

NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XXV. Isomers of Pedicinin

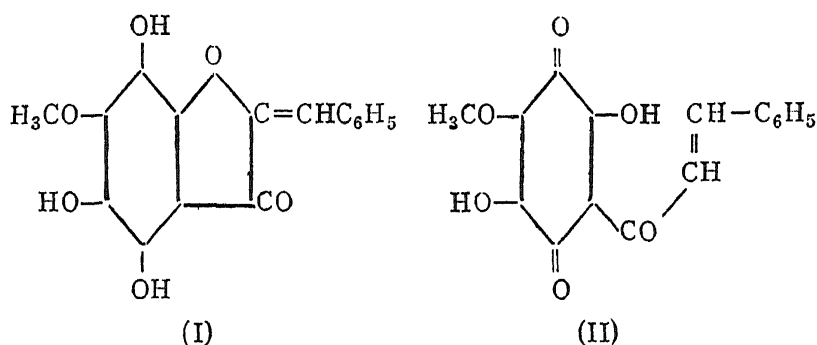
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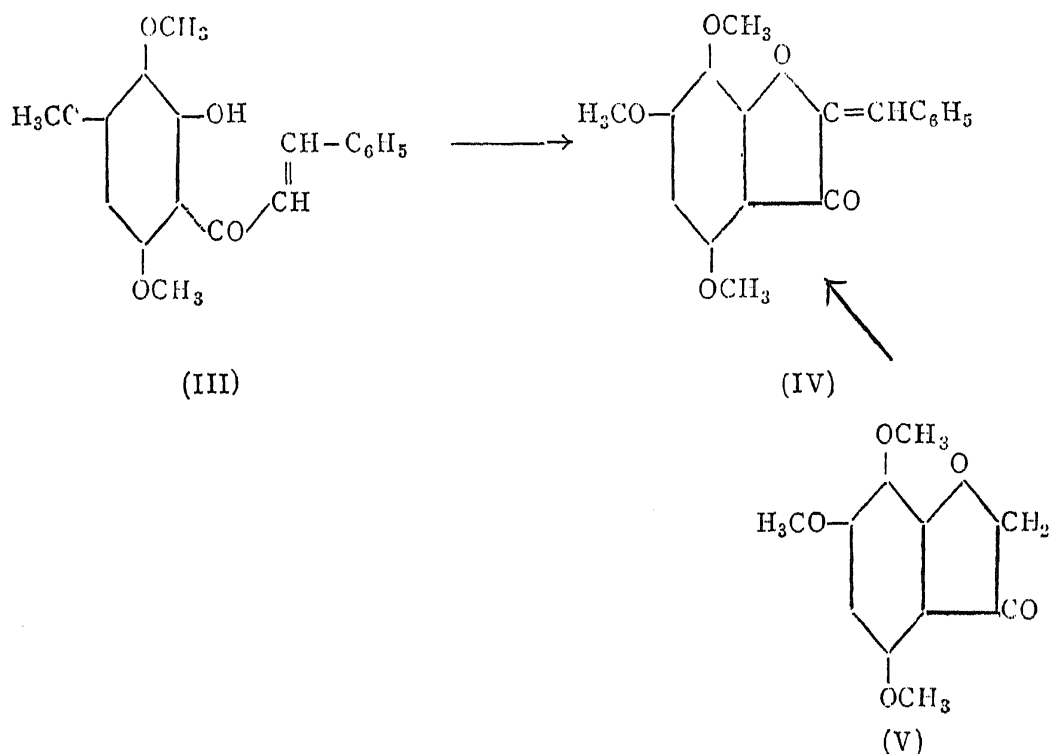
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PEDICININ was first investigated by Sharma and Siddiqui¹ who proposed for it the constitution of 4:5:7-trihydroxy-6-methoxy-benzal-coumaran-3-one (I). This was based mainly on its molecular formula and its colour reaction with ferric chloride. Using this structure there was difficulty in explaining the conversion of pedicin and pedicellin into pedicinin. Later Bose and Dutt² found that pedicinin has quinone and acid properties and concluded that it should have the formula (II), *i.e.*, 2:5-dihydroxy-4-methoxy-3:6-quinone-chalkone. In a subsequent publication Salooja, Sharma and Siddiqui³ pointed out the existence of certain difficulties in the full acceptance of the new formula and contended that besides the quinone chalkone structure their original benzal-coumaranone formula was also necessary and that the substance should be considered to exhibit tautomerism. In the course of work in these laboratories on the formation of quinones by oxidative demethylation and on nuclear oxidation in flavones and related compounds fresh light was thrown on this question. Bose and Dutt's formula was definitely supported by the studies on oxidative demethylation⁴ and most of the difficulties pointed out by Sharma and Siddiqui were eliminated by the establishment of the correct constitution of pedicin⁵ and the isolation of the various stages in its transformation to pedicinin. Thus there seemed to be definite support for the quinone-chalkone formula and none for the benzal-coumaranone structure. But there was one point raised by Salooja, Sharma and Siddiqui³ requiring further attention. It related to the existence of two melting points for pedicinin: (1) the sample obtained by the precipitation of pedicinin from its solution in aqueous alkali (potash) was found to melt at 207–208°, (2) but after crystallisation from an organic solvent (chloroform) the sample melted lower at 203–204°. These were considered to represent two tautomeric structures (I) and (II).

