NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XII. Constitution and Synthesis of Pedicin and Its Allies

BY K. VISWESWARA RAO AND T. R. SESHADRI

(From the Department of Chemistry, Andhra University, Waltair)

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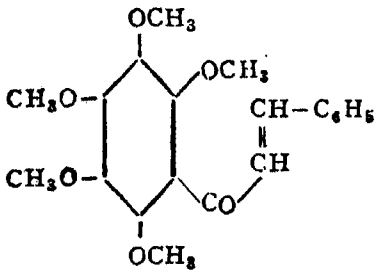
PEDICELLIN[1] (I) is an important member of the chalkone group having a fully oxidised and methylated benzene ring and in this respect it is analogous to nobiletin (flavone, II) and calycopterin (flavonol, III). In connection with our study of the toxic properties of chalkones towards fish,[2] we had occasion to prepare it from the leaves of *Didymocarpus pedicellata*. In the course of his careful work Siddiqui[1] obtained from this source besides pedicellin the related compounds pedicin, isopedicin and pedicinin. Using a modification of the extraction procedure we have now been able to isolate some quantity of methyl pedicinin also and this is of significance as it indicates a stage in the formation of pedicinin.



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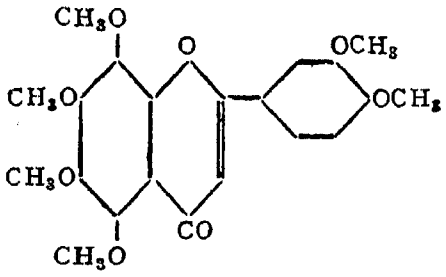

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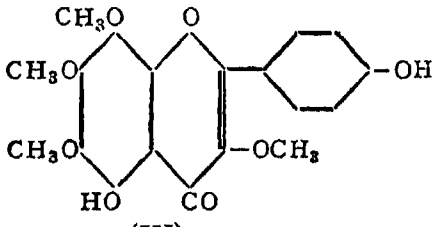
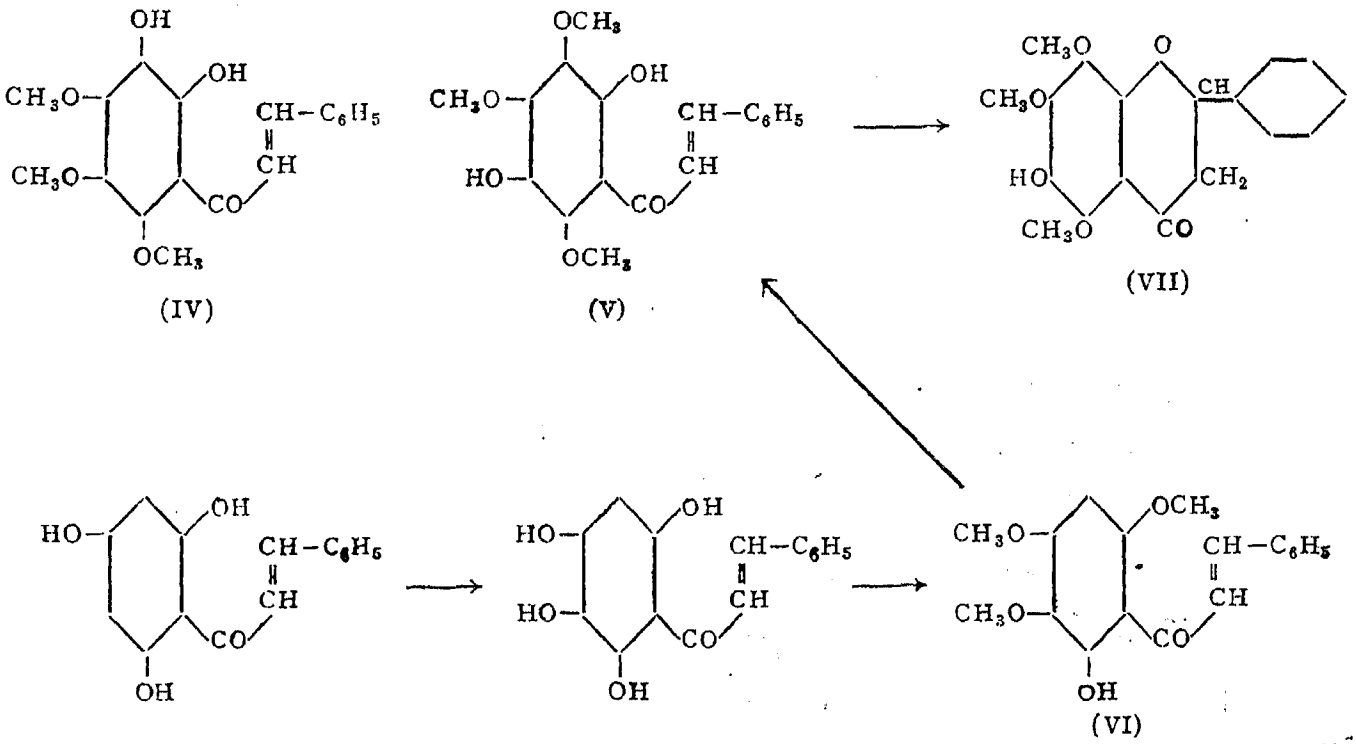


(III)

Among the components of *D. pedicellata*, the chemical constitution of pedicellin has been definitely established by degradation studies[3] and also by synthesis.[4] Though pedicin and pedicinin are closely related to it and the conversion of pedicin into pedicellin on the one hand and into pedicinin on the other and the preparation of pedicinin from pedicellin have been carried out, the exact constitutions of these two do not appear to have been conclusively established.

