0}$ −13.5° (*c* 0.6, $CHCl_3$) were obtained.

Treatment of (+)-oxypeucedanin (V) with sulfuric acid. 22 mg of (+)-oxypeucedanin (VI) (m.p. 103.5–104.0, $[\alpha]_D^{24.3}$ +26.2° (*c* 0.4, pyridine) were dissolved in 2 ml of dioxane-water (95:5) and 100 µl of 4 N sulfuric acid were added. Upon standing at room temperature for 20 min 2 ml of water were added and the reaction mixture was extracted with five times 5 ml of methylene chloride. The combined methylene chloride phases were dried and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel (Merck, 10 g). As eluent was used chloroform to which methanol was added gradually until a concentration of 2 % methanol was reached. 21 mg of (+)-oxypeucedanin hydrate (I) (m.p. 130–131.5, $[\alpha]_D^{21.5}$ +15.2° (*c* 1, chloroform)) were eluted.

Treatment of (+)-oxypeucedanin (VI) with potassium hydroxide. (+)-Oxypeucedanin (VI) (23.5 mg) were disolved in 2 ml of 2.5 N potassium hydroxide and the solution kept in a boiling water bath for 1 h. The reaction mixture was acidified with glacial acetic acid and extracted with five times 5 ml of methylene chloride. The combined methylene chloride phases were dried and evaporated under reduced pressure. The residue was chromatographed as described above. 17 mg of oxypeucedanin hydrate (m.p. 131–132°, $[\alpha]_D^{24.1}$ +4° (*c* 0.6, chloroform)) were obtained.

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