ACTA CHEMICA SCANDINAVICA 18 (1964) 2111–2114

Constituents of Umbelliferous Plants

V.* On the Configuration of Archangelicin and Related Coumarins

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The configuration of the coumarin (+)-dihydro-oroselol (I) is related to that of (−)-tubaic acid (II), and is shown to be 8 (*S*).

Accordingly, the coumarins archangelicin (III),[1] athamantin (IV),[2] columbianadin (V),[3,4] and columbianin (VI)[4] also possess the configuration 8 (*S*).

The configuration of the coumarins marmesin (VII), nodakenetin (VIII), and the chromone visamminol (IX) are determined tentatively by optical comparison.

Furthermore the configuration of archangelicin (III) and athamantin (IV) at C-9 is discussed and the 9 (*S*) configuration is tentatively assigned to these coumarins.

Previously it has been shown,[3,4] that (+)-dihydro-oroselol (I), obtainable from columbianadin (V) and columbianin (VI) has the same configuration at C-8 as archangelicin (III) and athamantin (IV). The conclusions were based on the fact that these coumarins could be converted to (+)-tetrahydro-oroselol (X).

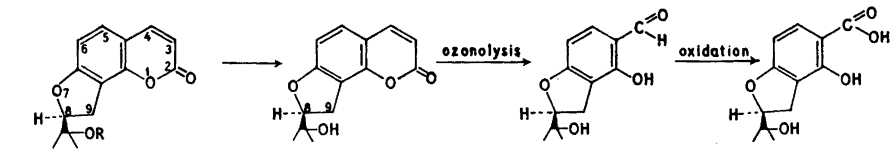
The present paper presents the determination of the absolute configuration of (+)-dihydro-oroselol (I) at C-8.

Ozonolysis of (I) afforded the aldehyde (XI), which upon oxidation yielded (+)-hydroxydihydrotubaic acid (XII).

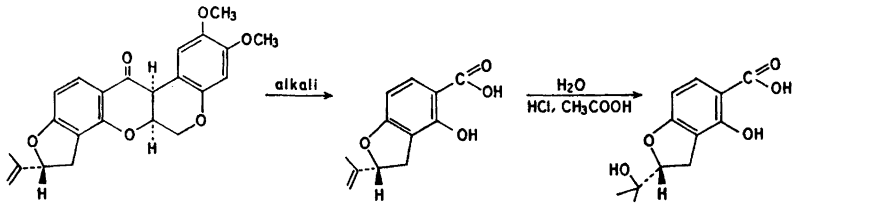
(−)-Hydroxydihydrotubaic acid (XIII) was prepared from natural rotenone (XIV). Rotenone was cleaved by alkali to give (−)-tubaic acid (II).[5] This was dissolved in a mixture of acetic acid and concentrated hydrochloric acid and upon standing at room temperature it was converted into (−)-hydroxydihydrotubaic acid (XIII).

None of the samples of hydroxydihydrotubaic acids were optically pure as indicated by broad melting ranges and the fact that further crystallisations afforded crops with distinctly different optical rotations. The racemate prepared by mixing the components, followed by a single crystallisation showed a considerably sharper melting point.

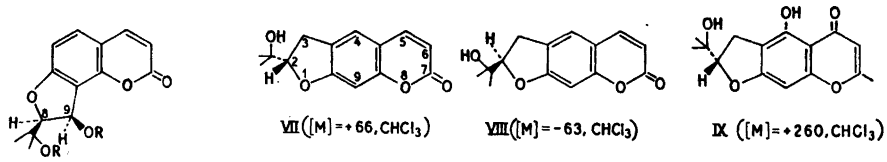
* Part IV *Acta Chem. Scand.* 18 (1964) 1379.



