

FORMATION OF QUINONES BY OXIDATIVE DEMETHYLATION

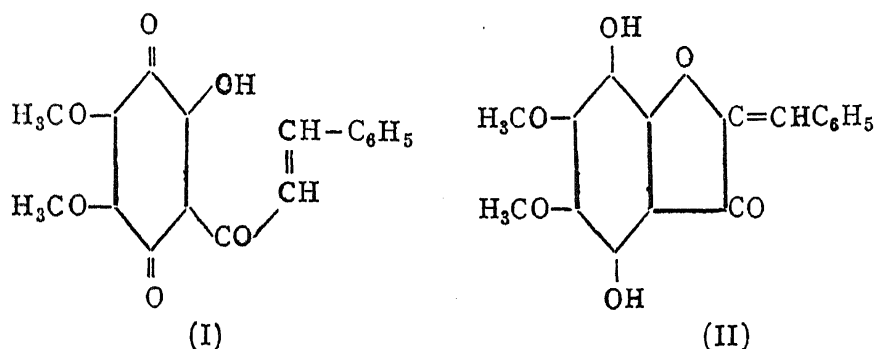
Part IV. Isomers of Methyl Pedicinin

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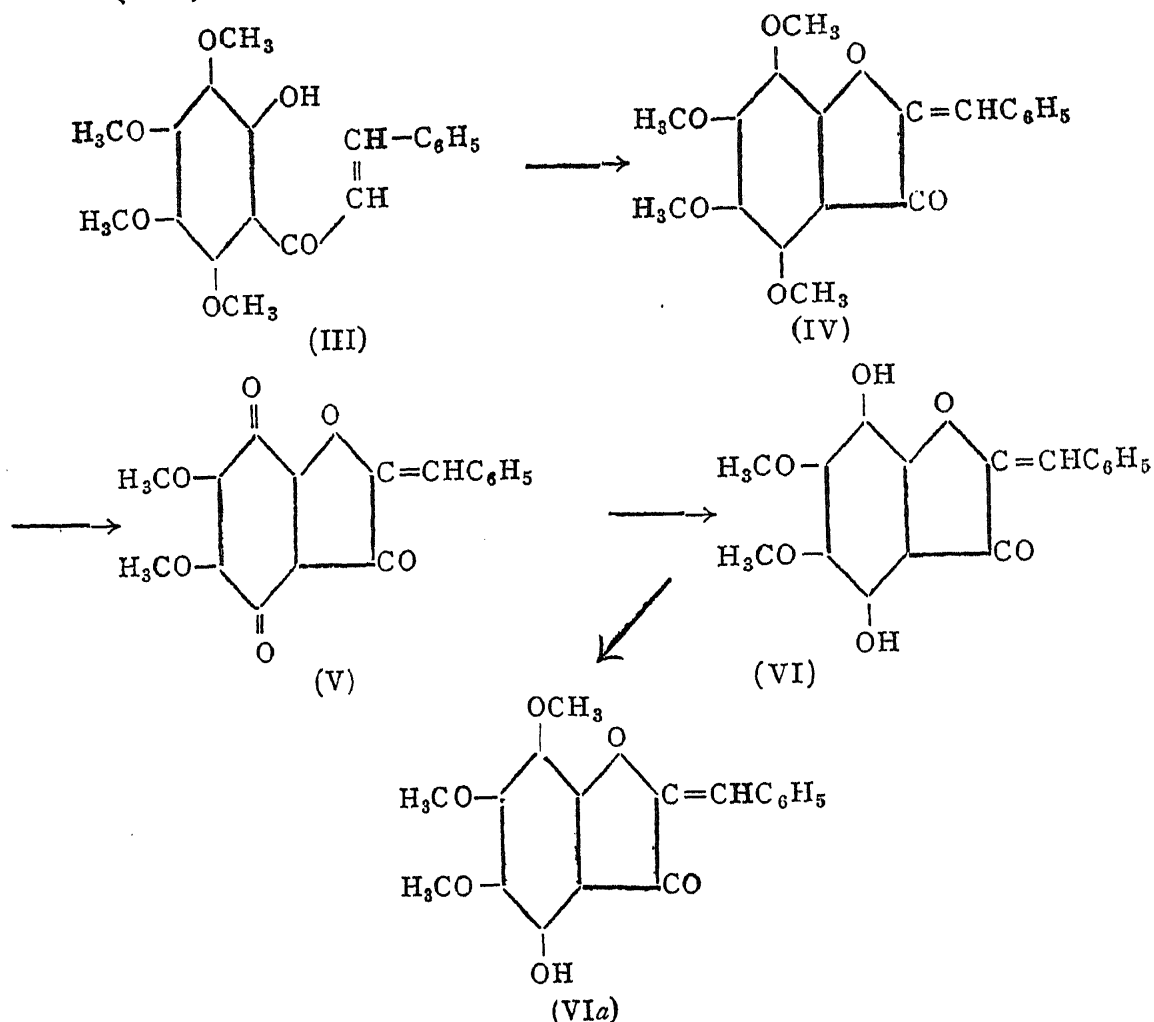
Received July 4, 1949

