FORMATION OF QUINONES BY OXIDATIVE DEALKYLATION

*Part II. Constitution of Pedicinin

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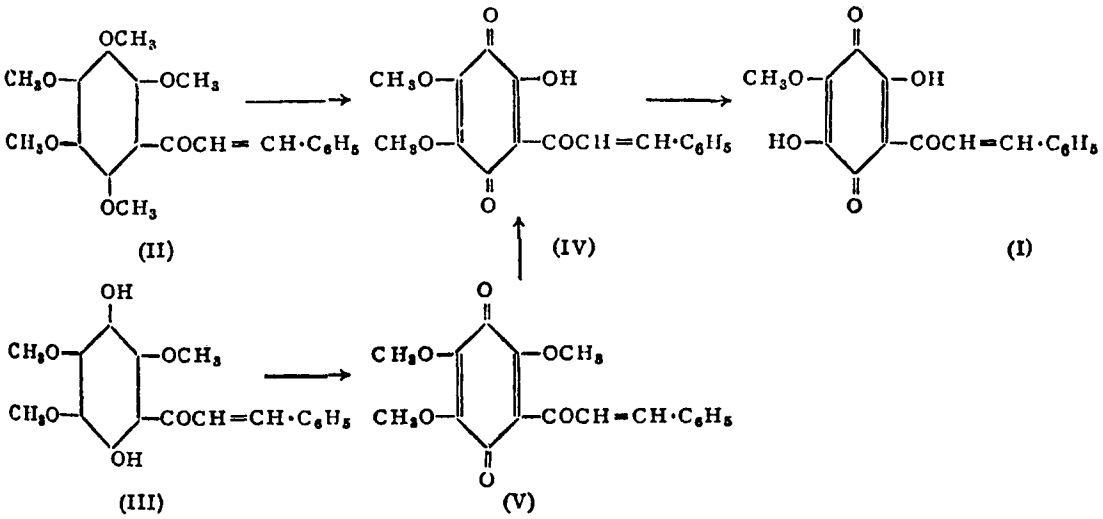
BESIDES its composition and properties the main information on the constitution of pedicinin (I) is derived from its preparation from pedicellin (II) and pedicin (III) involving oxidative demethylation. In the case of pedicellin, nitric acid has to be employed and methyl pedicinin (IV) can be obtained as an intermediate.[1] For the conversion of pedicin, bromine was first used and in this case the stages in the conversion could not be isolated and further dibromopedicin was a by-product.[1 2] On the other hand, by employing benzoquinone or moist silver oxide as dehydrogenating agent it has been possible to isolate two intermediate stages, dimethyl (V) and monomethyl pedicinin[3] (IV).



The details of the constitution of pedicinin had formerly to be based to a considerable extent on theoretical considerations and on analogies.[3] For example, it was argued that a quinone carbonyl is capable of activating only

