A NOTE ON THE BIOGENESIS OF PEDICIN

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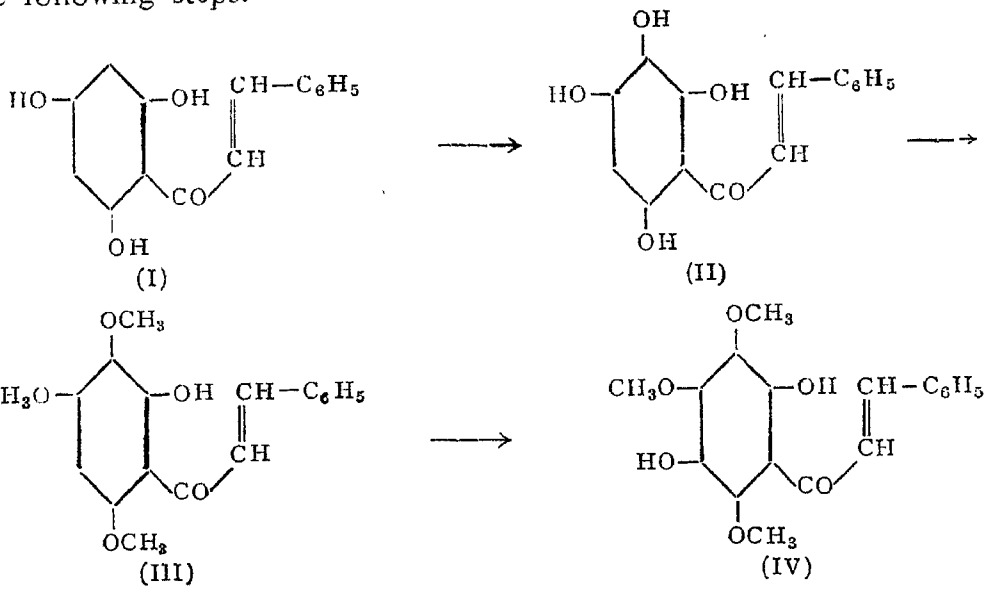
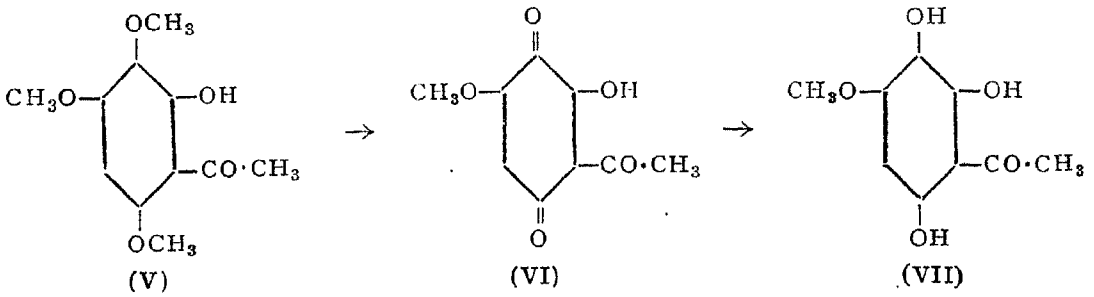
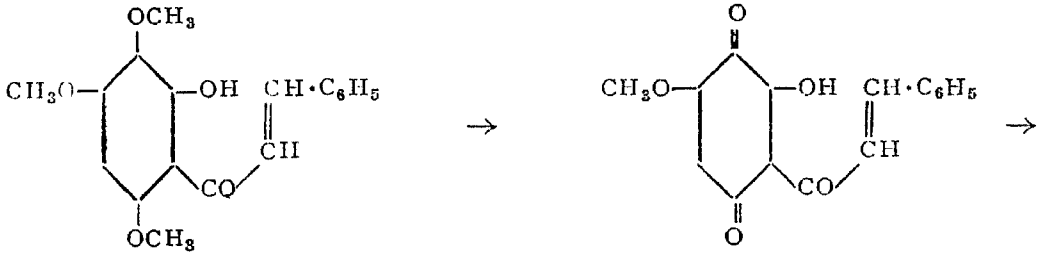
In an earlier publication[1] the biogenesis of pedicin was considered to involve the following steps.