CLOSELY related to pedicinin is methyl pedicinin. It can be converted into pedicinin by demethylation and could also be obtained from it by methylation. All its properties seem to be very satisfactorily explained by the quinone-chalkone formula, *i.e.*, 2-hydroxy-4:5-dimethoxy-3:6-quinone-chalkone (I). While discussing the benzal-coumaranone structure for pedicinin (see Balakrishna, Seshadri and Viswanath¹) it seemed to be relevant to examine a similar structure (II) for methyl pedicinin which was originally proposed for it by Sharma and Siddiqui.²



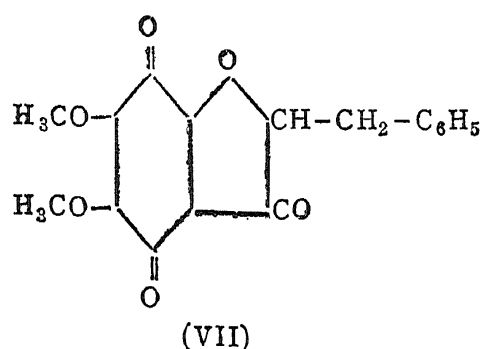
A substance of this constitution has now been synthesised starting from 2-hydroxy-3:4:5:6-tetramethoxy chalkone (III). This readily undergoes change into 4:5:6:7-tetramethoxy-benzal coumaranone (IV) when oxidised with alkaline hydrogen peroxide. A very similar case has been reported recently.¹ The product exhibits all the expected properties, particularly the strong red colour with concentrated sulphuric acid. It undergoes oxidative demethylation with nitric acid yielding 5:6-dimethoxy-4:7-quinone-benzal coumaranone (V). In this reaction the above tetramethoxy benzal-coumaranone resembles the related 5:6:7:8-tetramethoxy-flavones³ and flavanones (see also Balakrishna, Seshadri and Viswanath¹). Simple oxidative demethylation of the para positions takes place and there is no further change. When this quinone is dissolved in sodium hydroxide it gives rise to the corresponding quinol, 4:7-dihydroxy-5:6-dimethoxy-benzal-coumaranone (VI). But a more satisfactory method of obtaining

it is to reduce the quinone by means of sulphur dioxide. As a check of its constitution this quinol is subjected to partial methylation; the product is found to be identical with 4-hydroxy 5:6:7-trimethoxy-benzal coumaranone (VI *a*) obtained earlier by an independent method.¹



The quinol (VI) is very different from methyl pedicinin not only in melting point but in other respects too, particularly its colour, solubility and stability in alkali and the mixed melting point (92-96°) was depressed.