V R=angeloyl ([M]=+1100, CH_3OH)
VI R=D-glucosyl
I ([M]=+620, CH_3OH) XI ([M]=+410, CH_3OH) XII ([M]>+340, CH_3OH)

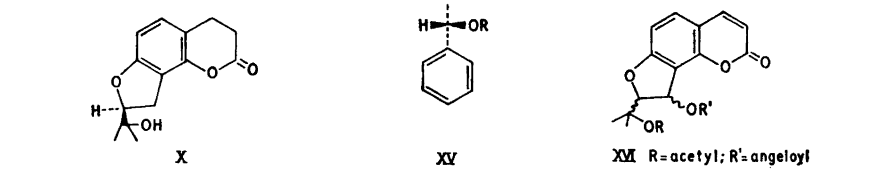


XIV
II ([M]=-170, $CHCl_3$)
XIII ([M]<-300, CH_3OH)



VII ([M]=+66, $CHCl_3$) VIII ([M]=-63, $CHCl_3$) IX ([M]=+260, $CHCl_3$)

III R=angeloyl ([M]=+480, CH_3OH)
IV R=Isovaleryl ([M]=+440, CH_3OH)



X XV XVI R=acetyl; R'=angeloyl

$$[M] = 0.01 \times [\alpha]_D \times \text{Mol.wt.}$$

As the configuration of (−)-tubaic acid (II) has been shown to be (*R*),[6] it follows that the configuration of (+)-dihydro-oroselol (I) and hence of the coumarins III—VI is 8 (*S*).

A comparison of the rotation values of marmesin (VII) from *Aegle marmelos* (Rutaceae) and the chromone visamminol (IX) from *Ammi visnaga* (Umbelliferae) made Bencze *et al.*[7] suggest, that these compounds possessed the same configuration at C-2. Later Schmid and coworkers[2] suggested the same configuration to be present at C-8 in athamantin (IV).

When these suggestions are combined with the results presented in this paper the configuration 2 (*S*) may be assigned to marmesin (VII) and visamminol (IX).

The coumarin nodakenetin (VIII) from *Peucedanum decursivum* (Umbelliferae) has been shown to be the optical antipode of marmesin (VII).[8]

According to Schmid and coworkers [2] the hydrogen atoms of athamantin at C-8 and C-9 in all probability are *cis*. This conclusion was based on the facts, that athamantin is relatively thermostable whereas treatment with acids easily leads to the elimination of isovaleric acid and the formation of a furan ring.

In accordance with the suggestions of Schmid and coworkers [2] and the results presented in this paper, the configuration 9 (*S*) is now tentatively assigned to athamantin (IV).

Further support can be derived from work carried out by Freudenberg *et al.*[9–12] (see also [13,14]). It is stated by these authors that the configuration shown in (XV) either alone or in combination with other asymmetric carbon atoms is laevorotatory or less dextrorotatory than its enantiomer (epimer).

Since in the case of athamantin no epimeric compounds are known, it is difficult to decide experimentally whether the asymmetric centre at C-9 provides a laevorotatory or a dextrorotatory contribution to the rotation value. Furthermore, as the asymmetric carbon atoms in athamantin are so close to each other, there may exist interactions, which change the contribution to the total rotation from what it would have been if the asymmetric carbon atoms were independent. In the case of athamantin (IV) and columbianadin (V), however, the remarkable difference between the molecular rotations seems to make the comparison reasonably safe. The considerable drop in the dextrorotatory value from [M] = 1100 to [M] = 440 when going from columbianadin (V) to athamantin (IV) makes it likely that the contribution at C-9 in the latter is strongly laevorotatory. According to Freudenberg this indicates the configuration (XV), which agains is identical with 9 (*S*) in athamantin.

From a comparison of the rotation values of archangelicin (III), athamantin (IV), and columbianadin (V) it appears that also archangelicin possesses the configuration 9 (*S*).

Mitshuhashi and Itoh [15] have reported on the constitution of edultin (XVI). Since they have not converted this coumarin to tetrahydro-oroselol we shall refrain from discussing the configuration of edultin. (Lit.[15] $[\alpha]_D^{10.7}$ + 41.5 (*c* 26.8, pyridine)).

EXPERIMENTAL

Ozonolysis of (+)-dihydro-oroselol (I). A flow of 2 % ozonized oxygen (50 ml/min) was passed for 1½ h through a solution (at 0°) of (+)-dihydro-oroselol (481 mg) in ethyl acetate (20 ml). The reaction mixture was evaporated under reduced pressure at 30° to give an oil, which was refluxed for 10 min with water (5 ml). The mixture was extracted with chloroform and the dried chloroform solution chromatographed on silica gel (Merck) activated at 120°, and impregnated with 10 % of water. As eluent was used chloroform to which ethyl acetate was added gradually until a concentration of 30 % of ethyl acetate was reached. Besides unreacted alcohol (I), 195 mg of the aldehyde (XI) were obtained. Recrystallised from benzene-petroleum ether, m.p. 94.5–95.0°, $[\alpha]_D^{27}$ + 184 (*c* 1.0, methanol). The compound (XI) gave analytical data concordant with the composition $C_{13}H_{14}O_4$. (Found: C 65.16; H 6.36. Calc.: C 64.85; H 6.35).