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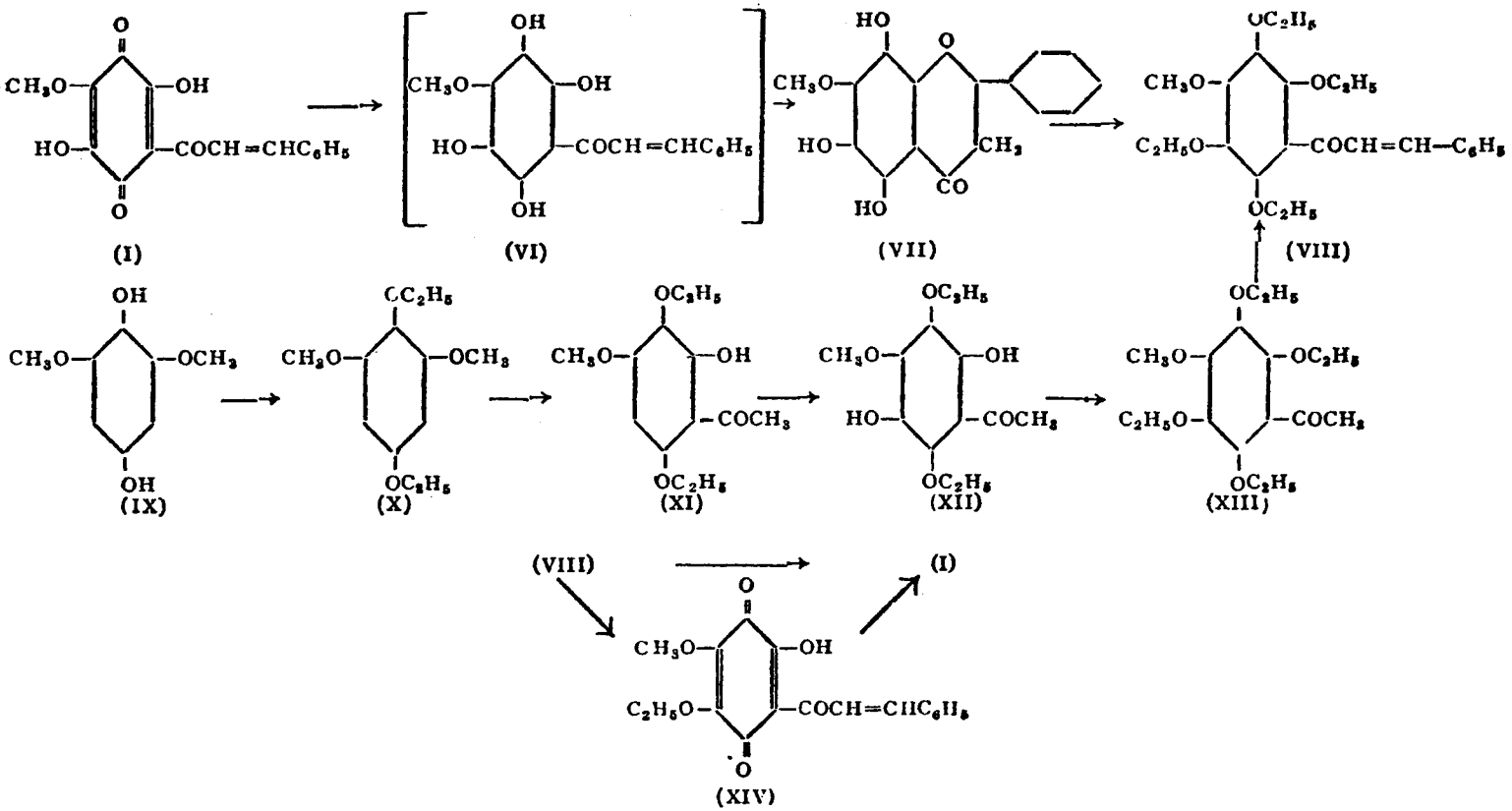
one methoxyl group situated in the β-position of the katiœnoid system and further when there are two such methoxyls the one that suffers demethylation should be ortho to the ketonic carbonyl because it is activated by two katiœnoid systems. That the methoxyl in the 4-position is left out has also been shown by the analogy of 2-hydroxy-4-methoxy-3 : 6-quino-acetophenone.[4] It is a very essential point but is not unequivocally established in a simple way by the above mentioned synthesis of pedicinin from pedicellin and pedicin. It has now been settled in an unambiguous manner by the process of ethylation which has been earlier adopted in the study of partial methyl ethers of flavones. For this purpose pedicinin is reduced using stannous chloride following the procedure of Salooja, Sharma and Siddiqui[2] to dihydropedicinin. From the properties of this compound it would appear that it does not have the chalkone structure (VI) but has undergone change into the corresponding flavanone (VII). But this point need not be specially considered here because, as a result of complete ethylation in the next stage, a chalkone is formed with four ethoxyl and one methoxyl groups. This product is found to be identical with 4-methoxy-2 : 3 : 5 : 6-tetraethoxy chalkone (VIII) prepared synthetically starting from 2 : 6-dimethoxy-quinol (IX). The various stages in this synthesis are as follows :— (1) Ethylation to form the quinol diethyl ether *i.e.*, 2 : 6-dimethoxy-1 : 4-diethoxy-benzene (X). (2) Friedel and Craft's reaction using acetyl chloride in ether solution. The product is 2-hydroxy-4-methoxy-3 : 6-diethoxy-acetophenone (XI). This constitution is not only based on the analogy of this reaction with 1 : 2 : 3 : 5-tetramethoxy benzene[5] but is also confirmed by the capacity of the compound to undergo presulphate oxidation, thus indicating the presence of a free nuclear position para to the phenolic hydroxyl group. (3) Nuclear oxidation of the above ketone with alkaline persulphate to (XII) and (4) complete ethylation using diethyl sulphate yielding 4-methoxy-2 : 3 : 5 : 6-tetraethoxy acetophenone (XIII). (5) Condensation of the ketone with benzaldehyde to form the corresponding chalkone, 2 : 3 : 5 : 6-tetra-ethoxy-4-methoxy chalkone (VIII).

