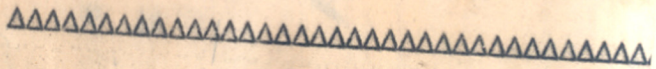


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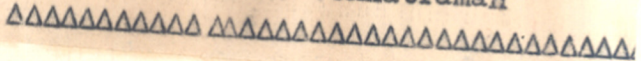
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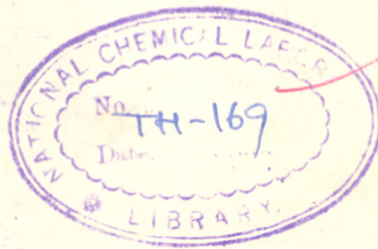
by

Dr. K. Venkatraman



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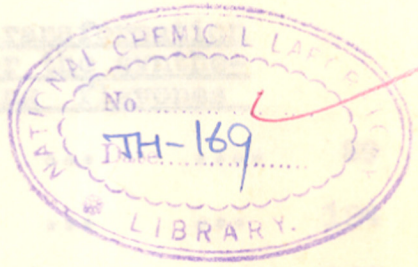
SOME NATURALLY OCCURRING FLAVONES AND RELATED
SYNTHETICAL EXPERIMENTS

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as a natural product

A Thesis
submitted by
S. A. TELANG,
B.Sc.(Hons.)
to the
UNIVERSITY OF BOMBAY
for the Degree of Ph.D.



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PART I

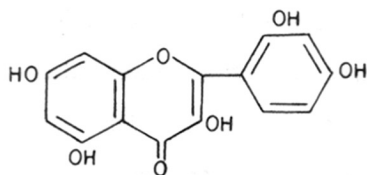
THREE NEW COLOURING MATTERS FROM THE
HEARTWOOD OF ARTOCARPUS INTEGRIFOLIA

Artocarpus integrifolia, the well-known jack fruit tree belonging to the Urticaceae, is a large tree cultivated in South India, Burma and Ceylon. The heartwood is yellow when freshly cut, but on long exposure to air gradually changes to brown. The wood is fairly strong, durable and moderately resistant to fungi and white ants. It is used in the villages of India for beams, doors, and window-frames in the construction of buildings. The rasped wood also finds some use as a yellow mordant dye in conjunction with alum for dyeing silk and for general purposes. In Cambodia the wood is considered to be a nervous sedative and is administered in convulsions.

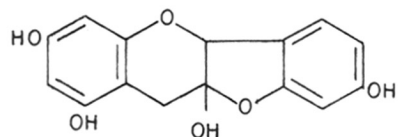
From the heartwood of *Artocarpus integrifolia* Perkin and Cope^{1,2} isolated morin (3,5,7,2',4'-pentahydroxyflavone) (I) and the colourless cyanomaclurin which is characterized by the deep blue colour produced by warming an alkaline solution and to which Appel and Robinson³ assigned the structure of a cyclic hemiketal of 5,7,2',4'-tetrahydroxy-3-ketoflavan (II). By extraction of the powdered heartwood with hexane Dave and Venkataraman⁴ isolated another colouring matter, artocarpin, m.p. 174-175°. The elementary analysis of artocarpin and its derivatives together with degradative experiments, such as alkaline hydrolysis, alkali fusion and permanganate oxidation,

established the structure of artocarpin as 5,2',4'-trihydroxy-7-methoxyflavone with alkenyl substituents in the 3- and 6-positions (III). The nature of the side-chains was further investigated by Mani⁵ by studying the action of ozone on artocarpin and its derivatives. Ozonolysis of artocarpin and its dimethyl and trimethyl ethers gave isobutyraldehyde and acetone in each case, together with a dialdehyde which analysed for a tetrahydroxyflavone mono-, tri- or tetramethyl ether containing a CHO and a CH₂CHO group. Ozonization of dihydroartocarpin dimethyl ether gave acetone and a flavone which analysed for a hydroxytrimethoxyflavone containing a C₅H₁₁ and a CH₂CHO group. Permanganate oxidation of this monoaldehyde gave a carboxylic acid, which on decarboxylation yielded 3-methyl-6-isoamyl-5-hydroxy-7,2',4'-trimethoxyflavone, the constitution of which was confirmed by an unambiguous synthesis. The isoamylene side-chain in the 6-position proved therefore to be Me₂CH-CH=CH-, and that in the 3-position to be Me₂C=CH-CH₂-. In conclusive proof of the structure of artocarpin the synthesis of tetrahydroartocarpin dimethyl ether was achieved by the interaction of 3-isoamyl-2,4,6-trihydroxyisoheptophenone with 2,4-dimethoxybenzoyl chloride in acetone in the presence of