Pedicin was given the constitution of an ortho-dihydroxy chalkone as in (IV) by Sharma and Siddiqui.[3] As evidence they recorded that it was capable of undergoing methylation to yield pedicellin and ring closure to form an isomeric compound and that it gave colour with ferric chloride and formed a coloured insoluble lead salt. The conclusion that it was an ortho-dihydroxy compound did not appear to us to be well supported. A para

dihydroxy structure as in formula (V) seemed to be more probable and this was in accordance with the considerations of biogenesis based on the general theory of Robinson[5] in which the stages in the oxidation of the phloroglucinol part may be expected to be as given below:



Siddiqui[1] recorded that pedicin gave with ferric chloride an evanescent greenish blue colouration quickly changing to pale yellow which then slowly developed into deep red and later reddish brown. We have repeated this test and confirm it except for the small difference that the initial evanescent colour is an opaque brown and not greenish blue. On the whole the behaviour of the substance with ferric chloride is characteristic of a quinol ketone and not of a catechol derivative which could be expected to give a stable green. On treatment with lead acetate the solution remains clear for about two hours and only afterwards a brown precipitate is slowly formed. This agrees with the reaction of quinol ketones; catechol derivatives on the other hand give precipitates immediately.

The new structure of pedicin is confirmed by its synthesis using the nuclear oxidation of 2-hydroxy-3 : 4 : 6-trimethoxy chalkone (VI) by means of alkaline persulphate. The reaction takes place readily and a good yield of pedicin (V) is obtained. That such oxidation of hydroxy chalkones is feasible has been shown recently by Rajagopalan and Seshadri[6] using simpler examples. The synthetic pedicin undergoes methylation to pedicellin and reacts with bromine to yield pedicinin. The methylation of pedicinin has been studied

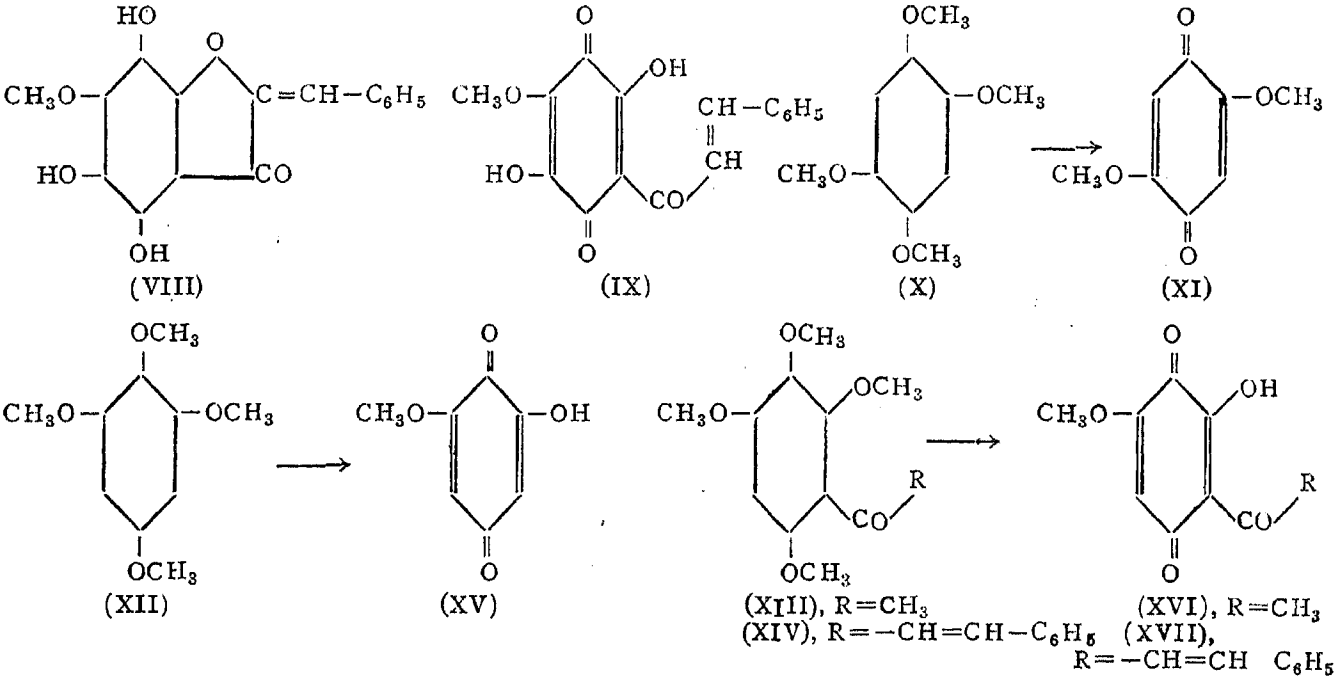
using several methods (Rao, Rao and Seshadri[11]). Methyl iodide or dimethyl sulphate and potassium carbonate did not work satisfactorily; on the other hand, diazomethane effects partial methylation readily yielding methyl pedicinin. Thus these experiments constitute a new total synthesis of all the four compounds.

Just as the quinol derivatives of flavones, pedicin also undergoes ready oxidation when treated with *p*-benzoquinone, forming the corresponding quinone (XIX). This has three methoxyl groups in it and is the direct oxidation product. This quinone is also more conveniently prepared by employing moist silver oxide as oxidising agent. It can be subjected to stepwise hydrolysis giving successively methyl pedicinin (XX) and pedicinin (XXI). These interesting reactions again constitute an alternative synthesis of methyl pedicinin and pedicinin and definitely establish the stages through which the pedicin—pedicinin change proceeds with the help of bromine. A detailed discussion of this change will be made later.

