ACTA CHEMICA SCANDINAVICA 18 (1964) 932–936

Constituents of Umbelliferous Plants

III.* The Structure of Archangelicin, a Coumarin from *Angelica archangelica* L. subsp. *litoralis* Thell.

BENT EICHSTEDT NIELSEN and JOHN LEMMICH

The Royal Danish School of Pharmacy, Chemical Laboratory B, Copenhagen, Denmark

A coumarin, $C_{24}H_{26}O_7$, obtained from the root of *Angelica archangelica* subsp. *litoralis* is shown to be identical with archangelicin, previously found in the root of *Angelica archangelica* L. subsp. *norvegica* Thell. but erroneously reported to possess the elemental composition $C_{16}H_{20}O_4$.

Archangelicin is shown to be 9-angeloyloxy-8-(1-angeloyloxy-1-methylethyl)-8,9-dihydro-2H-furo[2,3-*h*]-1-benzopyran-2-one (I).

The coumarin kvannin is proved to be identical with oroselone.

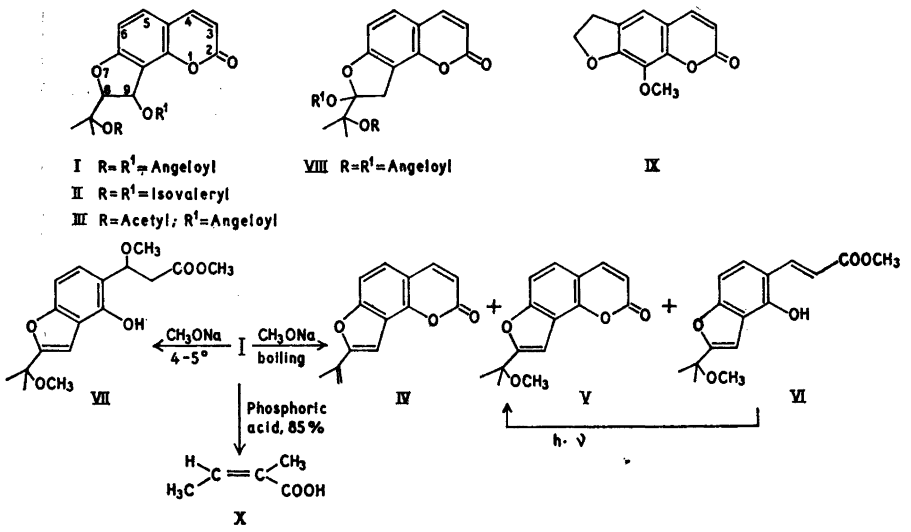
From roots of *Angelica archangelica* subsp. *norvegica*, Bœrheim Svendsen [1] recently isolated the new coumarin archangelicin, for which the empirical formula $C_{16}H_{20}O_4$ was presented, whereas no optical rotation was reported. In addition, the same author isolated some other coumarins of which kvannin, $C_{14}H_{10}O_3$ and archangin, $C_{15}H_{16}O_4$, were considered to be new. Both were isolated by the lactone separation method of Späth.[2] Root material of *Angelica archangelica* subsp. *litoralis*, when processed by the same separation method, also afforded kvannin.

In our hands the diethyl ether extract of the root material of *Angelica archangelica* subsp. *litoralis* afforded a blue-fluorescent compound with the elemental composition $C_{24}H_{26}O_7$, and the same melting point as archangelicin.

Its coumarin character was strongly indicated by the fluorescence, the absorption bands at 1716—1743, 1623, 1584, 1497, and 1458 cm^{-1}, and by its UV-absorption: λ_{max} 258 mμ (3.55) and 322 mμ (4.14), λ_{min} 255 mμ (3.53), and 266 mμ (3.24), shoulders at 216 mμ (4.56), 246 mμ (3.67), and 301 mμ (3.95).

Treatment of (I) with boiling sodium methoxide, afforded orosolone (IV), m.p. 178—180°, oroselol methyl ether (V), m.p. 116°, and the phenol (VI), m.p. 154—156°.

* Part II, *Acta Chem. Scand.* **17** (1963) 1167.