The abovementioned tetraethoxy-monomethoxy-chalkone (VIII) as well as tetraethyl-dihydropedicinin undergo oxidation with nitric acid forming ethyl pedicinin (XIV) and pedicinin (I) as products. Thus all the ethyl groups can be removed in this reaction and it is strictly analogous to pedicellnin-pedicinin conversion.[3] This confirms that the progress of the reduction and ethylation of pedicinin has been as expected because the reverse process is effected by nitric acid and the original compound (pedicinin) is again obtained.


(I)
(VI)
(VII)
(VIII)
(IX)
(X)
(XI)
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(XIV)

In the course of this work, we have examined the toxic properties of 2:4:5-trimethoxy-3:6-quino-chalkone which is the immediate oxidation product of pedicin. In a concentration of 100 mg. per litre it exhibits strong toxic effect on fish (*Haplochylus panchax*) which lose balance and turn upside down in 11 minutes. The fish do not recover on removal to fresh water after this period and they die rapidly. But at a concentration of 50 mg. per litre no appreciable toxic effect could be noticed. Though this compound would appear to be weaker than pedicin in regard to the rapidity with which toxic effect is exhibited (*cf.* turning time for pedicin 3½ minutes for 100 mg. per litre), this quinone appears to be eventually stronger in its toxic effect because the fish die at this concentration whereas in the case of pedicin such death did not occur after removal to fresh water.

Experimental

Dihydropedicinin (VII)

The reduction of pedicinin was carried out according to the procedure of Salooja, Sharma and Siddiqui,[2] the amount of stannous chloride used being lowered to 15 g. per gram of pedicinin. The product was purified by crystallisation from hot aqueous alcohol and later from a mixture of ethyl acetate and benzene when it formed pale yellow silky needles melting at 162–63°. It was easily soluble in alcohol but sparingly in ether. In 5% aqueous sodium carbonate, it gradually dissolved to a yellow solution. In 5% sodium hydroxide it readily formed a deep red solution which changed to yellow on shaking with air. With ferric chloride in alcoholic solution a deep brown colour was obtained and with lead acetate an immediate pinkish brown precipitate. When the alcoholic solution was treated with *p*-benzoquinone, a deep red colour resulted immediately. Contrary to the reports of Salooja, *et al.*, the alcoholic solution of the substance was stable and no change could be observed on boiling.

Ethylation: Tetraethyl-dihydropedicinin (VIII)

A solution of dihydropedicinin (2 g.) in anhydrous acetone (25 c.c.) was treated with diethyl sulphate (5 c.c.) and anhydrous potassium carbonate (15 g.). The mixture was refluxed for 15 hours with occasional shaking. The solvent was then distilled off and the residue treated with water (200 c.c.). The mixture was extracted with ether twice and the ether extract shaken with 5% aqueous sodium hydroxide. After washing with water, it was dried over anhydrous sodium sulphate and the ether distilled when a brownish yellow liquid product was obtained. It did not crystallise on keeping in the ice-chest for a long time. In an attempt to purify it, the liquid was dissolved in a small quantity of ether and the solution treated with excess of

light petroleum. The mixture was heated to boiling and the clear very pale yellow solution decanted from the brown insoluble matter. On concentrating it only a pale yellow viscous oil was obtained and it did not crystallise though it had been rendered pure. It was not soluble in aqueous alkali and did not give any colour with ferric chloride in alcoholic solution. It was characterised as the phenyl hydrazone as described below:—

The above product (0·5 g.) was treated with phenylhydrazine (0·5 c.c.) and glacial acetic acid (2 drops). The viscous mixture was heated in a boiling water-bath for one hour, cooled and poured into ice-cold dilute hydrochloric acid (100 c.c.). The mixture was extracted with ether twice and the ether extract shaken successively with dilute hydrochloric acid, aqueous sodium hydroxide (5%) and water. It was then dried over calcium chloride and distilled. The residual thick viscous mass, on dissolving in a small quantity of ether and cooling, deposited an almost colourless crystalline solid which was filtered and washed with a little ether. Crystallisation from alcohol gave glistening colourless big rectangular plates and prisms melting at 147–49°. (Found: C, 71·4; H, 7·5; $C_{30}H_{36}O_5N_2$ requires C, 71·4; H, 7·1%.) Yield, 0·3 g.