In the course of the above synthesis of pedicin the isomeric flavanone (VII) could also be readily obtained. It melted at 105–7° and had all the properties described by Siddiqui[1] for isopedicin. The transformation of pedicin into this substance can be effected under the usual conditions of chalkone-flavanone conversion. We have not been able to obtain pseudo isopedicin melting at 125° as described by Warsi and Siddiqui.[7] Viewing all these results together and particularly the spontaneous conversion of isopedicin into pseudo-isopedicin as reported by the above authors[7] it would appear that these two are forms of the same substance, isopedicin which should now be given the 6-hydroxy-flavanone structure (VII). Thus in *D. pedicellata* we meet with the occurrence of the related pair, chalkone (pedicin, V) and flavanone (isopedicin, VII) together. Such a combination is not unknown; as a relevant example may be mentioned the presence of butein and butin in the flowers of *Butea frondosa.*[8]

A knowledge of the correct structure for pedicin is of importance in arriving at the constitutions of methyl pedicinin and pedicinin which accompany it in the leaves. Pedicinin was first given the benzylidine coumaranone formula (VIII) by Sharma and Siddiqui.[3] Subsequently Bose and Dutt[9] showed that it had the characteristic properties of a quinone and hence should be given the quinone-chalkone constitution (IX), thus supporting the earlier suggestion of Price and Robinson[10] that the pedicin group might have some resemblance to dunnione since the plant sources, Streptocarpus and Didymocarpus are closely related botanically. They[9] explained the conversion of pedicellin (I) into pedicinin as due to combined oxidation and

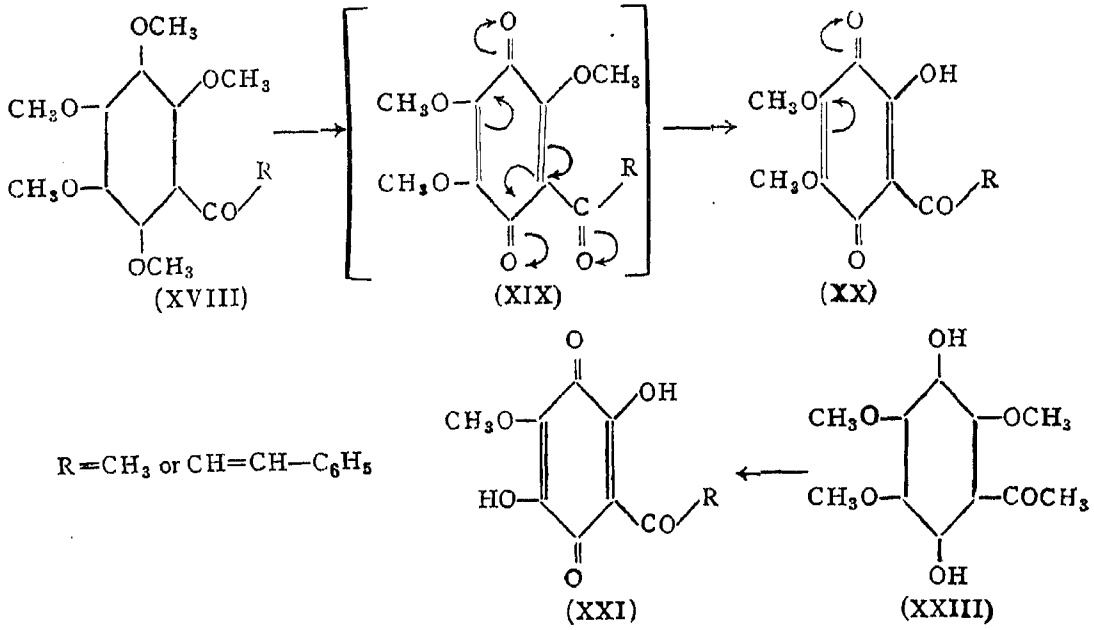
demethylation with nitric acid and showed that the unsaturation in the side chain plays no part in this change. In support of this they quoted the only analogy available at that time of the conversion of 1:2:4:5-tetramethoxy benzene (X) into the dimethoxy-quinone (XI). It might be said that this analogy was not adequate. Actually, as they themselves showed, the treatment of pedicellin with nitric acid alone is enough not only to form the quinone structure, but further to demethylate two more methoxyl groups. On the other hand the above mentioned tetramethoxy benzene gives only the quinone dimethyl ether (XI) with nitric acid and further treatment with alkali is necessary for the formation of the corresponding hydroxy-quinone. Even in the ketone derivative of this dimethoxy-quinone obtained in the degradation of gardenin, the methoxyl groups are not removed by the action of nitric acid[16] and alkali is required for this purpose (unpublished observation).



However, the correctness of their interpretation is amply supported by the recent publication of Rao, Rao and Seshadri[11] on oxidative demethylation with nitric acid employing a variety of compounds, some of which are closely analogous to pedicellin. It has been shown by them that a number of these and particularly 1:2:4:5-tetramethoxy benzene and its derivatives yield only methoxy quinones. On the other hand, 1:2:3:5-tetramethoxy benzene (XII) and its derivatives, ketones (XIII) or chalkones (XIV), invariably yield directly hydroxy quinones due to the combined effect of oxidative demethylation to form the quinone structure along with further demethylation of suitably located methoxyl groups. It should be noted

that only one of the methoxyl groups of the 2:6-dimethoxy quinone undergoes hydrolysis. The other methoxyl is stable and cannot be hydrolysed even with alkali. This stability to alkali has now been definitely proved using as examples the ketone (XVI) and chalkone (XVII). They are recovered unchanged from their solutions in aqueous alkali. The hydroxy-methoxy quinone (XV) itself is unsuitable for this test since it undergoes rapid polymerisation in alkali. The above partial demethylation could be understood from the fact that a quinone carbonyl is capable of activating only one methoxyl group present in the β-position of the katioenoid system. In the case of the ketones (XVI) and chalkones (XVII) the particular methoxyl group involved in this second stage demethylation is also ortho to the ketonic carbonyl. The orientation of the hydroxyl and methoxyl groups given in formulæ (XVI and XVII) has already been proved in the earlier paper[11] not only from the reactions of the compounds but also by their preparation in different ways leaving no doubt about their structure.