The compounds (V) and (VI) have been previously reported as products formed by a similar treatment of the coumarin athamantin [3] (II) (from *Athamanta oreoselinum* L. (Umbelliferae)). Furthermore, orosolone (IV) and oroselol methyl ether (V) have both been described as products formed by saponification in methanol of the coumarin edultin [4] (III) (from *Angelica edulis* Miyabe, (Umbelliferae)). As in the case of athamantin,[3] treatment of (I) with sodium methoxide, at 4—5°, yielded the compound (VII), m.p. 105.0—105.5°.

The volatile acid formed upon hydrolysis of (I) with 85 % phosphoric acid, was shown to be angelic acid (X). The presence of two moles of angelic acid per mole of (I) was confirmed.

This evidence limited the structural possibilities for the isolated coumarin to (I) or (VIII), of which only (I) was reconcilable with the PMR-data. From Fig. 1 it appears that signals at 316, 323, and 424, 431 cps (J = 7 cps) must arise from the two protons at C-8 and C-9 in structure (I). The absence of CH_2-signals provides further support for structure (I). Dihydroxanthotoxin (IX) served as a model in studies of the PMR-spectra.

Accordingly the isolated coumarin is 9-angeloyloxy-8-(1-angeloyloxy-1-methylethyl)-8,9-dihydro-2H-furo[2,3-*h*]-1-benzopyran-2-one. Studies of its stereochemistry are in progress.

At this stage, it occurred to us that archangelicin might be identical with the coumarin (I), and kvannin and archangin, accordingly, identical with oroselone and oroselol methyl ether. Since the latter two compounds could not be detected by thin layer chromatography of the root extract, kvannin and archangin might be artefacts produced during the separation procedure.

Samples of archangelicin and kvannin were kindly placed at our disposal by Dr. Bœrheim Svendsen. Thin layer chromatography and IR-spectra showed these to be identical with coumarin (I) and oroselone (IV), respectively. As no

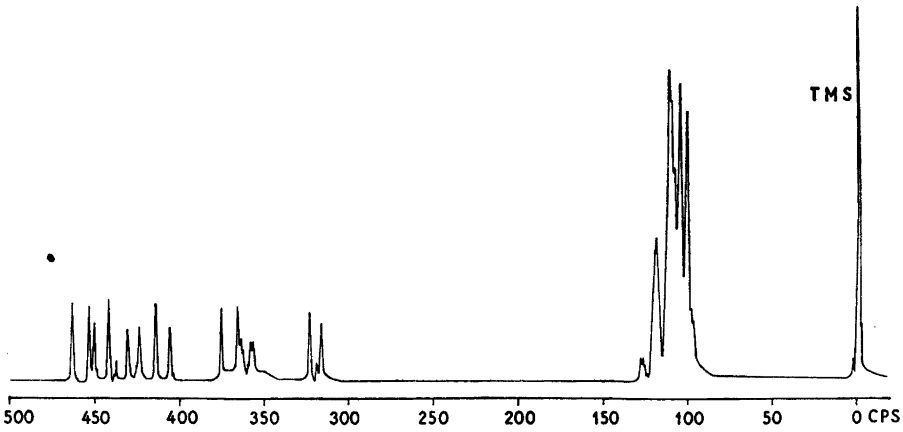


Fig. 1. PMR spectrum of archangelicin (deutero chloroform). Internal standard, tetramethylsilane (TMS).

sample of archangin was available its identity with oroselol methyl ether could not be verified.

Accordingly, we wish to adopt the name archangelicin for the coumarin (I), isolated from *Angelica archangelica* subsp. *litoralis*.

EXPERIMENTAL

Plant material. Roots of *Angelica archangelica* subsp. *litoralis*, collected in the neighbourhood of Copenhagen in October.

