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THE CONSTITUTION OF ANGELOL, A NEW COUMARIN ISOLATED FROM THE ROOT OF ANGELICA PUBESCENS MAXIM. (UMBELLIFERAE)

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From the root of Angelica pubescens Maxim., a stout herb widely distributed in Japan, four crystalline compounds have been isolated. Three of these are known coumarins: osthol, $C_{15}H_{16}O_3$, m.p.83-85°, bergapten, $C_{12}H_8O_4$, m.p.188-190° and glabra-lactone (1), $C_{16}H_{16}O_5$, m.p.129-130°. Other one is a new coumarin, $C_{20}H_{24}O_7$, m.p.104-105°, $[\alpha]_D^{24}$: -94.7° ($CHCl_3$), which is designated as angelol.

The present communication presents the elucidation of the structure of angelol (I).

The ethereal extract of the plant material upon chromatography over silica gel during elution with n-hexan - ethylacetate (1:1) furnished osthol, bergapten, glabra-lactone and viscous oil. The oil crystallized from ether as fine needls, which upon rechromatography over silica gel during elution with benzene - ethylacetate (4:1) gave pure angelol.

Angelol is freely soluble in benzene, ethylacetate, chloroform and ethanol, sparingly soluble in diethylether and scarcely insoluble in n-hexane and petroleum ether. It is

free from phenolic group and gives no reaction towards 2,4-dinitrophenylhydrazine.

Its coumarin character is indicated by the fluorescence, the UV-absorption: λ_{max}^{EtOH} 223mμ (logE, 4.29), 243mμ (logE, 3.82 shoulder), 254mμ (logE, 3.72 shoulder), 296mμ (logE, 3.93 shoulder) and 330mμ (logE, 4.20) and by the absorption bands corresponding to conjugated lactone and benzene nucleus in the IR spectrum.

The NMR spectrum of angelol shows a pair of doublet at 2.36 and 3.78τ (J,9.5cps) which can be assigned to protons at position 4 and 3 of the coumarin nucleus. Peaks at 2.40 and 3.25τ are assigned to protons at positions 5 and 8 respectively. Further absorptions are observed at 8.43 and 8.75τ ($\begin{matrix}H_3C\\H_3C\end{matrix}$>C<), 6.03τ($CH_3O$), 5.20 and 6.75τ(2 OH), and 4.35 and 4.84τ(2 -CH-). The absorptions at 8.16τ(6H, multiplet) and 4.10τ(1H, multiplet) can be assigned to methyl and olefinic protons of angeloyl group.

Hydrogenation of angelol in ethanol using Pd/C catalyst afforded dihydroangelol, $C_{20}H_{26}O_7$, m.p.113-114°, under absorption of 1 mole of hydrogen.

Upon saponification with aqueous base, angelol and dihydroangelol gave angelic- and methylethylacetic acid respectively, which were identified as their p-phenylphenacyl ester, but no further crystalline product was obtained except small amount of amorphous substance.

Chemical confirmation for this structural suggestion was found in the degradation of angelol with dilute aqueous sulfuric acid resulting the formation of acetone, identified as its 2,4-dinitrophenylhydrazone derivative, and 6-formyl-

methyl-7-methoxy-coumarin (II), identified from the fact that its thioacetal derivative gave 6-ethyl-7-methoxy-coumarin (IV) upon desulfurization with Raney nickel, besides angelic acid.

Small amount of isobutylaldehyde, identified as its 2,4-dinitrophenylhydrazone derivative, and 6-formyl-7-methoxy-coumarin (III), which has been previously reported as a product from the ethereal extract of the same plant material as that of angelol upon vacuum distillation and designated as angelical (2), were simultaneously formed besides degradation products above mentioned. These results indicate that angelol is formed of 7-methoxy-coumarin and isopentyl chain, which would be composed from the carbon skeletons of formylmethyl group and acetone or formyl group and isobutylaldehyde, attached to position 6 bearing three hydroxyl groups one of which is present as an angelate.

Taking into consideration the NMR spectrum, therefore, possible structure for angelol could be written as Ia, Ib or Ic.

Now, angelol underwent glycol cleavage with lead tetra acetate forming acetone and a aliphatic aldehyde (V), which was identified by its positive reaction towards Fehlings solution and carbonyl reagents. Periodic acid oxidation of angelol afforded the same products. The structure of the aldehyde V must be represented as formula V from the fact that angelic acid was formed upon saponification of V, and catalytic hydrogenation of V led to formation of 6-ethyl-7-methoxy-coumarin (IV).