Properties	Methyl pedicinin	4 : 7-Dihydroxy-5 : 6-dimethoxy benzal-coumaranone (VI)
Melting point	110-111°	103-4°
Crystal structure	.. Orange prisms	Pale yellow prisms
Solubility in alcohol	.. Fairly soluble	Sparingly soluble
Concentrated sulphuric acid	.. Blood red colour changing to reddish brown	Stable blood-red colour
Behaviour towards sodium hydroxide	.. Yields pedicinin on acidification of the alkali solution	No change
Sodium bicarbonate	.. Red solution	Insoluble



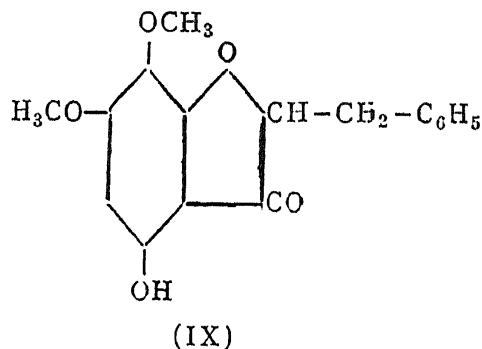
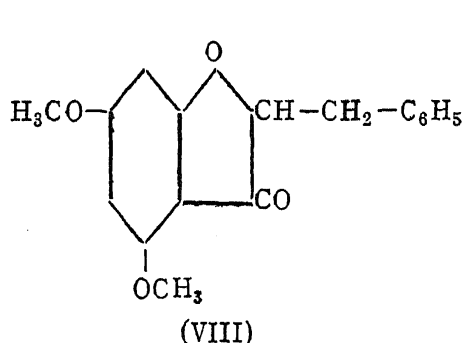
In spite of the intimate relationship between pedicinin and methyl pedicinin, Salooja, Sharma and Siddiqui⁴ newly suggested for methyl pedicinin a third formula, benzyl-quino-coumaranone (VII) which does not have a parallel in any of the formulæ proposed for pedicinin. In justification of this they pointed out that it dissolves in sodium bisulphite and gets reduced by it more readily than pedicinin, that it is saturated to bromine and on catalytic reduction with platinum black it absorbs two hydrogen atoms only. They, however, realised that methyl pedicinin dissolves readily in sodium or potassium bicarbonate and gives also phenolic colour reactions with alcoholic ferric chloride. These, however, were considered by them to be apparent discrepancies in the behaviour of methyl pedicinin and were explained by assuming that under the influence of certain reagents it isomerises into the rather unstable benzal-coumaranone structure (II) originally proposed by Sharma and Siddiqui. The proposal of this isomeric change for which no analogies seem to exist, is now clearly not valid because it has been shown in the foregoing pages that 5:6-dimethoxy-4:7-dihydroxy-benzal-coumaranone exhibits considerable stability in the presence of alkali and other reagents. But one general point which could be considered in this connection is the possible existence of chalcone-benzylcoumaranone interconversion just like the chalcone-flavanone interconversion. The former does not seem to have been met with though the latter is familiarly known. Since no information is available regarding the properties of benzyl-coumaranones, attempts have now been made to prepare some of them and study their properties and if possible to prepare a compound of the structure suggested by Salooja, Sharma and Siddiqui for methyl pedicinin. In this effort we have been successful and the results are discussed below.

For the synthesis of benzyl-coumaranones the reduction of the corresponding benzal-coumaranones with hydrogen at a pressure of 2 to 3 atmospheres in the presence of platinum oxide was adopted by Drumm, Macmahon and Ryan,⁵ but Freudenberg, *et al.*⁶ reported that side reactions occurred with the above catalyst and hence used nickel on kieselghur for the reduction. An independent method for the synthesis was reported by Shriner and Damschroder.⁷ They condensed the appropriate phenol ether

and α -bromo- β -phenyl-propionyl-chloride in the presence of anhydrous aluminium chloride in carbon disulphide medium. Thus they synthesised 6-methoxy-benzyl-coumaranone, which was obtained as colourless crystals melting at 92-94°. Further, another method involving direct benzylation of a coumaranone using sodium methoxide and benzyl chloride was also attempted by them without success.

