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CHEMICAL EXAMINATION OF *HERACLEUM CANDICANS*—I

ISOLATION AND STRUCTURE OF A NEW FUROCOUMARIN—HERACLENIN

Y. N. SHARMA, A. ZAMAN and A. R. KIDWAI
Department of Research in Unani Medicine, Tibbiya College and Department of Chemistry, Aligarh Muslim University, Aligarh, India

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Abstract—A new furocoumarin, heraclenin, has been isolated from *Heracleum candicans* and its structure has been established as 8-(β,γ-oxido-isoamyloxy)-psoralen.

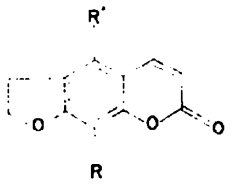
SKIN photosensitizing action of a number of furocoumarins has been discussed by Musajo and Rodighiero[1] and Pathak and Fitzpatrick.[2-3] The results of these investigations have established that the essential requirement for this property is the presence of a linear furocoumarin nucleus. Furocoumarins having free phenolic hydroxy groups are inactive but the activity is restored on alkylation. As regards these alkyl ethers, the methyl and ethyl ethers are most active and from there on the activity is gradually reduced with the lengthening of the side chain, even so oxypeucedanin was found to possess photosensitizing activity.

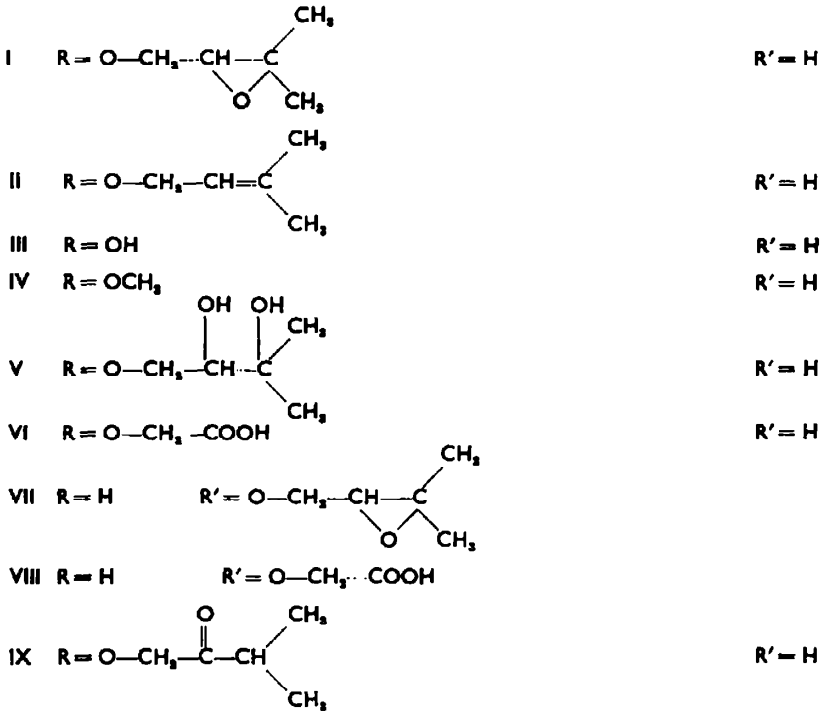
In this connexion it was felt that investigation of other naturally occurring coumarins could be of some interest. We report here the isolation of a new furocoumarin, heraclenin(I) which has been obtained from *Heracleum candicans* (Umbelliferae).

Heraclenin (I) m.p. 111°, $(\alpha)_D^{32} = +22$ analyses for $C_{16}H_{14}O_5$ and its UV spectrum is similar to that of imperatorin(II) (Fig. 1). The molecular formula differs from that of imperatorin by the presence of an extra oxygen atom. Treatment of the compound with acetic acid–sulphuric acid mixture, under conditions generally used for the cleavage of the side chain in furocoumarins, affords a phenolic product (III) $C_{11}H_6O_4$ m.p. 248–249°, which gives a pale green ferric chloride reaction, forms an acetate m.p. 178° and methyl ether m.p. 146–147°. These agree with the m.p. of xanthotoxol (III) and xanthotoxin (IV) respectively. Xanthotoxol acetate has not been reported. Identity of the cleavage product with xanthotoxol was confirmed by comparison with an authentic sample.