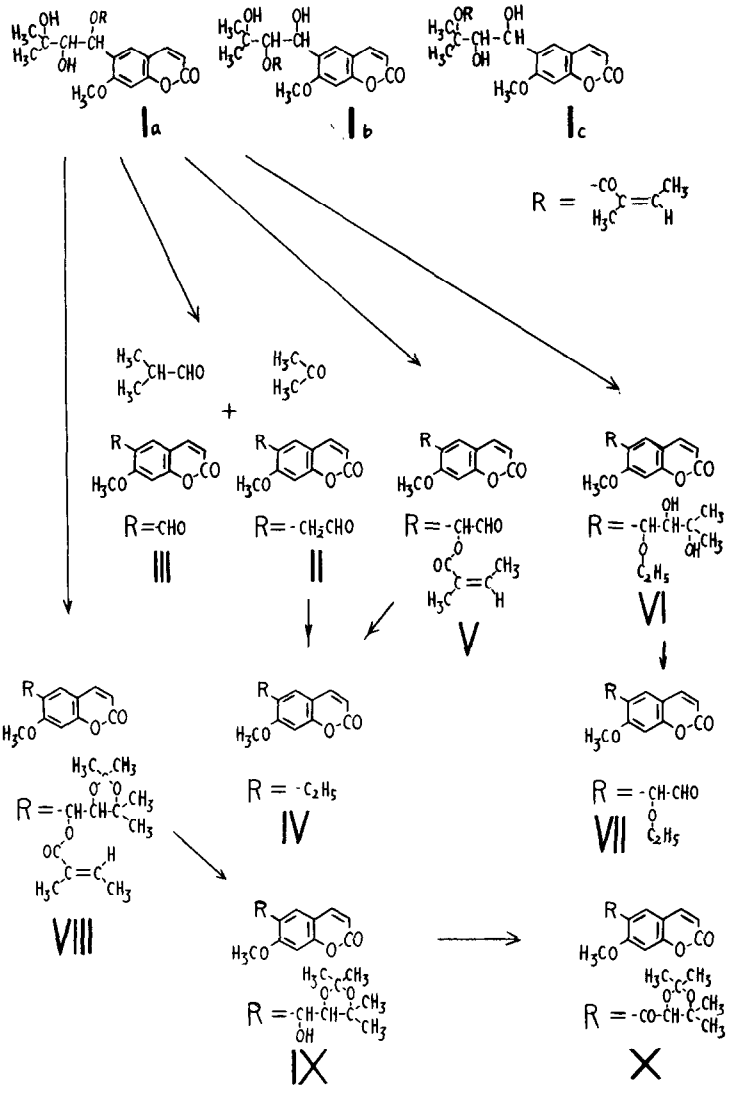
These results indicate that $\begin{matrix} H_3C \\ H_3C \end{matrix}\!>\!C(OH)\text{-}C(OH)H\text{-}$ group is present in angelol and, accordingly, Ia is the most likely

candidate for angelol. This assignment was further confirmed in following two ways.

For the first, it is well known that certain benzyl esters suffer ready solvolysis with O-alkyl cleavage under acidic or basic conditions (3). In the case of angelol, a crystalline compound (VI), $C_{17}H_{22}O_6$, m.p.187-188°, was obtained upon the treatment 15 minutes with 1N ethanolic sodium hydroxide at a room temperature. The NMR spectrum of VI shows the absorption corresponding to ethoxyl instead of angeloyl group. Methoxyl derivative was similarly formed by the treatment with methanolic base. Periodic acid oxidation of VI afforded acetone and a aldehyde (VII), $C_{14}H_{14}O_5$, m.p.97-98.5°, whose NMR spectrum is in confirmity with formula VII. These results demonstrate the presence of benzyl ester in angelol.

Finally, it was studied to prepare free benzyl alcohol from angelol in order to confirm the presence of angelated benzyl alcohol in angelol. Though angelol itself gave no crystalline product under any conditions when it is submitted directly to saponification, its isopropylidene derivative (VIII), $C_{23}H_{28}O_7$, m.p.191-192°, which was formed upon the treatment of angelol with phosphorous pentoxide in absolute acetone at a room temperature in good yield, afforded a crystalline compound (IX), $C_{18}H_{22}O_6$, m.p.183-185°, and tiglic acid upon saponification with aqueous base. The formation of tiglic acid suggests the occurrence of isomerization of angeloyl- into tigloyl group during the treatment with phosphorous pentoxide. The NMR spectrum of VIII also shows the absorption to be assigned to protons of tigloyl- instead of angeloyl group.

The compound IX gave a ketone (X), $C_{18}H_{20}O_6$, m.p.119-120°,


Ia
Ib
Ic
R = -CO-C(CH3)=CH-CH3
III
II
V
VI
IV
VII
VIII
IX
X

following oxidation with chromic acid, which was identified to be aromatic ketone by absorption band at 1685 cm^{-1} in the IR spectrum, marked change in the UV spectrum accompaning this oxidation and by the lower shift of the absorption due to proton at position 5 in the NMR spectrum showing the presence of carbonyl group at position 6.

This observation shows evidently that the compound IX is free benzyl alcohol which was expected, and Ia is to be assigned for angelol.

Stereochemical studies on angelol will be reported at later date.

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