THE STRUCTURE OF ARNIFOLIN, SESQUITERPENE LACTONE
FROM Arnica folio NUTT. AND Arnica montana L.

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Leafy arnica and mountain arnica are used in gynecological practice in the form of tinctures as styptic media. From the leaves and flowering calathides of these plants we have isolated a colorless crystalline material of composition C_{20}H_{26}O_{6}, mp 128-132°C (dec.), [a]_{D}^{25} +52.6°C (c 3.0; alcohol), which stimulates the smooth muscle of the uterus, i.e., a primary nutrient of arnica [1]. We have called the material arnifolin. The individuality of arnifolin was demonstrated by constancy of constants upon recrystallization from various solvents and by chromatography.

Arnifolin (I) does not dissolve in bases in the cold but dissolves easily upon heating. Upon short heating in weak solutions 1 g-eq. of base is consumed, and upon acidification arnifolin is again formed. In more concentrated bases and upon more prolonged heating 2 g-eq of base are consumed. Tiglic acid (II, C_{5}H_{8}O_{2}, mp 61-63°C, identified by IR and NMR spectra, was isolated from the hydrolysis products.

Arnifolin forms an oxime, mp 160°C (dec.), and gives a positive Zimmermann test for the CO-CH_{2} grouping.

Upon hydrogenation of arnifolin in the presence of both Pt and Ni catalysts in alcohol, 2 moles of hydrogen are consumed and the tetrahydro derivative (III) is formed, mp 64-66°C (hydrate form), which after drying is a colorless, glassy product of composition C_{20}H_{30}O_{6}. (See scheme on next page.)

In the IR spectrum of arnifolin are observed absorption bands at 3578, 3384, 3230 cm^{-1} (OH group), 1712 cm^{-1} (α,β-unsaturated ester), and 1655 (C = C), and also a broad band at 1754 cm^{-1}. In the tetrahydro derivative, in addition to absorption bands of the OH group, absorption maxima are present at 1770 cm^{-1} (α-lactone), 1750 cm^{-1} (cyclopentanone), and 1725 cm^{-1} (ester).

It follows from these data that arnifolin is an ester of a sesquiterpene hydroxyketolactone and tiglic acid. The broad band at 1754 cm^{-1} in arnifolin is due to merging of absorption bands of the α-lactone and cyclopentanone.

![Fig. 1. NMR spectrum of arnifolin in CDCl_{3}. All NMR spectra were taken on a 100 MHz INM-4H-100 instrument.](image1)

![Fig. 2. NMR spectrum of tetrahydroarnifolin in CDCl_{3}.](image2)
The UV spectrum of arnifolin contains an absorption maximum at 219 m\(\mu\), \(\epsilon\) 14,410, characterizing the presence of conjugated double bonds; this absorption maximum is not present in (III).

Treatment of tetrahydroarnifolin with acetic anhydride yields anhydrotetrahydroarnifolin (IV), \(C_{20}H_{25}O_5\), mp 122-126\(^\circ\); \(\nu_{\text{max}}\): 1765 (\(\gamma\)-lactone), 1730 (ester), 1710 and 1585 cm\(^{-1}\) (cyclopentenone). The presence of the latter is confirmed by the UV spectrum (\(\lambda_{\text{max}}\) 226 m\(\mu\), \(\epsilon\) 8,673), characteristic for an \(\alpha,\beta\)-cyclopentenone [2-5]. Consequently, the hydroxyl is situated in a five-membered ring.

Dehydrogenation of arnifolin, and the tetrahydro derivative over selenium at 310-360\(^\circ\) for 1, 2, and 6 h gave only traces of a blue material; no other aromatic derivatives were obtained. Dehydrogenation over selenium of the lithium aluminum hydride reduction product of arnifolin and tetrahydroarnifolin led to chamazulene (V) and guaiazulene (VI), but also in very low yield. It is known that sesquiterpene lactones of the ambrozan type [6] often give such dehydrogenation results. The similarity of arnifolin to sesquiterpenes of this type is confirmed by NMR spectral data of arnifolin which show the characteristic methyl singlet at 0.83 ppm (angular methyl).

The NMR spectrum of arnifolin (Fig. 1) also contains the signal of the vinyl proton as a quartet at 6.86 ppm and signals of two vinyl methyls at about 1.85 ppm, \(-2\text{CH}_3-\text{C}=-\text{C}\). These signals virtually co-

![Fig. 3. NMR spectrum of anhydrotetrahydroarnifolin in CDCl\(_3\).](image)

![Fig. 4. NMR spectrum of the hydroxy-ketoacid in pyridine.](image)