The extra oxygen atom in heraclenin must, therefore, be present in the C_5H_9 side chain, possibly in an epoxide linkage since the IR spectrum of the compound does not show hydroxy band. This is supported by the hydrolysis, under mild acidic conditions, to a diol (V) $C_{16}H_{16}O_6$ m.p. 117–118°. Oxidation with chromic acid in acetic acid gave acetone and an acid (VI) $C_{12}H_8O_6$ m.p. 215°. This indicates that the C_5H_9O residue in heraclenin is similarly constituted as in the isomeric oxypeucedanin

[1] L. Musajo and G. Rodighiero; *Experimentia* **18**, 153 (1962).
[2] M. A. Pathak and T. R. Fitzpatrick, *J. Investig. Dermatol.* **32**, 255 (1959).
[3] M. A. Pathak and T. R. Fitzpatrick, *J. Investig. Dermatol.* **32**, 509 (1959).





(VII), which gives acetone and oxypeucedaninic acid (5-ω-carboxymethoxy-4′,5′,6,7-furocoumarin), on chromic acid oxidation. Compound VI has accordingly been formulated as 8-ω-carbomethoxy-4′,5′,6,7-furocoumarin. Schönberg and Sina,[4] who synthesized this acid, have reported 210° as the melting point.

On refluxing in toluene over phosphorous pentoxide or on boiling with dilute mineral acids heraclenin is converted in good yield to a ketone (IX) $C_{16}H_{14}O_5$ m.p. 132–134° formed by opening and rearrangement of the epoxide ring. The IR spectrum of this compound has a doublet in the carbonyl region (5·75 and 5·8 μ). It has been named isoheralcenin in conformity with the nomenclature adopted by Späth for the rearrangement product of oxypeucedanin.[5] Treatment of oxypeucedanin with sodium acetate–acetic anhydride gives a diacetate, however, heraclenin does not form a diacetate on refluxing with this mixture. In all other reactions heraclenin and oxypeucedanin are analogous.

The structure of heraclenin (I) as 8-(β,γ-oxido-isoamyloxy)-psoralen was further confirmed by the oxidation of imperatorin with perbenzoic acid according to Späth,[6]

[4] A. Schönberg and A. Sina, *J. Amer. Chem. Soc.* **72**, 4826 (1950).
[5] E. Späth and K. Klager, *Ber. Dtsch. Chem. Ges.* **66**, 914 (1933).
[6] E. Späth and H. Holzen. *Ber. Dtsch. Chem. Ges.* **68**, 1123 (1935).

when a compound m.p. 114–115°, reported by him, was obtained. The synthetic compound oxyimperatorin, being racemic, gives a depression in m.p. with heraclenin (I) but has a superimposable IR spectrum.

Heraclenin has not so far been reported to occur naturally though its presence in the extract of masterwort (*Imperatoria ostruthium*) was suspected by Späth.[6]

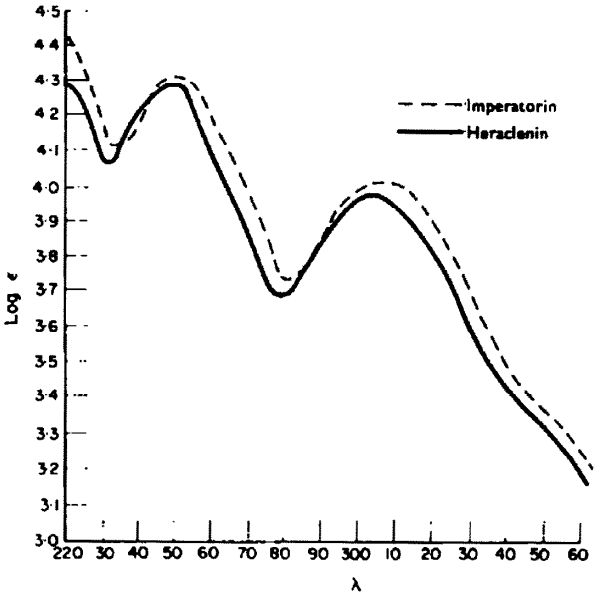


FIG 1

EXPERIMENTAL

All UV spectra were measured in a Beckmann model DU instrument in 95% ethanol. IR spectra were taken on a Perkin Elmer Infracord either in chloroform solutions or as mulls in nujol.

Isolation of heraclenin (I). Air dried finely powdered roots (2 kg) of *Heracleum candicans* were extracted with pet. ether (40–60°) in a soxhlet for 20 hr. On cooling the extract deposited a yellow solid (120 g), 5 g of which was dissolved in benzene and chromatographed over deactivated alumina (250 g) prepared by shaking with 10% aqueous acetic acid for 2 hr. Elution with pet. ether (40–60°) afforded a small quantity of a low melting product. Further elution with benzene–pet ether mixture (1:5) gave a crystalline product m.p. 82°. Finally, elution with benzene–pet ether mixture (1:1) yielded heraclenin (1·5 g). After crystallization from methanol it melted at 111°, $(\alpha)_D^{28} = +22$ (pyridine), λ_{max} 250 mμ (log ε 4·31), 305 mμ (log ε 4·02). (Found: C, 67·08; H, 4·99; $C_{16}H_{14}O_5$ requires: C, 67·12; H, 4·93%).