Oxidative dealkylation of tetraethyl-dihydropedicinin: Ethyl pedicinin (XIV) and pedicinin (I)

A solution of tetraethyldihydropedicinin (1 g.) in glacial acetic acid (3 c.c.) was treated with concentrated nitric acid (1 c.c.). The solution which immediately turned deep red was stirred well for 2 minutes and diluted with water (100 c.c.). An orange red sticky mass separated out which solidified when kept in the ice-chest for 3 hours. It was filtered, washed well with water and dried. When crystallised from a mixture of benzene and ligroin two fractions were obtained. The first one consisted of carmine red rectangular prisms melting at 202–3° alone or in admixture with an authentic sample of pedicinin; yield, 0·3 g. The second fraction, an orange yellow solid, was recrystallised from a mixture of benzene and ligroin. It formed orange coloured rectangular prisms melting at 113–14°. (Found: C, 65·4; H, 5·2; $C_{18}H_{16}O_6$ requires C, 65·8; H, 4·9%.) Yield, 0·4 g. This compound designated ethyl pedicinin as analogous to methyl pedicinin, was readily soluble in alcohol and benzene, sparingly in ether and very slightly in ligroin. It was easily soluble in aqueous sodium bicarbonate giving a reddish brown solution. It gave a deep red colour with ferric chloride in alcoholic solution.

Conversion of ethyl pedicinin into pedicinin

Ethyl pedicinin (0·2 g.) was dissolved in 5% aqueous sodium hydroxide (25 c.c.) and the clear red solution was acidified with concentrated hydro-

chloric acid after two minutes. The orange red solid was filtered, washed and crystallised from benzene. It formed carmine red rectangular plates and prisms melting at 202–3° and identical with pedicinin.

2-Hydroxy-4-methoxy-3 : 6-diethoxy-acetophenone (XI)

2 : 6-Dimethoxy-1 : 4-diethoxy benzene (X) was made by the ethylation of 2 : 6-dimethoxy quinol[6] with diethyl sulphate and potassium carbonate in dry acetone medium. It will be described in detail in another connection.

Powdered anhydrous aluminium chloride (23 g.) was dissolved in dry ether (60 c.c.) with cooling and then a solution of 2 : 6-dimethoxy-1 : 4-diethoxy benzene (25 g.) in dry ether (60 c.c.) added. To the mixture which was vigorously shaken and cooled in an ice-bath was added acetyl chloride (12 c.c.) in small quantities during the course of an hour and the shaking continued occasionally for another four hours keeping the mixture in the ice-bath. A heavy dark greenish brown oily layer first separated out and slowly changed into a yellowish green hard mass. After the mixture was allowed to stand for 24 hours, the supernatant ether layer was decanted off and crushed ice and concentrated hydrochloric acid (30 c.c.) were added to the remaining solid and vigorously stirred. The reaction mixture was then heated on a water-bath for 30 minutes to complete the decomposition of the aluminium chloride complex. While still hot, it was extracted with benzene twice and the benzene layer washed with dilute hydrochloric acid. It was then shaken repeatedly with 5% aqueous sodium hydroxide and the combined alkaline extracts acidified with concentrated hydrochloric acid. The pale yellow crystalline solid that separated out was filtered and washed with water. Yield, 25 g. Crystallisation from alcohol yielded very pale yellow prismatic needles melting at 104–5°. (Found: C, 61·5; H, 7·5; $C_{13}H_{18}O_5$ requires C, 61·4; H, 7·1%). In alcoholic solution it gave a reddish violet colour with ferric chloride.

2-Hydroxy-4-methoxy-3 : 6-diethoxy chalkone

To a solution of the above ketone (10 g.) in alcohol (100 c.c.) was added benzaldehyde (40 c.c.) and the mixture treated with strong aqueous potash (80 g. in 80 c.c.) with cooling. Sufficient alcohol was then added to get a clear homogeneous solution. The flask was tightly stoppered and left at the laboratory temperature for three days. The dark red reaction mixture was then poured into water (1,000 c.c.) and filtered from an amorphous yellow solid that separated out. The clear alkaline filtrate was extracted with ether and acidified with concentrated hydrochloric acid. The chalkone separated out as an orange coloured solid which was filtered and washed with aqueous sodium bicarbonate followed by water. Crystallisation from

alcohol gave it in the form of long orange needles melting at 135-36°. (Found: C, 68·7; H, 6·6; $C_{20}H_{22}O_5$, $\frac{1}{2}H_2O$ requires C, 68·4; H, 6·5%.) It was sparingly soluble in aqueous sodium hydroxide and in alcoholic solution gave a deep reddish brown colour with ferric chloride. Yield, 9 g. Oxidation of this chalkone with alkaline persulphate did not proceed satisfactorily.