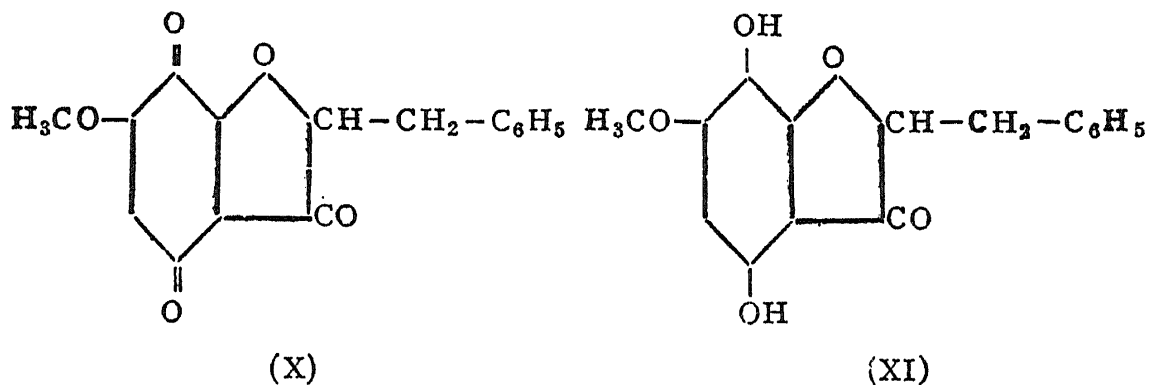
Of the above methods the one selected now as most convenient is that of Shriner and Damschroder with the modification that cold ether is used instead of carbon disulphide as solvent. α -Bromo- β -phenyl-propionyl-chloride is condensed first with fully methylated resorcinol and phloroglucinol ethers. When the products are heated with sodium acetate solution, 6-methoxy- and 4:6-dimethoxy-benzyl-coumaranones (VIII) are obtained. The former has the same melting point as given by Shriner and Damschroder. These benzyl-coumaranones are colourless crystalline compounds which do not give any colour with alcoholic ferric chloride and are insoluble in aqueous sodium hydroxide. With concentrated sulphuric acid they form yellow solutions. They are stable to treatment with cold alcoholic potash (10%, half an hour) and can be recovered unchanged on dilution with water.

1:2:3:5-Tetramethoxy-benzene undergoes the same condensation forming 4-hydroxy-6:7-dimethoxy-benzyl coumaranone (IX). The partial demethylation in the course of this condensation seems to be peculiar to this particular case. It is explicable on the basis that the benzyl coumaranone ring closes up rather readily during the course of the first stage of the condensation and the 4-position of the coumaranone undergoes demethylation in the presence of the aluminium chloride still present.

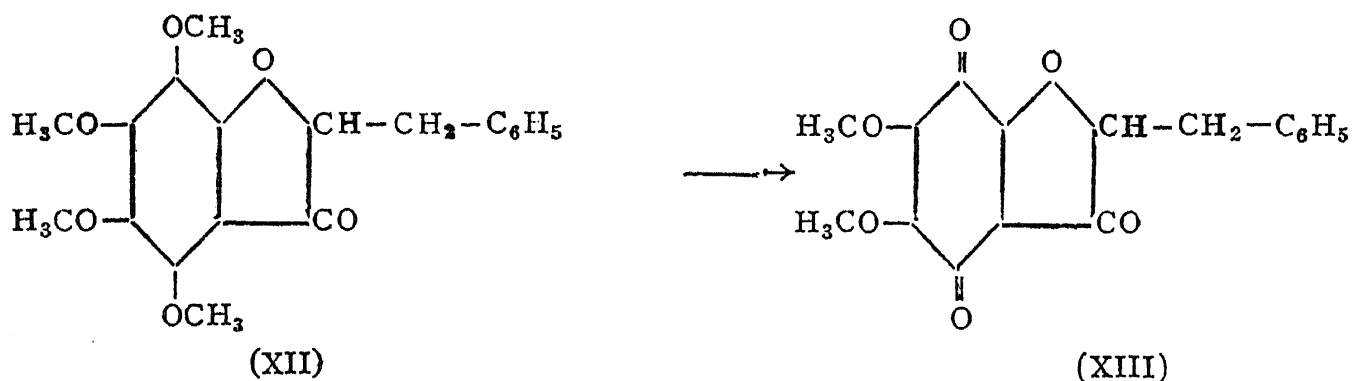


The above compound (IX) suffers oxidative demethylation with nitric acid readily forming 6-methoxy-4:7-quinone-benzyl-coumaranone (X). It could be reduced to the corresponding quinol (XI) which is stable in cold aqueous alkali and does not undergo isomeric change.