The IR- and PMR-spectra supported the structural assignments.

Oxidation of the aldehyde (XI). 168 mg (XI) were dissolved in 2 ml methanol and kept in a water bath at 55°. During 30 min and with mechanical stirring 0.5 N sodium hydroxide in 50 % methanol (7 ml) and 10 % silver nitrate in 50 % methanol (5 ml) were added in small alternating portions. The reaction mixture was kept at 55° for 3 h, filtered, acidified, and extracted with chloroform. The chloroform solution was extracted

with 10 ml of a sodium hydrogen carbonate solution, 5 %. On evaporation of the dried chloroform phase a residue of unreacted aldehyde (XI) was obtained. The process described above was repeated twice with unreacted aldehyde.

The alkaline phases were acidified and extracted with chloroform. The brown residue obtained by evaporation of the dried chloroform solutions was chromatographed on 80 g of silica gel (Merck) activated at 120° and impregnated with 10 % of water. As eluent was used chloroform to which ethyl acetate was added gradually until a concentration of 50 % of ethyl acetate was reached. The fractions containing the acid (XII) were evaporated and the residue recrystallised from ether-carbon disulphide. 32 mg (XII), m.p. 99–108°, $[\alpha]_D^{25}$ + 121 (*c* 0.4, methanol) were obtained. Further crops with the rotation values $[\alpha]_D^{26}$ + 113 (18 mg) and $[\alpha]_D^{29}$ + 142 (33 mg) were obtained.

The compound gave analytical data concordant with the composition $C_{12}H_{14}O_5$. (Found: C 60.37; H 6.09. Calc.: C 60.50; H 5.92).

Preparation of (−)-hydroxydihydrotubaic acid (XIII). Rotenone (XIV) was degraded to (−)-tubaic acid (II), m.p. 129.5–130.0°, $[\alpha]_D^{25}$ −75 (chloroform), according to Takei and Koide's procedure [5] (lit.[5] m.p. 129°).

(−)-Tubaic acid (II) (1.2 g) was dissolved in 40 ml of glacial acetic acid mixed with 20 ml of concentrated hydrochloric acid and left for 4 days at room temperature.

The reaction mixture was diluted with 600 ml of water and extracted with diethyl ether. The combined ether solutions were washed 3 times with 100 ml portions of saturated sodium chloride solution, dried and evaporated. The residue obtained was chromatographed on 80 g of silica gel (Merck) activated at 120° and impregnated with 10 % of water. As eluent was used benzene to which ethyl acetate was added gradually until a concentration of 50 % of ethyl acetate was reached. With 10–20 % ethyl acetate in benzene 1.0 g of unreacted tubaic acid was obtained. With 50 % ethyl acetate in benzene 103 mg of the compound (XIII) were obtained. Recrystallised from ether-carbon disulphide, m.p. 96–107°, $[\alpha]_D^{29}$ −127 (*c* 0.5, methanol). The compound (XIII) gave analytical data concordant with the composition $C_{12}H_{14}O_5$ and the IR-spectrum was identical to that of compound (XII).

On thin layer chromatography the samples of (XII) and (XIII) were shown to cochromatograph and to be chromatographically pure. Silica gel (Merck) was used as the absorbent, chloroform: ethanol:acetic acid 89:10:1 as the eluent. The chromatograms were sprayed with phosphomolybdic acid 10 % in ethanol and heated to 120° for 15 min.

Preparation of (±)-hydroxydihydrotubaic acid. 14.9 mg of (XIII) ($[\alpha]_D^{29}$ −127) and 15.6 mg of (XII) ($[\alpha]_D^{29}$ + 121) were crystallised together from carbon disulphide to yield 22 mg of the racemate, m.p. 160.5–162.0°.

Melting points, IR- and PMR-spectra were determined as in a previous paper.[3]

Microanalyses were performed by Dr. A. Bernhardt, Mülheim.

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Received July 10, 1964.