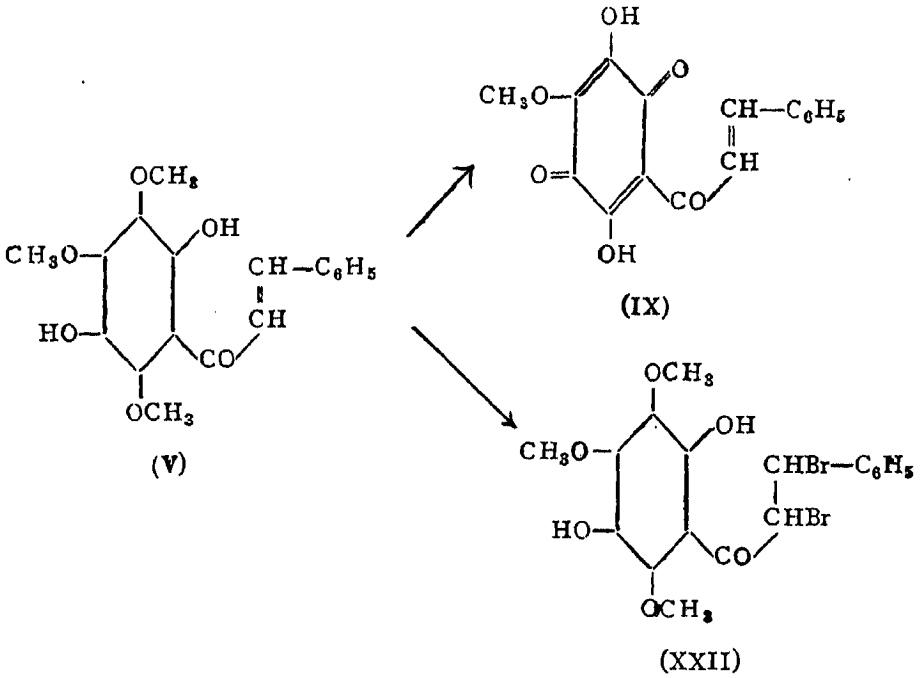
It is significant that the side chain unsaturation is unnecessary for the changes discussed above, since the simpler tetramethoxy benzene and ketones undergo the reaction readily. Additional evidence is given in the present paper by the oxidative demethylation of 2:3:4:5:6-penta-methoxy-acetophenone (XVIII, R = CH_3) which behaves quite analogous to pedicellin (I) and forms a dihydroxy-quinone (XXI, R = CH_3) similar to pedicinin (IX). The reaction in both cases could be represented as taking place in stages as given below:



The first stage (XIX) has not been isolated in this reaction but has been obtained from pedicin. The second stage is represented by methyl

pedicinin (XX, R = $-CH=CH-C_6H_5$). In this change the methoxyl in the 2-position is more easily hydrolysed since, as already explained, it is subjected to the influence of two katioenoid systems whereas that in the 5-position is affected by only one. The methoxyl in position 4- is left out for reasons already given.

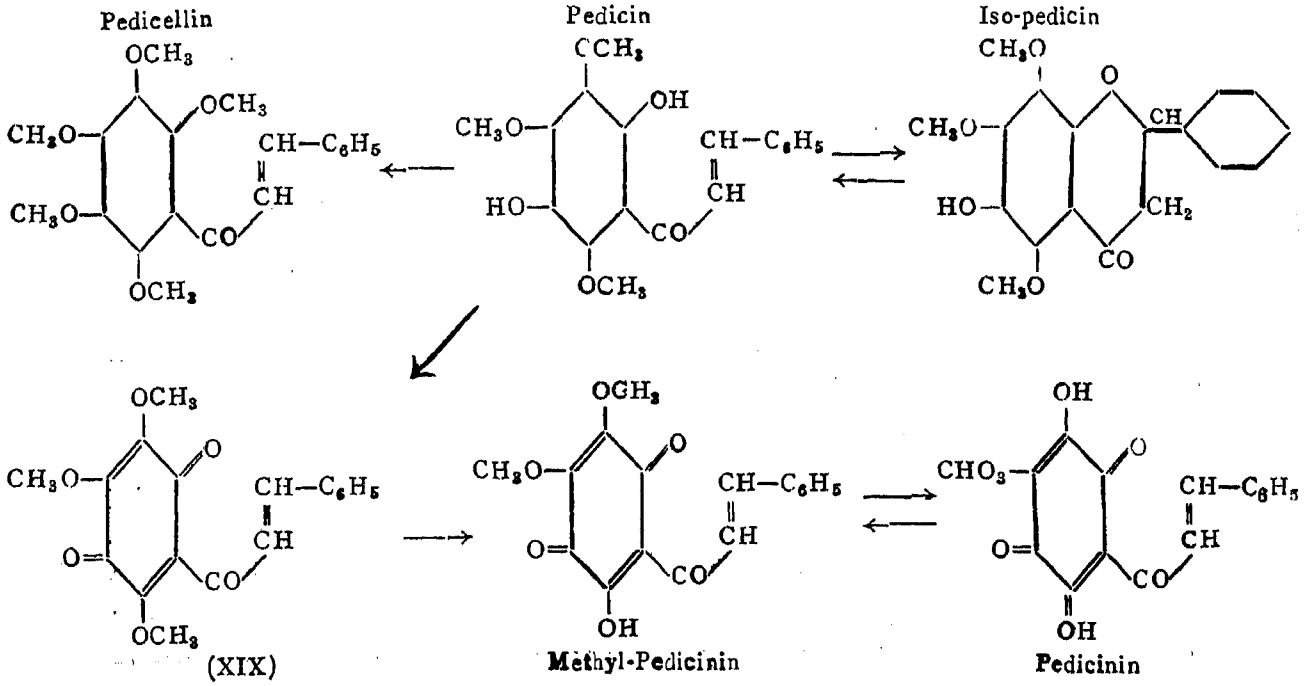
As pointed out by Salooja, Sharma and Siddiqui, Bose and Dutt did not explain the pedicin-pedicinin change by means of bromine and we may add, the permanganate oxidation to pedicinin. There was definite difficulty at that time because the constitution adopted for pedicin was wrong. No such difficulty exists with the new correct constitution (V) now presented. The reaction is a simple dehydrogenation of a quinol to quinone with the hydrolysis of the susceptible methoxyl groups by the hydrogen bromide formed. That this is so is definitely proved by the dehydrogenation of pedicin using benzoquinone or silver oxide to the quinone (XIX) which subsequently undergoes stepwise demethylation and in these changes the extranuclear double bond is evidently unaffected. The quantitative studies of Salooja, *et al.*, using one molecular proportion of bromine would indicate that there are two simultaneous reactions, one involving the quinol grouping and leading to the formation of pedicinin (IX) and the other involving the side chain double bond and leading to the formation of dibromo-pedicin (XXII).