As a result of other work in progress in these laboratories it has now become possible to prepare synthetically 4:5:7-trihydroxy-6-methoxy-benzal-coumaranone (I) and compare it with pedicinin. The first stage *i.e.*

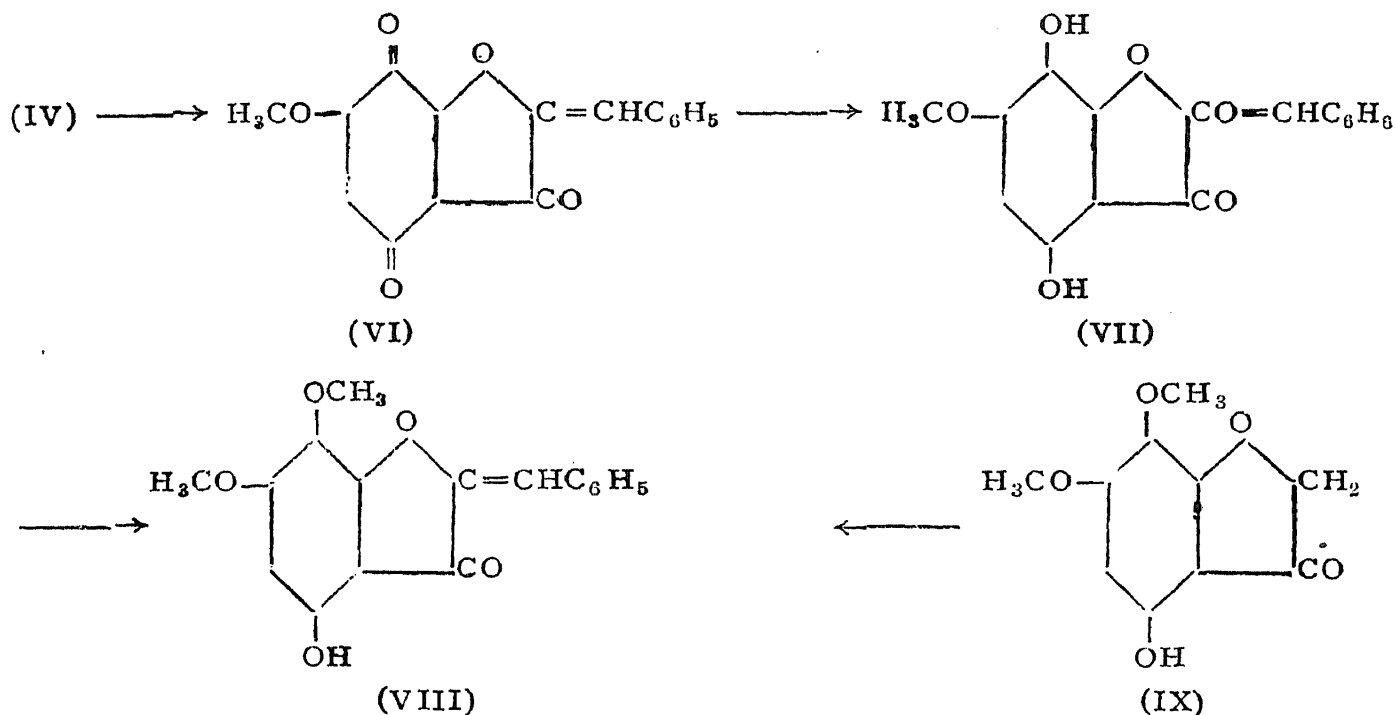


the synthesis is the preparation of 4:6:7-trimethoxy-benzal-coumaranone (IV). The compound was easily obtained from 2-hydroxy-3:4:6-trimethoxy-chalkone⁵ (III) by means of alkaline hydrogen peroxide. The nature of the reaction involved has been studied recently by Geissman, *et. al.*⁷; in the present case it gives a very good yield of the required benzal-coumaranone. The constitution of the product is confirmed by its preparation from 4:6:7-trimethoxy coumaranone (V) and benzaldehyde.