As a next stage 4:5:6:7-tetramethoxy benzyl-coumaranone (XII) was prepared starting from pentamethoxy benzene (Baker).⁸ By the action



of nitric acid it underwent change into the corresponding 5:6-dimethoxy-4:7-quinone-benzyl-coumaranone (XIII), the required isomer of methyl pedicinin. It melts at 127-28° which is much higher than the melting point of methyl pedicinin. It could be reduced to the corresponding quinol. It does not dissolve in sodium carbonate and bicarbonate and does not undergo change into pedicinin in the presence of mineral acids and does not give any ferric chloride colour. Hence methyl pedicinin cannot be given the constitution of this compound.



Properties	Methyl pedicinin	4:7-quinone-5:6-dimethoxy-benzyl coumaranone (XIII)
Melting point	110-11°	127-28°
Crystal structure	.. Orange prisms	Yellow prisms
Concentrated sulphuric acid	.. Blood-red colour changing to reddish brown	Yellow
Behaviour towards sodium hydroxide	.. Yields pedicinin on acidification	Dissolves
Sodium bicarbonate	.. Red solution	Insoluble

From the above study it has to be concluded that the quino-chalkone formula (I) is the only correct one for methyl pedicinin as the other alternative formulæ represent substances of very different properties. Further the possibility of reversible isomeric change between chalkones and benzyl-coumaranones does not find experimental support.

EXPERIMENTAL

5:6-Dimethoxy-4:7-quinone-benzal-coumaranone (V)

I stage.—2-Hydroxy-3:4:5:6-tetramethoxy-chalkone (III) was originally prepared by the partial methylation of despedicellin.³ For the present work it was obtained by the condensation of 2-hydroxy-3:4:5:6-tetramethoxy-acetophenone⁸ with benzaldehyde in the presence of alcoholic potash. It was in the form of thick orange yellow oil and was characterised by conversion into the corresponding 5:6:7:8-tetramethoxy-flavanone melting at 78-79°.

The above chalkone (5 c.c.) was dissolved in alcohol (50 c.c.) and treated in small quantities with sodium hydroxide (6%; 15 c.c.) and hydrogen peroxide (6%; 10 c.c.) alternately, all the while shaking the mixture vigorously. The mixture was set aside for two hours. It was then diluted with water and extracted with ether. When the ether extract was concentrated, a deep orange liquid (4 c.c.) separated out. It did not solidify at room temperature. With alcoholic ferric chloride it did not give any colour and was insoluble in sodium hydroxide. With concentrated sulphuric acid it formed a blood-red solution. This sample of tetramethoxy benzal-coumaranone (IV) was used directly for the following reaction.

II stage.—The above tetramethoxy compound (4 c.c.) was treated with nitric acid (20 c.c.; d. 1.2) in the cold (20-25°) for 15 minutes and the solution diluted with water. The brown solid that separated out was filtered and crystallised from alcohol. It was obtained as light orange prisms melting at 188-89°. Yield 0.8 g. (Found: C, 65.3; H, 4.1; C₁₇H₁₂O₆ requires C, 65.4; H, 3.8%.) With alcoholic ferric chloride it did not give any colour.

4:7-Dihydroxy-5:6-dimethoxy-benzal-coumaranone (VI)

Sulphur dioxide was passed through an alcoholic suspension of the above quinone (0.5 g.) for 15 minutes. When the solution was clear it was concentrated on a boiling water-bath and the product allowed to crystallise, the dihydroxy compound being obtained as small yellow prisms melting at 103-104°. Yield, 0.2 g. (Found: C, 65.2; H, 4.8; OCH₃, 20.2; C₁₇H₁₄O₆ requires C, 65.0; H, 4.5; OCH₃, 19.8%.) With alcoholic ferric chloride it gave a brown colour and was soluble in aqueous alkali. It was insoluble in sodium carbonate and bicarbonate solutions. With concentrated sulphuric acid it gave a blood-red colour. The mixed melting point with an authentic sample of methyl pedicinin was depressed (92-96°).