That side chain unsaturation does not play any part in the oxidation is further supported by our experiment on 2: 5-dihydroxy-3: 4: 6-trimethoxy-acetophenone (XXIII) using bromine whereby the hydroxy-quinone-ketone (XXI, R = CH_3) is readily obtained.

That the conversion of a quinol into quinone involves a dehydrogenation is well established. A number of dehydrogenating agents could be used. The successful use of bromine for this purpose would depend on the possibility of other simultaneous reactions that can be promoted by bromine. One of the earliest dehydrogenations of this type was mentioned by Perkin[17] in connection with the study of excœcarin. This compound which was isolated from green ebony (*Excœcaria jacarandi*) when treated with bromine was converted into the corresponding quinone excœcarone which could be reduced to the original compound by sulphurous acid. As a further example, the action of bromine on 2: 6-dimethoxy quinol has been studied now. This yields 2: 6-dimethoxy-3: 5-dibromo-quinone by dehydrogenation and bromination. With pedicin, bromine effects demethylation besides dehydrogenation. In this reaction the successful production of pedicinin would appear to depend upon the rather poor ethylenic reactivity of chalkones; as a side reaction the addition of bromine to pedicin will not be helpful for the formation of pedicinin.

The new total synthesis of pedicin and its derivatives recorded in this paper has a strong biogenetic significance. The occurrence of methyl pedicinin in the leaves of *D. pedicellata* along with the other four has been established. Pedicin would appear to be the primary compound of this group and it occurs as a major component. The stages of its evolution from the simplest phloroglucinol derivative have already been indicated. The first stage, *i.e.*, the formation of the tetrahydroxy chalkone is supported by the persulphate oxidation of 2-hydroxy-4: 6-dimethoxy chalkone reported



in an earlier publication.[6] The plant should be using some protective mechanism other than methylation. The second stage (VI to V) leading to the synthesis of pedicin has been described in this paper. The later transformations can be represented as given above:

In the experiments described in this paper each of these stages has been obtained. The simple oxidation of pedicin has to be carried out with *p*-benzoquinone or better with silver oxide and the subsequent hydrolysis can be effected in stages. Bromine as a reagent is unsuited for these graded transformations. From the plant source, though methyl pedicinin could be isolated by careful extraction, the simple quinone (XIX) has not so far been isolated.

It is appropriate here to emphasise the close relationship between methyl pedicinin and pedicinin. They are mutually inter-convertible. Sharma and Siddiqui effected the conversion of methyl pedicinin into pedicinin by the action of dilute alkali. From the experiments of Bose and Dutt it is clear that this change could be brought about by nitric acid itself. As a result of experiments on methylation it has now been shown that the reverse change of pedicinin to methyl pedicinin can be effected very satisfactorily by means of diazomethane. Since it is known that in plants methylation and demethylation mechanisms exist, it may be more correct to say that methyl pedicinin can not only be formed as a stage in the conversion of pedicin to pedicinin, but also that it is capable of being produced independently by the methylation of pedicinin. In this connection another point should also be mentioned. Though pedicinin contains two hydroxyl groups as pointed above, only one of these undergoes methylation with diazomethane; the other is resistant just as in the case of ortho-hydroxy carbonyl compounds. This is in agreement with the suggestion made earlier,[11] that though the compound is quinonoid the conditions necessary for chelation exist and ortho-hydroxy-quino ketones are chelated compounds.

Contradictory reports have been made by previous workers regarding certain reactions of pedicinin and methyl pedicinin and have been used to support different points of view. As a typical example may be mentioned the colour reaction with ferric chloride. Siddiqui, *et al.*, reported that they give a red colour whereas Bose and Dutt failed to observe this colour. In agreement with the former authors we find that they give definite deep red colour but this positive colour reaction is not at all against the hydroxy quinone chalkone constitution given by the other authors for these compounds. Actually this is a characteristic reaction of all the hydroxy-quinone-ketones and chalkones that we have examined. Indeed, all positive

experimental results so far recorded, for example their marked acidic property, could be satisfactorily explained only on the basis of these structures and other alternative formulations seem to be unnecessary and to lack support from chemical possibilities and analogies. For properly understanding some of the other observations it may be useful to emphasise here that quinones do differ in their reducibility and that the side chain double bond of chalkones has somewhat diminished ethylenic reactivity owing to conjugation with the neighbouring carbonyl forming part of the well-known katioenoid system.[13]

Experimental

Extraction of the leaves: (Isolation of methyl pedicinin and other compounds)

Air-dried leaves of *Didymocarpus pedicellata* were extracted with ether and the ether extract concentrated to small bulk. On allowing it to stand for a few days an orange red crystalline solid separated out which was filtered and washed with a little ether. When crystallised from ethyl acetate it appeared as orange red elongated rectangular prisms melting at 143–45° thus agreeing with the melting point reported for pedicin. The identity was confirmed by the preparation of the colourless dibenzoate melting at 181–83°.