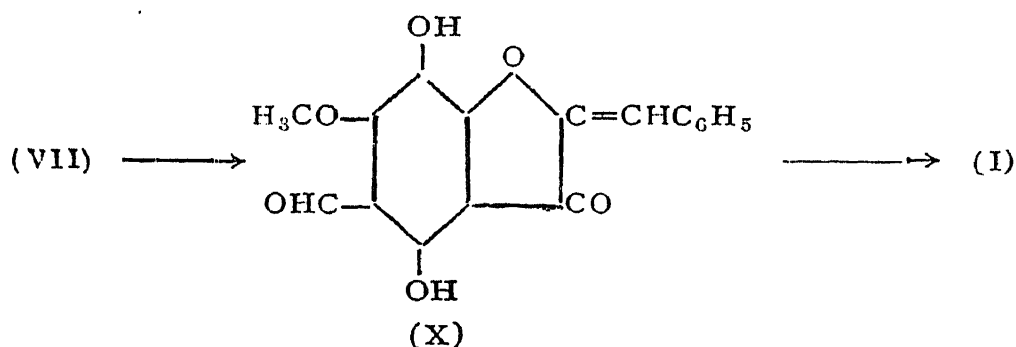


By treatment with cold nitric acid the above trimethoxy-benzal-coumaranone yields 6-methoxy-4:7-quinol-benzal-coumaranone (VI) involving oxidative demethylation of the para-positions alone. In this respect the reaction resembles that of 5:7:8-methoxy-flavones⁸. Reduction with sulphur dioxide yields the corresponding quinol, 4:7-dihydroxy-6-methoxy-benzal coumaranone (VII). In support of the constitution of this compound it was partially methylated using the requisite quantity of dimethyl sulphate and anhydrous potassium carbonate in dry acetone medium and the resulting 4-hydroxy-6:7-dimethoxy-benzal-coumaranone (VIII) was found to be

identical with the condensation product of benzaldehyde and 4-hydroxy-6:7-dimethoxy-coumaranone⁶ (IX) obtained from gossypetol-tetramethyl-ether.



The next stage is ortho-oxidation of (VII) introducing a hydroxyl in the 5-position. This does not take place to any extent by means of alkaline persulphate but proceeds satisfactorily by the two stage process that has been recently studied in these laboratories. A further interesting point is that this quinol itself can directly be employed (see for the exploratory work Murti and Seshadri⁹). With hexamine in glacial acetic acid it gives a good yield of the 5-aldehyde (X) and subsequent oxidation with alkaline hydrogen peroxide produces the required 4:5:7-trihydroxy-6-methoxy-benzal-coumaranone (I). When the final product (I) is subjected to partial methylation using two moles of dimethyl sulphate a dimethyl ether (XII) is obtained which gives reactions for a free hydroxyl in the 4-position.

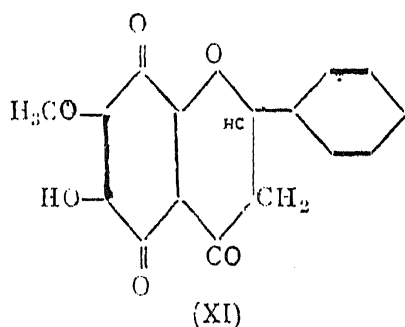


The properties of the pure product (I) are very different from those of either of the two samples obtained by Salooja, Sharma and Siddiqui. The most important differences are the low melting point, the lack of deep colour

and insolubility in sodium bicarbonate. Like all other benzal-coumaranones the new substance forms a deep blood-red colour with concentrated sulphuric acid. The differences are brought out in the following Table:—

	Pedicinin	4: 5: 7-Trihydroxy-6-methoxy-benzal-coumaranone
1. Solubility in alcohol ..	Fairly soluble	Sparingly soluble
2. Melting point ..	203-204° and 207-208°	182-83°
3. Crystal Structure ..	(i) Carmine-red stout rods and needles or (ii) Orange-red micro-crystalline powder	Bright yellow small prisms
4. Alcoholic ferric chloride ..	Deep reddish brown	Pale brown slowly changing to deep brown
5. Sodium carbonate or Ammonia ..	Orange-red to deep red solution	Yellow solution, sparingly soluble
6. Sodium bicarbonate ..	Orange solution	Insoluble

The explanation for the observation of Salooja, Sharma and Siddiqui regarding the two melting points for pedicinin should therefore be sought elsewhere. A plausible alternative would be the quino-flavanone isomer (XI) because of the known easy interconversion of chalcones and flavanones. A substance of this constitution (XI) was recently prepared by Rao, Rao and Seshadri¹⁰ by the gentle oxidation of dihydro-pedicinin with *p*: benzoquinone and the name allo-pedicinin given to it. But its properties are also very different from either of the two forms of pedicinin described by Salooja, *et. al.* Its melting point was also too low (183-84°).