The dihydroxy compound could also be prepared by the following method. The above quinone (0.2 g.) was treated with sodium hydroxide

(20%; 10 c.c.). It went into solution on warming. After allowing it to stand at room temperature for 15 minutes the solution was acidified with sulphuric acid and the separated solid filtered. It crystallised from alcohol in small yellow prisms and was identical in all respects with the dihydroxy compound obtained above; the mixed melting point was undepressed.

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

The above dihydroxy compound (VI) (0.2 g.) was dissolved in dry acetone (25 c.c.) and anhydrous potassium carbonate (5.0 g.) and dimethyl sulphate (0.1 c.c.) were added. The mixture was refluxed for six hours and the potassium salts were filtered off. The acetone filtrate was concentrated on a boiling water-bath. The residue crystallised from alcohol as yellow stout rectangular plates melting at 152-53°. It was identical with the partial methyl ether obtained from 4:5:7-trihydroxy-6-methoxy-benzal coumaranone¹ in all respects; the mixed melting point was undepressed.

6-Methoxy-benzyl-coumaranone

This was prepared by a slight modification of the method of Shriner and Damschroder.⁷

α -Bromo- β -phenyl-propionyl-chloride required for this purpose was made by the method of Fischer.⁹ It distilled at 132-33° under 12 mm. pressure and had all the properties described by Fischer.

O-Dimethyl-resorcinol (5 c.c.) was dissolved in dry ether (50 c.c.) and cooled in ice. Anhydrous aluminium chloride (20 g.) was added in small lots and the mixture was treated with the above acid chloride (7 c.c.) with vigorous shaking. It was allowed to stand overnight at the room temperature. Water (50 c.c.) and concentrated hydrochloric acid (50 c.c.) were added alternately in small quantities with shaking and cooling under the tap and the mixture was heated on a boiling water-bath for half an hour. The liquid that separated out was extracted with ether. After distilling off the ether, the residue was boiled with sodium acetate (10%) solution. The semi-solid that separated out on cooling was crystallised first from alcohol and then from petroleum ether. It was obtained as colourless rectangular prisms melting at 94-95°. (Found: C, 75.2; H, 5.6; C₁₆H₁₄O₃ requires C, 75.6; H, 5.5%.) With alcoholic ferric chloride it did not give any colour and was insoluble in aqueous sodium hydroxide.

4:6-Dimethoxy-benzyl-coumaranone (VIII)

O-Trimethyl phloroglucinol (4.0 g.) was dissolved in dry ether (50 c.c.) and treated with anhydrous aluminium chloride (15 g.) and α -bromo- β -phenyl-propionyl chloride (6 c.c.). The reaction was carried out and the product

worked up as in the above experiment. It crystallised from petroleum ether as colourless prisms melting at 105-6°. (Found: C, 72.0; H, 5.4; $C_{17}H_{16}O_4$ requires C, 71.8; H, 5.6%.) With alcoholic ferric chloride it did not give any colour and was insoluble in aqueous sodium hydroxide.

4-Hydroxy-6:7-dimethoxy-benzyl-coumaranone (IX)

To an ice-cooled dry ether solution of 1:2:3:5-tetramethoxy-benzene (15 c.c.) anhydrous aluminium chloride (25 g.) was added in small lots. α -Bromo- β -phenyl-propionyl-chloride (7 c.c.) was then added and the reaction mixture was allowed to stand overnight. The product was worked up as in similar experiments described above. When crystallised twice from methyl alcohol it was obtained as shining colourless hexagonal plates melting at 97-98°. (Found: C, 68.4; H, 5.0; $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%.) With alcoholic ferric chloride it gave a brown colour and was sparingly soluble in aqueous alkali. It gave a yellow colour with concentrated sulphuric acid.