The original ethereal filtrate was diluted with a large excess of ether (to prevent the formation of emulsions) and shaken with 5% aqueous sodium bicarbonate twice. The ether layer was separated out and marked (A). The dark reddish brown bicarbonate extract was acidified with concentrated hydrochloric acid and extracted with ether. On concentrating this ether solution an orange red solid crystallised out. It was filtered and washed with a mixture of ether and light petroleum. When crystallised from a mixture of benzene and ligroin the first crop consisted of dark red flat needles melting at 203–5° and this was identified as pedicinin. The mother-liquor on concentration yielded an orange yellow solid which when recrystallised from the same solvent came out as orange yellow short prismatic needles melting at 110–12° and agreed in all its properties with methyl pedicinin. (Found: C, 64·6; H, 4·2; $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5%.) For the above identifications authentic samples obtained from pedicellin by the method of Sharma and Siddiqui were used for direct comparison. The yield of methyl pedicinin was 0·5%.

Methyl pedicinin (0·5 g.) thus obtained was dissolved in 5% aqueous sodium hydroxide and the solution treated with solid sodium hydroxide whereby a red solid crystallised out. This sodium salt was rapidly filtered,

dissolved in water (10 c.c.) and the solution acidified. The orange coloured precipitate was filtered, washed with water and crystallised from chloroform. It formed deep red needles melting at 203–5° identical with pedicinin.

The ether solution (A) left after extraction with bicarbonate was then shaken with 5% aqueous sodium hydroxide twice and then with dilute acid. Acidification of the alkaline extract with hydrochloric acid and extraction with ether gave some more of pedicin. The residual pale greenish ether solution was concentrated to small bulk and treated with light petroleum whereby pedicellin crystallised out.

Pedicin

The sample of pedicin was purified by crystallisation from ethyl acetate when it came out as dark red big prisms. From benzene it separated as orange red elongated rectangular plates melting at 143–45°. In aqueous sodium hydroxide it readily dissolved to a reddish violet solution. In alcoholic solution it gave an opaque brown colour with a drop of ferric chloride solution. This very rapidly faded away to pale yellowish brown. Further small additions of the reagent led to a repetition of the colour changes till eventually the solution assumed a permanent reddish brown. It did not give any immediate precipitate with alcoholic lead acetate but on keeping for two hours a brown precipitate slowly formed.

Pedicin is considerably toxic to fish which show definite toxic symptoms (turning upside down) in 2·5 minutes for a concentration of 150 mg. per litre, and in 3·5 minutes for a concentration of 100 mg. per litre. But its easy oxidisability makes it feebly toxic at lower concentrations (*e.g.*, 50 mg. per litre) since, before the toxic effect could be exerted the compound seems to undergo change. As a possible oxidation product pedicinin has also been tested and is found to have no appreciable toxicity in a concentration of 150 mg. per litre.

Conversion of pedicin into isopedicin

A solution of pedicin (0·5 g.) in alcohol (20 c.c.) and water (10 c.c.) was treated with concentrated hydrochloric acid (2 c.c.). The mixture was refluxed on a water-bath for 24 hours. The alcohol was removed under reduced pressure, the residue treated with water (50 c.c.) and extracted with ether. The ether extract was dried over anhydrous sodium sulphate and distilled. The orange red liquid residue left behind, on the addition of a little ether yielded an almost colourless crystalline solid. It was treated with a mixture of ether and light petroleum (1 : 1) and the solid filtered. When recrystallised from a mixture of benzene and light petrol the product

appeared as almost colourless prismatic needles melting at 105–7°. Further crystallisation did not improve the melting point. It was easily soluble in alcohol and the alcoholic solution did not give any appreciable colour immediately with ferric chloride but a pale brown colour appeared slowly. Yield 0·4 g. In aqueous sodium hydroxide it readily dissolved to a bright yellow solution which quickly changed to reddish violet and on acidification this yielded pedicin.

2-Hydroxy-3 : 4 : 6-trimethoxy-chalkone (VI)

A solution of 2-hydroxy-3 : 4 : 6-trimethoxy acetophenone[4, 14] (3 g.) in alcohol (25 c.c.) was treated with benzaldehyde (10 c.c.) and aqueous potash (25 g. in 20 c.c. of water). Sufficient alcohol was added to get a homogeneous solution which was kept tightly stoppered for 3 days. It was then poured into water (800 c.c.) and the solution extracted twice with ether. The clear orange red alkaline solution was acidified whereby a red liquid product separated which readily crystallised. It was filtered, washed with aqueous sodium bicarbonate followed by water and crystallised from alcohol. It came out as orange red needles melting at 140–42°. (Found: C, 69·0; H, 5·9; $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·7%.) Yield 4 g. It was sparingly soluble in aqueous sodium hydroxide and gave a reddish brown colour with ferric chloride in alcoholic solution.

2 : 5-Dihydroxy-3 : 4 : 6-trimethoxy chalkone (Pedicin) (V)

To a stirred solution of 2-hydroxy-3 : 4 : 6-trimethoxy chalkone (VI) (2·5 g.) in a mixture of pyridine (15 c.c.) and aqueous potash (3 g. in 30 c.c.) was added potassium persulphate solution (3 g. in 100 c.c.) gradually with cooling to 10–15° during the course of 2 hours. The dark brown solution was allowed to stand for 24 hours, acidified with concentrated hydrochloric acid and the unchanged chalkone removed by extracting twice with ether. Th clear brown aqueous solution was treated with sodium sulphite (2 g.), concentrated hydrochloric acid (30 c.c.) and benzene (100 c.c.) and refluxed for 30 minutes. The benzene layer was separated and the aqueous layer extracted once more with a little benzene. The total benzene extract was dried over sodium sulphate and distilled when a red liquid was left behind which quickly crystallised. It was purified by recrystallisation from benzene when it separated out in the form of bright orange red elongated rectangular plates melting at 143–45°. Mixed melting point with an authentic sample of natural pedicin was not depressed. (Found: C, 65·2; H, 5·2; $C_{18}H_{18}O_6$ requires C, 65·5; H, 5·5%.) Yield 0·5 g. Its solubility and colour reactions were identical with those given by the natural sample.