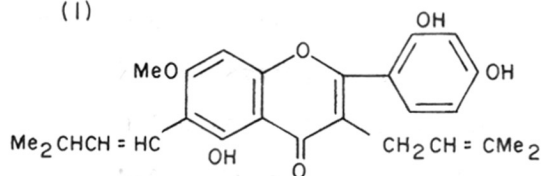
anhydrous potassium carbonate and subsequent monomethylation.



(I)



(II)



(III)

A more recent examination of samples of the heartwood of Artocarpus integrifolia obtained from the Indian Plywood Manufacturing Co. Private Ltd. and other sources has yielded, in addition to morin, cyanomaclurin and artocarpin, three new flavonoid pigments which have been named artocarpetin (m.p. 310°), artocarpanone (m.p. 210°), and isoartocarpin (m.p. 270°). Three lots of the heartwood (A, B and C) were supplied by the Indian Plywood Manufacturing Co. Private Ltd. (A) contained only artocarpin, (B) artocarpin and artocarpetin, and (C) only artocarpanone. Benzene extracted all the three pigments; artocarpin and artocarpetin were separated by taking advantage of the sparing solubility of the latter

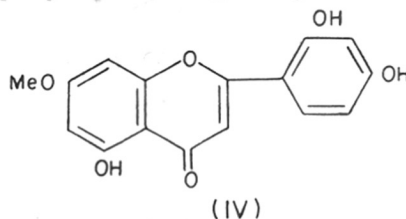
in methanol. | The heartwood of a log of Artocarpus integrifolia obtained from Kerala State has been found to contain ^{a new f} isoartocarpin, probably isomeric with artocarpin and for which, therefore, the name isoartocarpin is proposed; this wood also contained artocarpin and artocarpinone. Pillay and Rao (Professor P. P. Pillay, Kerala University, Trivandrum: private communication) have isolated from Artocarpus hirsutus artocarpin and a second yellow pigment, m.p. 263°, which has been found to be identical with isoartocarpin, m.p. 270°. Artocarpin and isoartocarpin were obtained by hexane extraction of the heartwood, and separated by taking advantage of the sparing solubility of the latter in methanol. Benzene extraction of the heartwood yielded artocarpin, artocarpinone and isoartocarpin. | Isoartocarpin was separated as above, while artocarpin and artocarpinone were separated by evaporating the methanol mother liquor to dryness and extracting the residue with benzene; the latter was sparingly soluble in benzene.

Artocarpetin

The elementary analysis of artocarpetin and its derivatives and the molecular weight of its trimethyl ether determined by the Rast method agree with the molecular formula $C_{16}H_{12}O_6$. Artocarpetin exhibits the following colour reactions: orange solution (with a green fluorescence in ultraviolet light) in concentrated sulphuric acid; yellow solution (with a green fluorescence in ultraviolet light) in aqueous sodium hydroxide; intense reddish brown with alcoholic ferric chloride; yellow in Wilson's boric acid test; orange with magnesium and hydrochloric acid; and purple in the sodium amalgam test. The colour reactions indicate that it is probably a flavone containing a hydroxyl group in the 5-position. Artocarpetin does not form a dinitrophenylhydrazone or an oxime. Artocarpetin contains one methoxyl and three hydroxyl groups, and yields a triacetate and a trimethyl ether. Two hydroxyl groups are not present in o- or p-positions since the o-dinitrobenzene and gossypetone tests are negative; the position para to one hydroxyl group is unoccupied, since a greenish blue colour is produced in the Gibbs test with dichloroquinone-chloroimide. Artocarpetin trimethyl ether was identical with synthetic 5,7,2',4'-tetramethoxyflavone. The ultraviolet absorption

