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BITTER PRINCIPLES OF PHYSALIS ALKEKENGI VAR FRANCHETI: STRUCTURE OF PHYSALIN A

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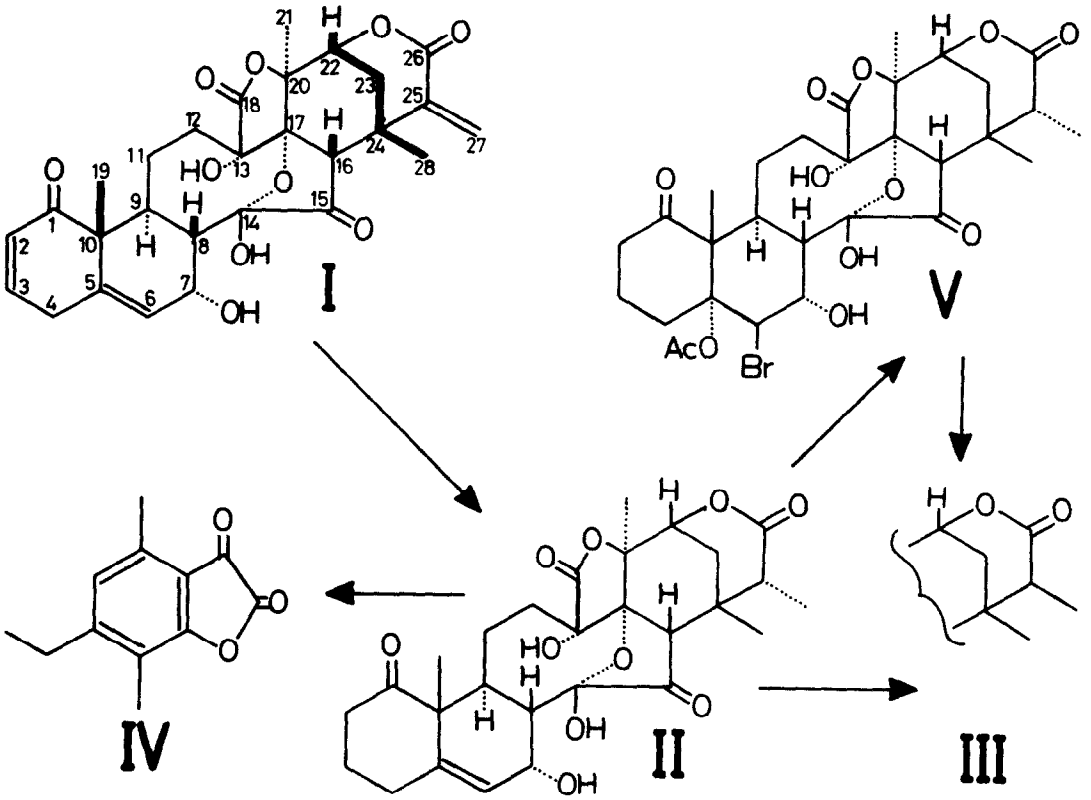
More than a hundred years ago Dessaigne et al[1] isolated the amorphous bitter substance from the leaves of winter cherry (Physalis Alkekengi), and named it physalin. In 1961 Völksen[2] reported the isolation of a crystalline bitter compound from Ph. Franchettii,[3] which is a species very close to Ph. Alkekengi. A formula $C_{21}H_{26}O_8$ was given for the bitter substance but no further studies on its structure were reported.

All parts of the fresh herb of Ph. Alkekengi var Francheti (Japanese name: Hôzuki) were boiled in hot water and the water layer was extracted with chloroform. Repeated recrystallizations of the chloroform extracts from methanol and from acetone yielded a very bitter substance (0.05%) along with a slightly bitter substance (0.005%). We propose the name physalin A for the former and physalin B for the latter. In this communication the structure of physalin A is described.[4]

Physalin A ($C_{28}H_{30}O_{10}\cdot CH_3COCH_3$; mp. 266° from acetone: $C_{28}H_{30}O_{10}\cdot CH_3OH$; mp. 262° from methanol) (I) gave a molecular peak at m/e 526 on mass spectrometry. Complicated IR-absorptions between 1600 and 1800 cm^{-1} showed the existence of several carbonyl functions including a five membered lactone ring (1780 cm^{-1}). The presence of a conjugated ketone group and probably another conjugated system was indicated by UV-spectroscopy (λ_{infl} 218 mμ; ε 10,000). The n.m.r. spectrum (DMSO-d_6) of I exhibited five multiplets (δ 5.63, 5.70, 5.84, 6.43, 6.94) corresponding to five olefinic protons in addition to three singlets (δ 1.05, 1.55, 1.72) of tertiary methyl groups.