Benzoylation

The above dihydroxy chalkone (0·1 g.) was dissolved in pyridine (3 c.c.) and treated with benzoyl chloride (0·2 c.c.). The orange coloured solution was kept for one hour and poured into dilute hydrochloric acid. The white solid obtained after keeping for 3–4 hours was filtered, ground well with very dilute sodium hydroxide followed by water. Crystallisation from a mixture of benzene and ligroin yielded colourless narrow rectangular plates melting at 181–83°. A mixture of this and dibenzoyl pedicin prepared from the natural sample according to the method of Sharma and Siddiqui also melted at 181–83°.

Methylation

The above dihydroxy chalkone (0·1 g.) on being heated for 6 hours with dimethyl sulphate (0·2 g.) and potassium carbonate (1 g.) in anhydrous acetone solution yielded a colourless crystalline methyl ether melting at 97–98° identical with pedicellin.

Methylation of Pedicinin to Methyl Pedicinin

A clear solution of pedicinin (0·5) g. in absolute alcohol (50 c.c.) was treated with an ethereal solution of diazomethane prepared from nitroso-methyl urea (1·5 g.). The mixture was kept for 48 hours in the ice-chest with a stopper carrying a capillary tube serving as an outlet for the escaping gases. The solvents were then distilled off, and the residue extracted with ether. On concentrating the ether extract an orange coloured solid was slowly deposited. It was filtered, washed with a little ether and recrystallised from a mixture of benzene and ligroin. It appeared as orange coloured rectangular prisms melting at 110–12° alone or in admixture with the sample of methyl pedicinin prepared from pedicellin.

Dehydrogenation of Pedicin to 2:4:5-trimethoxy-3:6-quino-chalkone

First Method.—A solution of pedicin (0·2 g.) in ether (20 c.c.) was treated with *p*-benzoquinone (0·2 g.). The bright orange colour of the solution did not appreciably change. After keeping for 30 minutes, the solvent was distilled off and the greenish yellow solid left behind was extracted with boiling ligroin. The solution was filtered from the greenish black crystals of quinhydrone also formed in the reaction. The filtrate deposited on cooling bright golden yellow rectangular plates of the trimethoxy-quino-chalkone which was filtered and washed with a little ether. It melted at 113–14°. (Found: C, 65·7; H, 5·1; OCH_3, 27·9; $C_{18}H_{16}O_6$ requires C, 65·9; H, 4·9; for 3 OCH_3 28·4%.) It was sparingly soluble in ether and ligroin and in alcoholic solution it did not give any colour with ferric

chloride. It was not soluble in aqueous sodium bicarbonate but on keeping in contact with the solution it dissolved very slowly in the course of a few hours. In aqueous sodium hydroxide it dissolved within 2 minutes forming a deep red solution. Yield, 0·1 g.

It is necessary to note that the quinone corresponding to pedicin is only yellow as compared with the deep orange red pedicin. Consequently in the gossypetone test (treatment with *p*-benzoquinone) there is no intensification in colour in the case of pedicin though it readily undergoes oxidation.

Second Method.—Pedicin (0·35 g.), dissolved in ether (40 c.c.) was shaken vigorously with moist silver oxide (about 0·5 g., freshly prepared and thoroughly washed) for about 15 minutes. It was then stirred well with anhydrous sodium sulphate (5 g.) and filtered. On evaporating the filtrate the quinone separated out as bright golden yellow thin rectangular plates melting at 113–14°. The mixed melting point with the quinone prepared using *p*-benzoquinone was not depressed. Its properties were also identical. Yield, 0·32 g.

Reduction of the Trimethoxy-quino-chalkone to Pedicin

The trimethoxy-quino-chalkone (50 mg.) prepared by the above methods was dissolved in glacial acetic acid (3 c.c.) and treated with sodium sulphite (0·5 g.). The solution was heated for a minute and kept at the room temperature for 15 minutes. Water (50 c.c.) was added and the orange coloured crystalline solid filtered and washed with water. It melted at 143–45° and was identical with pedicin.

Hydrolysis of the trimethoxy-quino-chalkone

(*a*) *To Methyl Pedicinin.*—The trimethoxy-quino-chalkone (50 mg.) was dissolved in alcohol (5 c.c.) and the solution treated with 5% aqueous sodium bicarbonate (10 c.c.). After mixing thoroughly, water (50 c.c.) was added, the mixture filtered and the clear red filtrate acidified with dilute hydrochloric acid. After keeping for 30 minutes the orange coloured fine woolly needles that separated out were filtered and washed with water. They melted at 110–12° alone or in admixture with methyl pedicinin. This sample of methyl pedicinin could be hydrolysed to pedicinin by the already known methods used in the past.

(*b*) *To Pedicinin.*—When the trimethoxy-quino-chalkone (50 mg.) was treated with 5% aqueous sodium hydroxide (10 c.c.) it gradually dissolved in two minutes. The deep red solution, when acidified, yielded an orange coloured solid which crystallised from chloroform as deep red flat needles

melting at 202–03° and identical with pedicinin. This hydrolysis could be effected even by treating the alcoholic solution with concentrated hydrochloric acid (1 c.c.) and diluting it with water after a minute.