Isolation of archangelicin (I). The dried and ground root (10 kg) was percolated with 15 l of ether. Upon evaporation of the solvent 490 g of a viscous oil remained. This residue was extracted with 1 l portions of petroleum ether (b.p. below 50°) in a perforator equipped with a mechanical stirrer. Each extraction was carried out for 20 h, and a total of 25 fractions were collected. The first fraction, containing large amounts of fats and sterols, was not investigated. Upon standing a resinous deposit formed in the fractions 2—6 from which the clear mother liquors were decanted and discarded. The deposits were mixed with the evaporated fractions 7—25, yielding a total of 143 g. This resinous material was dissolved in 600 ml of benzene:petroleum ether 1:2 and chromatographed on 385 g of silica gel (Light & Co 200/300 mesh), activated at 120°, and impregnated with 10 % of water. Benzene:petroleum ether 1:2 was used as the eluent. The first fraction (1.5 l) was evaporated, and from the viscous residue (54 g) osthol (4 g) crystallised upon standing for a few days. The filtrate was dissolved in 100 ml of methanol and stored at −15° for a month. The crystals (19.8 g) were collected on a filter and purified on 200 g of silica gel (Merck 0.05—0.20 mm) activated at 120° and mixed with 10 % of water. Benzene was used as the eluent. From the first fraction (1.2 l) additional osthol (3.6 g) was obtained. The second fraction (2.4 l) contained 2.0 g of a mixture of osthol and archangelicin (I). Further elution with benzene to which chloroform was gradually added, until a concentration of 75 % of chloroform was reached, afforded nearly pure archangelicin (8.2 g). Crystallisations from cyclohexane gave about 6 g of colourless crystals, m.p. 100.5—102° (Found: C 67.38; H 6.48; Calc. for $C_{24}H_{26}O_7$: C 67.59; H 6.15), $[\alpha]_D^{26}$ + 112.7 (*c* 4.5, methanol).

Reaction with 1 N sodium methoxide, at 4—5°. 302.9 mg of (I) were treated with 1 N sodium methoxide, and the reaction mixture was fractionated by column chromatography as described by Halpern *et al.*[3] A crystalline compound (56.5 mg), m.p. 105.0—105.5°,

was obtained. The melting point, analytical composition, and the UV-data were in close agreement with those published by Halpern *et al.*[3] for the compound (VII). Furthermore, the IR-spectrum showed absorption bands corresponding to a phenolic OH-group.

Reaction with boiling 1 N sodium methoxide. 612 mg of (I) were treated with boiling 1 N sodium methoxide, according to Halpern *et al.*[3] Upon acidifying with glacial acetic acid, evaporation *in vacuo*, and standing for 0.5 h with water, the reaction mixture was extracted with diethyl ether. The ether layer was washed with a solution of sodium hydrogen carbonate and sodium carbonate as described by Halpern *et al.*[3] We preferred to carry out the fractionation of the washed ether extract by column chromatography: The extract was evaporated and chromatographed on 30 g of silicic acid (Fluka) activated at 120° and mixed with 10 % of water. As eluent was used benzene to which ethyl acetate was added gradually until a concentration of 25 % of ethyl acetate was reached. The following substances were obtained:

(a) 17 mg of a compound with a brownish fluorescence, recrystallised from ether, m.p. 178–180° (closed tube). The compound gave analytical data concordant with the composition $C_{14}H_{10}O_3$. The IR-spectrum proved the compound to be oroselone (IV),[4] (m.p. lit. 180.5°,[4] 188–189° in vacuum tube[5]).

(b) 13 mg of colourless crystals, which upon thin layer chromatography on silica gel G (Merck) with chloroform:ethyl acetate 88:12 as the eluent, appeared to consist of two components, one exhibiting blue and the other yellowish brown fluorescence. These compounds were not identified.

(c) 76 mg of a compound with a yellow fluorescence. Recrystallised from ether-petroleum ether, m.p. 116.0°. Occasionally the melt on further heating crystallised and remelted at 123.5°. The compound gave analytical data concordant with the composition $C_{15}H_{14}O_4$. The IR-spectrum proved that the compound was oroselol methyl ether (V),[4] (m.p. lit. 116–117°,[3] 118°[4]).

(d) 100 mg of a compound with a yellow fluorescence. Recrystallised from ether-petroleum ether it melted at 157.0–158.5° with evolution of gas (introduced in the silicone bath at 150°). The elementary analysis and the UV-data were in close agreement with those published by Halpern *et al.*[3] for compound (VI). Furthermore, the IR-spectrum showed absorption bands corresponding to a phenolic OH-group.

Finally it was shown that irradiation of (VI) with unfiltered UV-light, gave oroselol methyl ether (V). 8.2 mg of (VI) was irradiated for 4 h with UV-light in accordance with the method described by Halpern *et al.*[3] The reaction mixture was fractionated on 2 g of activated silicic acid (Fluka) with benzene:ethyl acetate 9:1 as the eluent. Oroselol methyl ether (2.7 mg) was obtained.