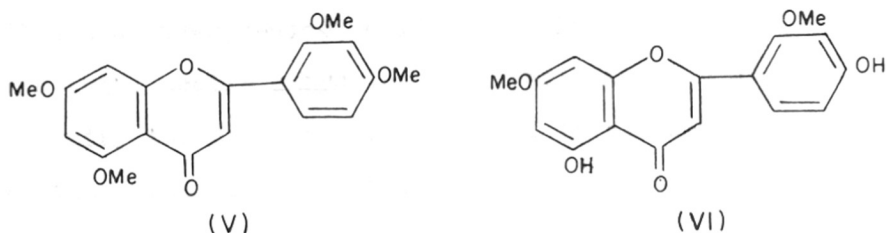
spectrum of artocarpetin is very similar to that of 5,7,2',4'-tetrahydroxyflavone (Fig. 1). Demethylation of artocarpetin by hydriodic acid gave 5,7,2',4'-tetrahydroxyflavone.⁶

Treatment of artocarpetin with boiling 33 per cent potassium hydroxide solution yielded β -resorcylic acid and phloroglucinol monomethyl ether, the latter being characterized as the bisbenzeneazo derivative obtained by coupling with diazotized aniline.⁷ Similar alkaline hydrolysis for a shorter time gave 2,6-dihydroxy-4-methoxyacetophenone. The constitution of artocarpetin is, therefore, 5,2',4'-trihydroxy-7-methoxyflavone (IV).

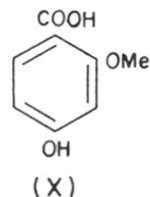
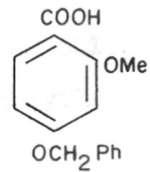
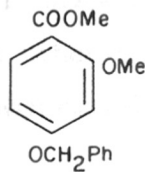
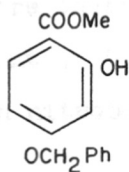


5,7,2',4'-Tetramethoxyflavone (V) was prepared by Anand⁸ by the action of selenium dioxide on the appropriate chalcone;⁹ other workers have prepared (V) by procedures involving the cyclization of 2-hydroxy-4,6,2',4'-tetramethoxydibenzoylmethane.¹⁰⁻¹² Following the observation of Seshadri¹³ that the 7-methoxyl group in an isoflavone is the most resistant to demethylation,

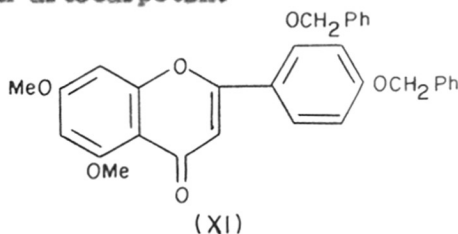
which he has used for the synthesis of prunetin and santal, an attempt to synthesize artocarpetin was made by heating (V) with hydriodic acid (d 1.7) in acetic anhydride at 120° for 45 min, but the product was 5,4'-dihydroxy-7,2'-dimethoxyflavone (VI), which was also obtained by the action of hydrobromic and acetic acids on (V) under prescribed conditions.



The constitution of (VI) was proved by alkaline hydrolysis to phloroglucinol monomethyl ether and 4-hydroxy-2-methoxybenzoic acid; the identity of the latter was established by a negative ferric reaction and direct comparison with the synthetic acid obtained from β -resorcylic acid by monobenylation of the methyl ester (VII), methylation to methyl 4-benzyloxy-2-methoxybenzoate (VIII), hydrolysis of the ester (IX), and debenylation with palladium and hydrogen (X).¹⁴



Artocarpetin was then synthesized from 2-hydroxy-4,6-dimethoxyphenyl 2,4-dibenzyloxystyryl ketone, which was cyclized with selenium dioxide to the flavone (XI). Unexpectedly, debenzoylation of (XI) could not be effected by the usual method of catalytic hydrogenation, but it proceeded smoothly by the alternative method of heating with acetic and hydrochloric acids. On heating 2',4'-dihydroxy-5,7-dimethoxyflavone thus obtained with acetic acid, acetic anhydride and hydriodic acid at 120° for 45 min, the product was identical in all its properties with artocarpetin.