Iso-Pedicin VII

2-Hydroxy-3 : 4 : 6-trimethoxy-chalkone (VI) (1 g.) was oxidised with alkaline potassium persulphate as described earlier, but the product was worked up in a different manner in which the effect of acid was prolonged. After removing the unchanged chalkone by extracting with ether the aqueous solution was treated with sodium sulphite (2 g.) and concentrated hydrochloric acid (25 c.c.) and kept in a boiling water-bath for 30 minutes. After cooling, the solution was extracted with ether and the ether distilled off whereby an orange red liquid product was obtained which after keeping for one week at the ordinary temperature became a very pale brown crystalline solid. Recrystallisation of this from a mixture of ether and light petroleum yielded almost colourless rectangular plates melting at 105–7°. It agreed in all its properties with the sample of isopedicin prepared from pedicin as described earlier and the mixed melting point was not depressed. (Found: C, 65·1; H, 5·2; $C_{18}H_{18}O_6$ requires C, 65·5; H, 5·5%.)

Action of bromine on 2 : 6-dimethoxy-quinol

A solution of 2 : 6-dimethoxy-quinol (0·5 g.) in chloroform (30 c.c.) was treated with a solution of bromine in the same solvent till there was a slight excess. After keeping for 15 minutes the solvent was evaporated in a basin and the red crystalline solid was recrystallised from chloroform. It formed bright red plates melting at 175–76° and was identical with 2 : 6-dimethoxy-3 : 5-dibromobenzoquinone made from 2 : 6-dimethoxy quinone by the method of Robinson and Vasey.[15] When exactly one molecular proportion of bromine was added the product was not homogeneous and the mixture could not be separated.

Action of bromine on 2 : 5-dihydroxy-3 : 4 : 6-trimethoxy acetophenone[4] (XXIII)

To a solution of the ketone (1 g.) in chloroform (10 c.c.) was added a solution of bromine in chloroform (7 c.c. containing 0·7 g. of bromine) and the reaction mixture allowed to stand for 2 hours. There was copious evolution of hydrogen bromide throughout the course of the reaction. The chloroform was then removed under reduced pressure and the residue treated with water (10 c.c.). The mixture was extracted with ether twice and the ether extract dried over sodium sulphate and evaporated. The dihydroxy-quinone-ketone was obtained as a dark red oil which solidified on the addition of a few drops of ether. It was filtered, washed with ether

and recrystallised from benzene when it separated out as dark red needles melting at 165–67°. (Found: C, 51·0; H, 3·9; $C_9H_8O_6$ requires C, 50·9; H, 3·5%.) Yield, 0·25 g. It was readily soluble in aqueous sodium bicarbonate with effervescence giving a red solution. With aqueous sodium hydroxide it gave a dark red solution. In alcoholic solution it produced a red colour with ferric chloride. It was sparingly soluble in ether and benzene but more easily soluble in chloroform. It was identical with the sample obtained by the action of nitric acid on pentamethoxy-acetophenone.

2:3:4:5:6-*Pentamethoxy acetophenone*[4] (*XVIII*, $R = CH_3$).

The above is more conveniently prepared as follows: A solution of 2:5-dihydroxy-3:4:6-trimethoxy-acetophenone (1·5 g.) in anhydrous acetone (25 c.c.) was refluxed with dimethyl sulphate (2 c.c.) and potassium carbonate (5 g.) for 8 hours. The solvent was then removed under reduced pressure and the residue treated with water. Extraction with ether, drying the ether extract with calcium chloride and evaporation gave a pale yellow liquid which on keeping for some time yielded an almost colourless crystalline solid melting at 43°. Yield 1 g.

Oxidative demethylation of the pentamethoxy acetophenone

The above pentamethoxy acetophenone (1 g.) was dissolved in anhydrous ether (10 c.c.) and the clear pale yellow solution cautiously treated with fuming nitric acid (d. 1·5, 1 c.c.). After keeping the bright red reaction mixture for 3 hours, water (20 c.c.) was added and thoroughly shaken. The ether layer was separated, the aqueous layer extracted twice with ether, the combined ether extract dried over anhydrous sodium sulphate and evaporated. The red liquid left behind crystallised on standing for some time at the ordinary temperature. The red crystalline solid was filtered, washed with ether and recrystallised from benzene when it formed red needles melting at 165–67° alone or in admixture with the sample of the quinone obtained from 2:5-dihydroxy-3:4:6-trimethoxy acetophenone by treatment with bromine. The properties were also identical.

Summary

Pedicin is considered to be a *para*-dihydroxy chalkone and this constitution is confirmed by its synthesis from 2-hydroxy-3:4:6-trimethoxy chalkone using the method of nuclear oxidation with persulphate. The synthetic pedicin could be readily converted into pedicellin and pedicinin. Under the ordinary conditions of chalkone-flavanone conversion it yields isopedicin which is therefore given the constitution of 6-hydroxy-5:7:8-trimethoxy flavanone. The constitutions of pedicinin and methyl pedicinin

are discussed on the basis of the analogies presented in an earlier paper on oxidative demethylation using nitric acid and fresh data derived from the conversion of 2:5-dihydroxy-3:4:6-trimethoxy acetophenone and pentamethoxy acetophenone into hydroxy-quinone-ketone analogous to pedicinin. It is concluded that pedicinin and methyl pedicinin have the hydroxy-quinone-chalkone structure. Methyl pedicinin which is an intermediate stage in the formation of pedicinin is now found to occur in the leaves of *D. pedicellata.* A scheme of biogenesis of pedicin and its allies is given. The most conclusive evidence for this scheme as well as for the mechanism of the pedicin-pedicinin change and incidentally for the pedicellin-pedicinin change also, is the gentle oxidation of pedicin to the trimethoxy-quino-chalkone and further stepwise hydrolysis to methyl pedicinin and pedicinin. Using diazomethane for partial methylation it is possible to methylate pedicinin to methyl pedicinin.

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