Hydrogenation of I over Pd-C yielded tetrahydrophysalin A ($C_{28}H_{34}O_{10}\cdot 2CH_3OH$; mp. 279°) (II), which was readily isomerized to epitetrahydrophysalin A ($C_{28}H_{34}O_{10}$; mp. 293°) (III) in boiling aqueous ethanol. In the n.m.r. spectrum (pyridine) of II a signal of one olefinic proton (δ 5.83) was observed indicating a remaining trisubstituted double bond. The appearance of a secondary methyl group (δ 1.70, J = 8cps) in II suggests the presence of an exo-methylene group

in the original compound I. This was confirmed by the formaldehyde formation on the ozonolysis of I. The n.m.r. spectrum (pyridine) of III was very similar to that of II except for the chemical shift of a secondary methyl group (δ 1.27), suggesting that III is epimeric to II with respect to the secondary methyl group, which must be located on a carbon atom adjacent to a carbonyl function.



In order to obtain informations on the carbon skeleton, I was dehydrogenated in the presence of Se at 260°. Among the products alkyl substituted naphthalenes were detected by UV-spectroscopy but no phenanthrene derivatives. Pyrolysis of II at reduced pressure gave a yellow crystalline product ($C_{12}H_{12}O_3$; mp. 153°), the structure of which was determined as IV spectroscopically and confirmed by synthesis.[5] The results of these degradation reactions suggest

that physalin A (I) contains neither usual steroidal nor triterpenoid skeleton.

Treatment of II with Br_2-AcONa/AcOH gave an acetoxy bromide ($C_{30}H_{37}O_{12}Br \cdot 2CH_3OH$; mp. 214°) (V). The n.m.r. spectra (DMSO-d_6) of V indicated the presence of an acetoxy group (δ 1.83) but no olefinic proton, suggesting that addition of a bromine atom and an acetoxy group to a double bond of II had occurred.[6] An X-ray crystallographic analysis was carried out and structure V was established for this bromine derivative.[7]

Since V has a 5α-acetoxy group and a 6β-bromine atom, the position of the double bond in II must be at C_5-C_6. The facile epimerization of II to III can be explained well by the steric repulsion between C_{27}-methyl and C_{15}-carbonyl and by the participation of 14-OH group which assists enolization of C_{20}-carbonyl function. (Fig. 1) V was deacetoxybrominated with Zn-Cu couple[6] to give III, suggesting that no skeletal rearrangement had occurred during the reaction from II to V.

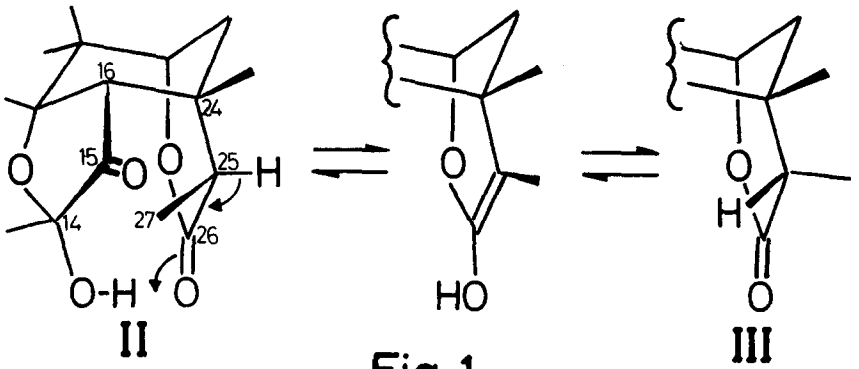


Fig. 1

The structure of the original bitter principle, physalin A (I), can be completed by adding two double bonds to tetrahydrophysalin A (II). The position of one of the double bonds is obviously C_{25}-C_{27} (terminal methylene). The intense and broad UV-absorption of I around 218 mμ can be explained as the overlapped bands of a conjugated ketone and a conjugated lactone. Consequently another double bond can be located at C_2-C_3 position and this was supported by the n.m.r. spectrum of I which shows a doublet at δ 5.84 (J = 10cps) and a broad doublet at δ 6.94 (J = 10cps), assigned to α- and β-protons of the conjugated enone system respectively.

It should be noted that a C-28 steroidal substance, withaferin A, which can be considered to be biogenetically related to physalin A, was isolated from plants of the same family

(Solanaceae).[8] Though physalin A (I) is also regarded as a member of C-28 steroids having one extra methyl at C_{24}-position, its carbon skeleton has following two biogenetically interesting features. i) The C_{13}-C_{14} bond between rings C and D is broken resulting a nine membered ring formation. ii) A bond is formed between C_{16} and C_{24} making a new six membered carbocycle.

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3) We consider that "Ph. Franchettii" in Völksen's report[2] is the same plant as our "Ph. Alkekengi var Francheti".

4) The structure of physalin B will be described elsewhere.

5) The results will be published in a full paper.

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