Xanthotoxol (III). Heraclenin (1 g) was dissolved in glacial acetic acid (20 ml) to which conc H_2SO_4 (20 drops) were added. The reaction mixture was heated on a water bath for 30 min, cooled and then poured over crushed ice. The gummy substance which separated out was sublimed at 1 mm, 190–200° (bath temp). Crystallization of the sublimate from ether gave crystals of xanthotoxol m.p. 248–249°.

Xanthotoxin (IV). Xanthotoxol (200 mg) in methanol (2 ml) was treated with excess diazomethane in ether and left overnight. The residue was dissolved in benzene and chromatographed over deactivated alumina with the same solvent. Xanthotoxin was crystallized from benzene–pet ether m.p. 146–147°.

Xanthotoxol acetate. Xanthotoxol (500 mg) acetic anhydride (5 ml) and fused sodium acetate (100 mg) were refluxed 1 hr. The mixture was cooled, poured over crushed ice and the acetate was crystallized from methanol m.p. 178°. (Found: C, 64·88; H, 3·51; $C_{13}H_8O_5$ requires: C, 63·94; H, 3·30%).

Heraclenin hydrate (V). A solution of heraclenin (200 mg) in water (50 ml) was heated on a water bath, oxalic acid (50 mg) was added and heating continued for 10 min. The material which separated on cooling was washed with water and crystallized from ethyl acetate m.p. 117–118°. (Found: C, 63·28; H, 5·39, $C_{16}H_{16}O_6$ requires: C, 63·15; H, 5·30%).

Isoheraclenin (IX). Heraclenin (1 g) was dissolved in dry toluene (50 ml) and brought to boiling P_2O_5 (4 g) was added and the mixture refluxed for another 10 min, cooled and filtered. The filtrate was diluted with ether and the ether–toluene solution extracted with $NaHCO_3$aq., washed with water and dried (Na_2SO_4). The solvent was removed under vacuum and the residue crystallized from ether, m.p. 132–134°. It formed a crystalline 2,4-dinitrophenylhydrazone. (Found: C, 67·33; H, 5·06; $C_{14}H_{14}O_5$ requires: C, 67·12; H, 4·93%). Heraclenin was also isomerized to isoheraclenin with 10% H_2SO_4.

8-ω-Carbooxymethoxy-4′,5′,6,7-furocoumarin (VI). To heraclenin (3 g) dissolved in glacial acetic acid (45 ml), chromium trioxide (1·2 g) in 50% aqueous acetic acid (60 ml) was added, and the solution allowed to stand for 24 hr at room temp. The reaction mixture was diluted with water and extracted with a large excess of ether. The ethereal solution was washed with water dried (Na_2SO_4) and solvent removed under vacuum. The reddish brown residue obtained was dissolved in methyl alcohol and methylated with excess diazomathane in ether. The methylated product was dissolved in benzene and chromatographed over acid treated alumina. The benzene eluate on evaporation deposited pale yellow needles. It was crystallized from alcohol m.p. 146–147° (Found: 61·16; H, 3·73; $C_{14}H_{10}O_6$ requires: C, 61·32; H, 3·68%).

The above ester (0·3 g) was refluxed with 50% acetic acid (16 ml) for 1 hr. It was cooled and diluted with water to 50 ml and after standing a yellow coloured solid separated. This crystallized from alcohol in pale yellow crystals m.p. 215° (m.p. reported by Schönberg and Sina 210°).[4] (Found: C, 59·66; H, 3·30; Calc. for $C_{13}H_8O_6$: C, 60·01; H, 3·10%).

Acetone. In another experiment the reaction mixture obtained by the above oxidation was neutralized with NaOH under cooling and immediately steam distilled. The distillate was collected in an aqueous solution of 2:4-dinitrophenylhydrazine and the 2,4-dinitrophenylhydrazone derivative of acetone crystallized from methanol and was identified by mixed m.p. with an authentic sample.

Oxy-imperatorin. Imperatorin (0·003 moles) was dissolved in chloroform (2 ml) and a solution of perbenzoic acid (0·004 moles) in chloroform was added with gradual shaking. The reaction mixture was then allowed to stand at room temp for 3 days, diluted with ether and washed with $NaHCO_3$aq. The ether–chloroform layer was dried (Na_2SO_4). The solvent was removed and the residue dissolved in benzene and chromatographed over deactivated alumina. The oily substance obtained crystallized from benzene–pet ether (40–60°) m.p. 114–115°, and was identical with that reported by Späth. (Found: C, 67·19; H, 5·07; Calc. for $C_{16}H_{14}O_5$: 67·12; H, 4·93%).

This product was found to be identical with heraclenin by superimposable IR spectrum.

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