We had occasion to repeat the experiments of Salooja, Sharma and Siddiqui regarding the melting points of pedicinin and we confirm their findings; but we also noticed that a mixture of the two samples melted in between and there was no depression thus showing that they were not really two different substances. It appeared to be possible that the formation of a small amount of allo-pedicinin by cyclisation during the heating involved in the crystallisation may account for the small lowering of the melting point of the crystallised sample. But no further lowering of the melting point could be brought about by longer heating of the chloroform solution. It

is rather remarkable that even when we heated an acidified alcoholic solution of pedicinin for two hours no change could be observed. Much longer heating of this solution (30 hours) produced some resinification, but pedicinin was recovered substantially unchanged. Hence this explanation involving flavanone conversion for the dual melting point is not satisfactory. A simple possibility is that pedicinin may be capable of existing in two crystal forms having two different melting points. The use of the term isopedicinin³ in this connection does not seem to be therefore justified.

EXPERIMENTAL

2-Hydroxy-3:4:6-trimethoxy-chalkone⁵ (III) was prepared from 2-hydroxy-3:4:6-trimethoxy-acetophenone and benzaldehyde.

4:6:7-Trimethoxy-benzal-coumaran-3-one (IV)

(1) The above chalkone (III) (2.0 g.) was dissolved in alcohol (100 c.c.) and sodium hydroxide (5%; 15 c.c.) added. To this solution hydrogen peroxide (6%; 10 c.c.) was added drop by drop with shaking. The mixture was allowed to stand for two hours and diluted with water and the solid that separated out was filtered and crystallised from alcohol. It was obtained as straw-yellow rectangular plates melting at 180–81°. Yield, 1.6 g. (Found: C, 68.8; H, 5.2; C₁₈H₁₆O₅ requires C, 69.2; H, 5.1%.)

With alcoholic ferric chloride it did not give any colour and was insoluble in aqueous alkali. It gave a blood-red colour with concentrated sulphuric acid.

(2) To an ice-cooled dry ether solution of 1:2:3:5-tetramethoxybenzene (10 c.c.) anhydrous aluminium chloride (20 g.) and chloracetyl chloride (7 c.c.) were added carefully (see Balakrishna, Rao and Seshadri⁶). The mixture was set aside overnight and then decomposed by carefully adding water (100 c.c.) and concentrated hydrochloric acid (50 c.c.) and heating the mixture on a boiling water-bath for half-an-hour. The semi-solid product was extracted with ether, the ether extract concentrated and the residue obtained was boiled with sodium acetate solution (10%). The trimethoxy-coumaranone (V) was extracted with ether and the ether extract distilled; a colourless liquid was obtained which did not solidify at room temperature. It (2 c.c.) was heated with benzaldehyde (3 c.c.) and concentrated sulphuric acid (a few drops) at 60°. The reaction mixture was diluted with water and allowed to stand overnight. The product that separated out was filtered and crystallised from alcohol. It was obtained as yellow rectangular plates melting at 180–81° and was identical with the product obtained by method (1); the mixed melting point was not depressed

6-Methoxy-4:7-quinone-benzal-coumaranone (VI)

The above trimethoxy compound (IV) (1.6 g.) was treated with nitric acid (15 c.c.; d., 1.2) in the cold (20–25°) for 15 minutes and the mixture diluted with water. The solid product that separated out was filtered. It crystallised from alcohol as yellow plates melting at 164–65°. Yield, 1.2 g. (Found: C, 68.2; H, 3.9; $C_{16}H_{10}O_5$ requires C, 68.1; H, 3.6%.) With alcoholic ferric chloride it did not give any colour but with concentrated sulphuric acid a bright red colour was produced.

6-Methoxy-4:7-dihydroxy-benzal-coumaranone (VII)

Sulphur dioxide was passed through an alcoholic solution of the above quinone (VI) (1.0 g.) for about 15 minutes. On concentrating the solution, the quinol separated out. It crystallised from alcohol as yellow elongated rectangular plates melting at 185–86°. Yield, 0.8 g. (Found: C, 67.3; H, 3.9; $C_{16}H_{12}O_5$ requires C, 67.6; H, 4.2%.) It was soluble in aqueous alkali. With alcoholic ferric chloride it gave a brown colour and with concentrated sulphuric acid a blood-red colour.