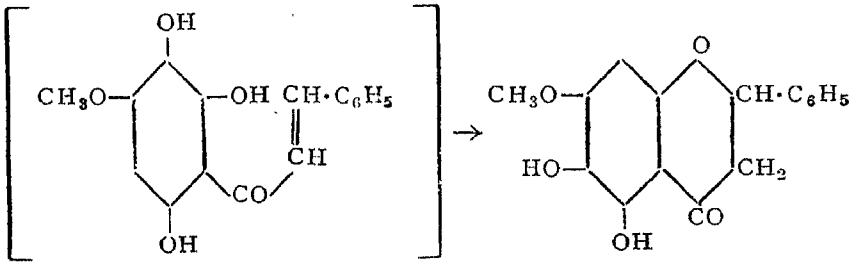
The possibility of oxidation of (I) to (II) can be granted based on well-known analogies, the conversion of (III) to (IV) was effected by nuclear oxidation using alkaline persulphate.[1] An important point that required to be established was the conversion of (II) to (III) by partial methylation. That this is the course of the reaction and not the alternative, *i.e.*, formation of 2-hydroxy-4: 5: 6-trimethoxy chalkone was not proved. In order to provide this proof the study of the partial methylation of a closely related but simpler case has now been undertaken. When 2: 3: 6-trihydroxy-4-methoxy acetophenone (VII), prepared from 2-hydroxy-3: 4: 6-trimethoxy acetophenone (V) by first carrying out oxidative demethylation to the quinone[2] (VI) and subsequent reduction with sodium hydrosulphite, is methylated with two moles of dimethyl sulphate the original 2-hydroxy-3 :4: 6-trimethoxy acetophenone (V) is obtained. Hence the validity of the biogenetic scheme is supported. It has not been possible to prove the above point strictly using the corresponding chalkone (X) itself since it is unstable and undergoes change into the corresponding flavanone. But the manner of flavanone ring closure again supports the greater reactivity of the hydroxyl in the 6-position, since the product is found to be 7-methoxy-5: 6-dihydroxy flavanone (XI).



(V) (VI) (VII)

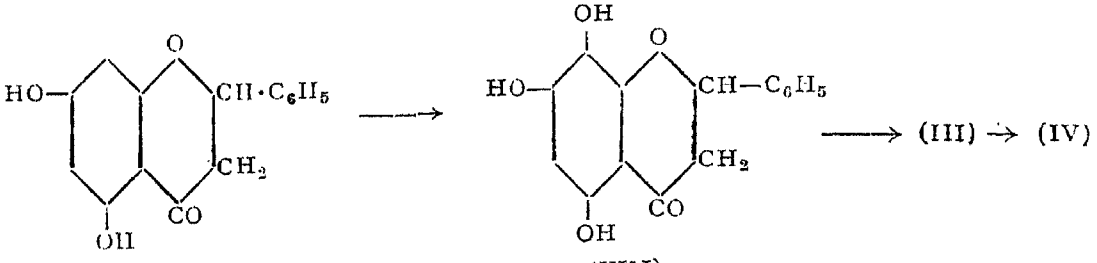


(VIII) (IX)



(X) (XI)

On account of the instability of chalkones having hydroxyl groups in the 2- and 6-positions and of the greater stability of flavanones having a hydroxyl group in the 5-position, an alternative scheme of biogenesis would suggest itself as more probable and is given below. 5 : 7-Dihydroxy flavanone (XII) represents a type which is widely distributed. When it undergoes nuclear oxidation it can give rise to (XIII) which belongs to the carthamidin type. If all the hydroxyl groups of this compound should be methylated then the ring structure would become unstable and the corresponding chalkone (III) would be produced which on further nuclear oxidation would give rise to pedicin.