On methylation with dimethyl sulphate and anhydrous potassium carbonate in dry acetone medium it gave the completely methylated compound. The trimethyl ether was a liquid at room temperature and did not give any colour with alcoholic ferric chloride and was insoluble in aqueous alkali.

4:7-Quino-6-methoxy-benzyl-coumaranone (X)

The above compound (IX) (0.5 g.) was treated with nitric acid (5 c.c.; d., 1.2) in the cold (15-20°) for 15 minutes and the product worked up as in similar cases. It crystallised from alcohol as yellow prisms melting at 115-16° (Found: C, 67.4; H, 4.4; $C_{16}H_{12}O_5$ requires C, 67.6; H, 4.2%.) With concentrated sulphuric acid it gave an orange colour.

6-Methoxy-4:7-dihydroxy-benzyl-coumaranone (XI)

The above quinone (0.2 g.) was reduced with sulphur dioxide in alcoholic solution. On concentrating the solution, the dihydroxy compound crystallised as yellow short needles melting at 87-88°. (Found: C, 66.9; H, 5.1; $C_{16}H_{14}O_5$ requires C, 67.1; H, 4.9%.) With alcoholic ferric chloride it gave a reddish-brown colour and formed a yellow solution with aqueous alkali. With concentrated sulphuric acid it gave a yellow colour.

5:6-Dimethoxy-4:7-quinone-benzyl-coumaranone (XIII)

Pentamethoxy-benzene⁸ (6.0 c.c.) was treated with anhydrous aluminium chloride (30 g.) and α -bromo- β -phenyl-propionyl-chloride (5 c.c.),

carefully in an ice-cooled dry ether (100 c.c.) medium. The mixture was allowed to stand overnight. Water (100 c.c.) and concentrated hydrochloric acid (50 c.c.) were added carefully and the ether was allowed to distil off. The mixture was heated at 100° on a boiling water-bath for 15 minutes. On cooling, an oily layer separated out. It was extracted with ether and the ether distilled off. The liquid that was left behind was boiled with aqueous sodium acetate (10%). On cooling a dark-coloured oily layer separated out. It was extracted with ether and the ether solution dried over anhydrous sodium sulphate. Removal of ether by distillation left behind a liquid which did not solidify at room temperature. So it was directly treated with nitric acid (10 c.c.; d., 1.2) in the cold (15-20°) for 15 minutes. On diluting the solution and working up the product that separated out, the quinone crystallised from methyl alcohol as yellow prisms melting at 127-28°. (Found: C, 65.2; H, 4.6; $C_{17}H_{14}O_6$ requires C, 65.0; H, 4.5%.) With alcoholic ferric chloride it did not give any colour and formed a yellow solution with concentrated sulphuric acid. It was insoluble in sodium carbonate and bicarbonate solutions, but slowly dissolved in aqueous sodium hydroxide.

When sulphur dioxide was passed for 15 minutes through an alcoholic solution of the quinone and the solution concentrated, a yellow solid was obtained. It crystallised from alcohol as yellow rectangular plates melting at 120-21°. With alcoholic ferric chloride it gave a reddish-brown colour and was converted back to the quinone by the action of *p*-benzoquinone in absolute alcoholic medium.

SUMMARY

Two isomers of methyl pedicinin are synthesised and studied: (1) 4:7-dihydroxy-5:6-dimethoxy-benzal-coumaranone and (2) 5:6-dimethoxy-4:7-quinone-benzyl-coumaranone. The first is made from 2-hydroxy-3:4:5:6-tetramethoxy-chalkone by conversion into the corresponding benzal-coumaranone, oxidative demethylation to 4:7-quinone and reduction to the quinol. The second synthesis condenses pentamethoxy-benzene with α -bromo- β -phenyl-propionyl chloride to yield tetramethoxy-benzyl-coumaranone and oxidises it with nitric acid to the quinone. Their properties are different from methyl pedicinin and they do not undergo conversion into it. It is therefore concluded that methyl pedicinin should be given only the quinone chalkone formula and that the alternative formulations are not valid. Further the possibility of reversible isomeric change between chalkones and benzylcoumaranones does not find experimental support.

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