2: 5-*Dihydroxy*-3: 6-*diethoxy*-4-*methoxy acetophenone* (*XII*)

2-Hydroxy-4-methoxy-3: 6-diethoxy acetophenone (10 g.) was dissolved in aqueous potassium hydroxide (9 g. in 50 c.c.) and the clear solution, while being stirred and cooled at 15–20°, was treated dropwise with a solution of potassium persulphate (15 g. in 250 c.c.) and aqueous potash (9 g. in 30 c.c.) during the course of 2 hours. The deep brown reaction mixture was allowed to stand for 24 hours and neutralised to Congo Red using hydrochloric acid. The unchanged ketone separated as a brown solid which was extracted twice with ether. The clear brown aqueous solution was then treated with sodium sulphite (2 g.), concentrated hydrochloric acid (50 c.c.) and benzene (100 c.c.) and the mixture refluxed for 30 minutes. The benzene layer was separated and the extraction repeated with some more benzene (50 c.c.) for 15 minutes. The combined benzene extracts were separated, washed with a small quantity of water and dried over anhydrous sodium sulphate. After distilling off the solvent, the dihydroxy ketone was left behind as a brownish yellow crystalline solid. It was recrystallised from a mixture of alcohol and aqueous sulphur dioxide when it separated out as glistening pale yellow leaflets melting at 131–32°. (Found: C, 58·0; H, 7·0; $C_{13}H_{18}O_6$ requires C, 57·8; H, 6·7%.) It was easily soluble in alcohol and benzene but sparingly in water. In aqueous sodium hydroxide it formed a yellowish-brown solution. With ferric chloride in alcoholic solution it gave an evanescent green colour which changed to deep brown red. Yield, 3·5 g.

2: 3: 5: 6-*Tetraethoxy*-4-*methoxy chalkone* (*VIII*)

The dihydroxy ketone described above (3 g.) was ethylated in anhydrous acetone medium (50 c.c.) with diethyl sulphate (8 c.c.) and anhydrous potassium carbonate (20 g.). On working up as usual, the ethyl ether (XIII) separated out as a brownish yellow viscous liquid (yield, 2·8 g.). This did not crystallise even on keeping in the ice-chest for a number of days. It was insoluble in alkali and did not give any colour with ferric chloride and was therefore directly used for the subsequent chalkone condensation. For this, a solution of the ethylated ketone (2 g.) in alcohol (15 c.c.) was treated with benzaldehyde (6 c.c.) and strong aqueous potash (15 g. in 10 c.c.). Sufficient alcohol was then added to get a clear solution which was allowed

to stand for 2 days. The mixture was poured into water (300 c.c.) and extracted with ether. The ether extract was distilled off employing a current of steam in the final stages to remove benzaldehyde and benzyl alcohol. The chalkone left behind was taken up in ether, the solution dried over calcium chloride and purified by treatment with light petroleum as described under tetraethyl-dihydropedicinin. The pale yellow viscous oil that was obtained did not crystallise and was therefore characterised in the form of the phenyl hydrazone which was made according to the procedure already described for the natural sample. It crystallised from alcohol as colourless rectangular prisms melting at 147–49°. The melting point was undepressed when mixed with the sample prepared from dihydro-pedicinin.

This synthetic sample of tetraethoxy-methoxy-chalkone underwent oxidative de-ethylation with nitric acid to yield ethyl pedicinin and pedicinin.

Summary

An essential point which has not been established in a simple manner by the previous study of pedicinin and its synthesis relates to the position of the methoxyl group. This has now been settled in an unambiguous manner by the reduction of pedicinin with stannous chloride to dihydropedicinin and its ethylation. The product is found to be identical with 4-methoxy-2:3:5:6-tetraethoxy chalkone obtained synthetically starting from 2:6 dimethoxy quinol. This chalkone undergoes oxidative de-ethylation with nitric acid yielding ethyl pedicinin and eventually pedicinin.

The toxic properties of dimethyl pedicinin (2:4:5-trimethoxy-quino chalkone) have been studied using fish.

References

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