In connection with the constitution of 'lotoflavin',¹⁵ Anand⁸ in 1947 prepared 5-hydroxy-7,2',4'-trimethoxyflavone, because the properties of 'lotoflavin' trimethyl ether, which according to Dunstan and Henry crystallized in dimorphic forms with different melting points, were more characteristic than those of 'lotoflavin.' Treatment of the tetramethyl ether (V) with aluminium chloride in nitrobenzene gave 5-hydroxy-7,2',4'-trimethoxyflavone,

which differed in its properties from the 'lotoflavin'
trimethyl ether of Dunstan and Henry.¹⁵

Artocarpanone

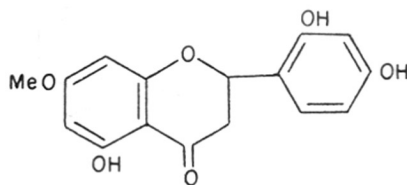
The elementary analysis of artocarpanone and its derivatives and the molecular weight of its trimethyl ether determined by the Rast method agree with the molecular formula $C_{16}H_{14}O_6$. The colour reactions of artocarpanone are different from those of artocarpetin. Artocarpanone exhibits the following colour reactions: yellow solution changing to red in aqueous sodium hydroxide; red solution in aqueous sodium carbonate; reddish brown with alcoholic ferric chloride; no yellow colour in Wilson's boric acid test; magenta with magnesium and hydrochloric acid; and wine-red in the sodium amalgam test. The presence of a carbonyl group is shown by the ready formation of a dinitrophenylhydrazone. The strong colours in the magnesium-hydrochloric acid (magenta) and sodium amalgam (red) tests indicate a flavanone structure. This was confirmed by the characteristic ultraviolet absorption spectrum (Fig. 1).

Artocarpanone contains one methoxyl and three hydroxyl groups, forming a triacetate. Artocarpanone, like artocarpetin does not contain two hydroxyl groups in o- or p-positions since the o-dinitrobenzene and gossypetone tests are negative; the position para to one hydroxyl group is unoccupied, since a greenish blue colour is

produced in the Gibbs test with dichloroquinone-chloroimide.

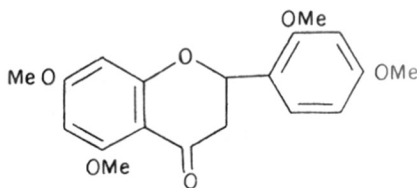
The flavanone character of artocarpanone was further supported by the production of two methyl ethers on treatment with dimethyl sulphate and potassium carbonate in acetone; one has the properties of a tetramethoxyflavanone and the other those of a pentamethoxychalcone (negative magnesium-hydrochloric acid reaction; characteristic absorption spectrum) (Fig. 1). The tetramethoxyflavanone was also obtainable by methylation with diazomethane in methanol-ether; using diazomethane in ether, the product was a hydroxytrimethoxyflavanone (red-brown ferric colour). A purple colour is given with concentrated nitric acid, showing that the 7-position in artocarpanone is probably occupied by a methoxyl group.¹⁶

By hydrolysis with 50 per cent aqueous potassium hydroxide, artocarpanone yielded the same phenol (phloroglucinol monomethyl ether) and acid (β -resorcylic acid) as artocarpetin. Artocarpanone is, therefore, the corresponding flavanone (XII).

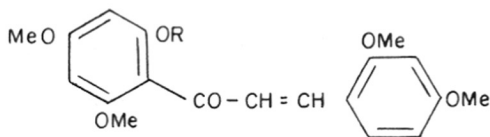


(XII)

The constitution (XII) was confirmed by a direct comparison of its trimethyl ether with the known 5,7,2',4'-tetramethoxyflavanone¹⁷ (XIII). Cyclization of 2'-hydroxy-2,4,4',6'-tetramethoxychalcone (XIV; R=H) proved to be very difficult, probably because of the steric hindrance of the 2-methoxyl group, but the trimethyl ether of (XII) was ultimately isolated in poor yield by prolonged treatment with aqueous ethanolic hydrochloric acid,¹⁷ followed by chromatographic separation of the flavanone from the unconverted chalcone. The product of the complete O-methylation of artocarpone was identical with the known 2,4,2',4',6'-pentamethoxychalcone (XIV; R=Me).¹⁸



(XIII)



(XIV)