The substances in the fractions (a)–(d) were all eluted with benzene:ethyl acetate 85:15. Further elution gave only trace amounts of compounds which were not identified.

Hydrolysis with phosphoric acid, 85 %. A solution of 120 mg of (I) in 2 ml phosphoric acid, 85 %, was heated for a few minutes on a steam bath. From the reaction mixture the volatile acids were isolated by steam distillation. About 15 ml of distillate was collected and diluted to 50.00 ml. One ml of this solution was diluted with 0.1 N hydrochloric acid to 100.00 ml. The concentration was estimated spectrographically by measuring the optical density at 219 mμ. As a standard, a sample of synthetic angelic acid was used. The distillate contained 45.7 mg of angelic acid corresponding to 1.62 mole of angelic acid per mole of (I).

The remaining part of the acid fraction was neutralized and the *p*-phenylphenacyl ester was prepared and chromatographed on a silicic acid column as described by Klohs *et al.*[6] Elution of the column with benzene-petroleum ether (30–60°) yielded, in the first fraction, unreacted bromide, m.p. 127.5°. The second fraction afforded colourless crystals which, after recrystallisation from ethanol-water, gave *p*-phenylphenacyl angelate, m.p. 86–87° (lit. m. p. 89.0–90.5°[7]). The identity was established by comparison of the IR-spectrum with the spectrum of an authentic sample of *p*-phenylphenacyl angelate (m.p. 90.0°). Furthermore, the IR-spectrum of the angelate was compared with that of *p*-phenylphenacyl tiglate to ensure, that no tiglic acid had been present in the fraction.

Dihydroxanthotoxin. Xanthotoxin (341 mg) was dissolved in 50 ml of methanol and hydrogenated at 30° using 151 mg of palladium on carbon (10 %) as a catalyst. Within 16 min, an amount of hydrogen corresponding to 1 mole was consumed and the reaction nearly ceased. The solution was filtered, evaporated *in vacuo*, and the residue was recrystallised from methanol. Dihydroxanthotoxin (255 mg), m.p. 159–160.5° (lit. m.p.

160—161.5°[8]), was obtained. The analytical data were concordant with the composition $C_{12}H_{10}O_4$, and the IR-spectrum closely resembled that published by Trojánek *et al.*[8]

Thin layer chromatography. Silica gel G (Merck) and chloroform:ethyl acetate 96:4 were used, unless otherwise stated.

The melting points are corrected and determined in capillary tubes in an electrically heated silicone bath. Rate of heating near the melting point 1°/min.

The UV-spectra were recorded in 96 % ethanol, on a Beckman spectrophotometer Model DK-2.

The IR-spectra were recorded in potassium bromide discs on a Perkin Elmer spectrophotometer, Model 21.

The PMR-spectra were made with a Varian V-4 300 NMR spectrophotometer operating at a fixed frequency of 60 Mc/s.

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

The authors are grateful to Dr. A. Bœrheim Svendsen for supplying the specimens of archangelicin and kvannin, to Mr. K. Schaumburg, Chemical Laboratory V, University of Copenhagen, for the measurement and the interpretation of the PMR-spectra and for valuable discussions, and to the Head of the laboratory, Professor H. Kofod, for suggestions and valuable comments on the manuscript.

REFERENCES

1. Bœrheim Svendsen, A. *Zur Chemie Norwegischer Umbelliferen* (Diss.) University, Oslo 1954.
2. Späth, E. *Ber.* **70 A** (1937) 83.
3. Halpern, O., Waser, P. and Schmid, H. *Helv. Chim. Acta* **40** (1957) 758.
4. Mitsuhashi, H. and Itoh, T. *Chem. Pharm. Bull. (Tokyo)* **10** (1962) 514.
5. Späth, E., Platzner, N. and Schmid, H. *Ber.* **73** (1940) 709.
6. Klohs, M. W., Arons, E., Draper, M. D., Keller, F., Koster, S., Malesh, W. and Petracek, F. J. *J. Am. Chem. Soc.* **74** (1952) 5109.
7. Pelletiér, S. W. and McLeish, W. M. *J. Am. Chem. Soc.* **74** (1952) 6292.
8. Trojánek, J., Hodková, J. and Cekan, A. *Planta Med.* **9** (1961) 200.

Received February 22, 1964.