(XII) (XIII)

EXPERIMENTAL

2 : 3 : 6-*Trihydroxy*-4-*methoxy acetophenone* (*VII*).—This was first prepared by Rao, Rao and Seshadri.[2] Their procedure has now been followed except for the last stage *i.e.*, the reduction of the quinone (VI) to the final product.

2-Hydroxy-4-methoxy-3 : 6-quinoacetophenone (VI) (5 g.) was added to boiling water (60 c.c.) followed by sodium hydrosulphite (10 g.) in small quantities. A clear solution was obtained which was boiled for further two minutes and quickly cooled under the tap when a pale yellow solid separated. It was filtered, washed with cold water and crystallised from dry benzene when the quinol was obtained as pale yellow prismatic needles melting at 170–1°; yield, 3 g.

The triacetate of this compound was prepared using acetyl chloride and a drop of pyridine and heating under reflux on a water-bath for an hour. It crystallised from dry benzene as colourless prismatic tablets, melting at 184–5°. (Found: C, 55·8; H, 4·8; $C_{15}H_{16}O_8$ requires C, 55·6; H, 4·9%.)

Partial methylation of 2 : 3 : 6-*trihydroxy*-4-*methoxy acetophenone* (*VII*).—The above quinol (1 g.) was dissolved in dry acetone (50 c.c.) and redistilled dimethyl sulphate 1 c.c.; 2·1 moles) and ignited potassium carbonate (5 g.) were added. The mixture was refluxed for 12 hours, the acetone solution was filtered hot and the potassium salts washed with hot acetone. The solvent was distilled off from the filtrate and the residue dissolved in benzene and extracted with dilute sodium hydroxide (5%) twice. The alkaline extract was cooled in ice and ice-cold concentrated hydrochloric acid was then added in excess and left overnight in the ice-chest. The solid that separated out was filtered and crystallised from benzene when 2-hydroxy-3 : 4 : 6-trimethoxy acetophenone (V) was obtained, m.p. 113°; the mixed melting point with an authentic sample was undepressed.

Reduction of 2-*hydroxy*-4-*methoxy*-3 : 6-*quino-chalkone* (*IX*).—The chalkone (VIII) was prepared by the method of Rao and Seshadri,[1] and oxidised to the quino-chalkone (IX) by the method of Rao, Rao and Seshadri.[2] Its reduction did not proceed satisfactorily with sodium hydrosulphite. Stand nous chloride[3] was found to be suitable.

2-Hydroxy-4-methoxy-3 : 6-quino-chalkone (IX) (1 g.) was dissolved in alcohol (100 c.c.) and the solution boiled under reflux. To this was added in small quantities a solution of pure stannous chloride (25 g.) in concentrated hydrochloric acid (20 c.c.) during the course of one hour while the mixture was kept refluxing. The heating was continued for another hour,

The initial dark brown colour of the mixture gradually became pale yellowish brown. The alcohol was then distilled off as much as possible under reduce-pressure and the brown solution left behind was diluted with water (100 c.c.). The brown yellow solid that separated out was filtered, washed with water and dried in a vacuum desiccator. The product crystallised from ethyl acetate as pale yellow large prisms melting at 248° (decom.) with sintering at 225°. It gave a bright green colour with alcoholic ferric chloride slowly changing to brown with excess of the reagent and no colour with alcoholic solution of *p*-benzoquinone. These reactions agreed with the requirements of a 5:6-dihydroxy flavanone structure. The compound was found to be identical with 5:6-dihydroxy-7-methoxy flavanone (IX) obtained by another method (unpublished results) and the mixed melting point was undepressed.

Summary

Of the two hydroxyl groups in the 2- and 6-positions of 2:3:6-trihydroxy-4-methoxy acetophenone and chalkone the 6-hydroxyl is shown to be more reactive. A modified biogenetic scheme is suggested for pedicin.

References

1. Rao and Seshadri .. *Proc. Ind. Acad. Sci.*, 1948, **27 A**, 375.
2. Rao, Rao and Seshadri .. *Ibid.*, 1948, **27 A**, 245.
3. Salooja, Sharma and Siddiqui *Journ. Sci. Indust. Res.*, 1947, **6 B**, 57.