6:7-Dimethoxy-4-hydroxy-benzal-coumaranone (VIII)

(a) The above dihydroxy compound (VII) (0.2 g.) was boiled with dimethyl sulphate (0.1 c.c.) and anhydrous potassium carbonate (5.0 g.) in dry acetone medium (25 c.c.) for six hours. The resulting 4-hydroxy-compound (VIII) crystallised from alcohol as yellow prismatic rods melting at 177–78°. (Found: C, 68.2; H, 5.0; $C_{17}H_{14}O_5$ requires C, 68.5; H, 4.7%.)

(b) 4-Hydroxy-6:7-dimethoxy-coumaranone⁶ (IX) (0.5 g.), obtained from gossypetol-tetra-methyl-ether, was heated at 60° with benzaldehyde (0.8 c.c.) and a few drops of concentrated sulphuric acid for 2 hours. The mixture was diluted with water. After allowing it to stand overnight the product that separated out was filtered and crystallised from alcohol. It was identical with the sample obtained by the method given under (a); the mixed melting point was undepressed.

6-Methoxy-4:7-dihydroxy-5-aldehydo-benzal-coumaranone (X)

The above quinol (VII) (1.5 g.) was dissolved in glacial acetic acid (10 c.c.) and hexamine (5.0 g.) added. The solution was kept gently boiling for 6 hours. Concentrated hydrochloric acid (20 c.c.) was added and the mixture heated to boiling and allowed to cool. The yellow solid that separated out was filtered. It crystallised from alcohol as lemon-yellow rectangular plates melting at 191–92°. Yield 1.0 g. (Found: C, 65.2; H, 4.0; $C_{17}H_{12}O_6$ requires C, 65.4; H, 3.8%.)

With alcoholic ferric chloride it gave a brown colour and was soluble in aqueous alkali. With concentrated sulphuric acid a deep red colour was produced. It condensed with phenylhydrazine in alcohol containing a few drops of glacial acetic acid to form a yellow phenyl-hydrazone which crystallised from alcohol as rectangular plates melting at 145–46°. (Found: C, 69.1; H, 4.2; $C_{23}H_{18}O_5N_2$ requires C, 68.7; H, 4.5%.)

4:5:7-Trihydroxy-6-methoxy-benzal-coumaranone (I)

The above aldehyde (X) (0.6 g.) was dissolved in alcohol (50 c.c.) and the solution was treated alternately with sodium hydroxide (5%; 15 c.c.) and hydrogen peroxide (6%; 10 c.c.) added in small quantities. After allowing it to stand for an hour the solution was diluted with water and the solid product that separated out filtered. It crystallised from alcohol as yellow short needles melting at 182–83°. Yield, 0.3 g. (Found: C, 63.8; H, 4.1; OCH_3 , 10.0, $C_{16}H_{12}O_6$ requires C, 64.0; H, 4.0, OCH_3 , 10.3%.) With alcoholic ferric chloride it gave a brown colour and was soluble in aqueous potash. It was very sparingly insoluble in aqueous sodium carbonate and insoluble in sodium bicarbonate solution. A blood-red colour was produced with concentrated sulphuric acid.

4-Hydroxy-5:6:7-trimethoxy-benzal-coumaranone (XII)

The above trihydroxy compound (I) (0.3 g.) was dissolved in dry acetone (25 c.c.) and treated with dimethyl sulphate (0.2 c.c.) and anhydrous potassium carbonate (5.0 g.). The mixture was refluxed for 6 hours and the potassium salts were filtered off. The filtrate was concentrated and the residue crystallised from alcohol. It was obtained as yellow rectangular plates melting at 152–53°. (Found: C, 66.0; H, 5.1; $C_{18}H_{16}O_6$ requires C, 65.9; H, 4.9%). With alcoholic ferric chloride it gave a brown colour and was sparingly soluble in aqueous sodium hydroxide.

SUMMARY

The structure of 6-methoxy-4:5:7-trihydroxy-benzal-coumaranone was suggested by Salooja *et. al.*³ for one of the forms of pedicinin. A substance of this constitution has now been synthesised by applying the two stage process of nuclear oxidation to an appropriate compound of the benzal-coumaranone series. The synthetic product differs markedly from pedicinin. Similar difference has been noticed earlier with the flavanone isomer, allo-pedicinin. It is concluded therefore that the two melting points noted for pedicinin are due to the existence of two crystal forms.

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