Isoartocarpin

The elementary analysis of isoartocarpin and its derivatives and the molecular weight of its diacetyl derivative determined by the Rast method agree with the molecular formula of artocarpin, $C_{26}H_{28}O_6$. Isoartocarpin exhibits the following colour reactions: orange solution in aqueous sodium hydroxide; deep red solution (with pale green fluorescence) in concentrated H_2SO_4 ; greenish brown with alcoholic ferric chloride; yellow in Wilson's boric acid test; pink with magnesium and hydrochloric acid; pale pink in the sodium amalgam test; and orange-yellow with a green fluorescence in concentrated nitric acid. The reactions indicate that isoartocarpin is a phenol and is probably a chromone or chromanone derivative, and that a phenolic hydroxyl group is chelated with a carbonyl group. Isoartocarpin does not form a dinitrophenylhydrazone or an oxime, and is therefore probably not a chromanone.

(B) [Isoartocarpin contains one methoxyl group like artocarpin, but it differs from artocarpin in containing only two phenolic hydroxyl groups, yielding a diacetate and a ditosylate. One of the hydroxyl groups was methylated by diazomethane in ether, and both the hydroxyl groups were methylated by dimethyl sulphate and potassium

carbonate in acetone. *is less difficult to* Isoartocarpin can be completely methylated ~~with relatively greater ease~~ than artocarpin.

According to Dave,⁴ the third hydroxyl group in artocarpin could not be methylated by dimethyl sulphate and potassium carbonate in acetone. A 5-hydroxyl group in a chromone or a chromanone can generally be methylated by treatment with excess of dimethyl sulphate and potassium carbonate in acetone for several hours, and he ~~postulated~~ *proposed* that the unusual resistance to methylation is probably due to a heavy alkyl or alkylene group in the 6-position. Mani⁵ however showed subsequently that it was possible to methylate the third hydroxyl group in artocarpin by prolonged treatment with dimethyl sulphate and potassium carbonate in acetone (or methyl n-propyl ketone) to give the fully methylated artocarpin trimethyl ether (m.p. 85°) which had no ferric colour. Similar instances are known in literature where a hydroxyl group which is difficult to methylate owing to chelation or steric hindrance can be methylated under drastic conditions.¹⁹ 3-(γ -Dimethylallyl)-phloracetophenone has thus been methylated to the trimethyl ether by boiling for 120 hours with dimethyl sulphate and potassium carbonate in acetone.²⁰ The preparation of the trimethyl ether of artocarpin did not proceed smoothly in every case and uniform yields were

not obtained in successive methylation experiments. The best yield of the completely methylated product (about 30 per cent) was obtained by carrying out the reaction in the lower boiling solvent, acetone, for a prolonged period (100 hr); the use of the higher boiling methyl *n*-propyl ketone, even for a shorter period (48 hr), led to partial resinification of the product, which was then difficult to purify.]

← Since the *o*-dinitrobenzene and gossypetone tests are both negative, two hydroxyl groups in isoartocarpin cannot be in *o*- or *p*-positions. The position para to one of the hydroxyl groups is unoccupied since a greenish brown colour is produced in the Gibbs test with dibromoquinone-chloroimide.

9) ← [By catalytic hydrogenation in presence of palladium on carbon, isoartocarpin absorbs ^{2.5} one mole of hydrogen in about half an hour and a second mole in about 20 hours. Both dihydro- and tetrahydroisoartocarpin are crystalline. Tetrahydro-isoartocarpin was also obtained by refluxing isoartocarpin in ethanol with Raney nickel for 6 hours.] Tetrahydro-isoartocarpin gives a yellow solution in aqueous sodium hydroxide, a reddish brown colour with alcoholic ferric chloride, and a pink colour with magnesium and hydrochloric acid. It does not form an

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oxime or dinitrophenylhydrazone.

(2) Alkaline hydrolysis of isoartocarpin dimethyl ether with boiling 10 per cent ethanolic potassium hydroxide for 14 hours yielded 2-hydroxy-4-methoxybenzoic acid (XV) as the bicarbonate soluble part. Although isoartocarpin is not a flavonol, it is remarkable that its dimethyl ether undergoes ring fission under conditions similar to those normally used for the degradation of flavonol methyl ethers. Under these conditions both artocarpin and artocarpin dimethyl ether ^{are} remained unaffected. The acid (XV) gives a red-violet colour with ferric chloride and its identity was established by a mixed melting point with authentic 2-hydroxy-4-methoxybenzoic acid. [The formation of the acid (XV) from isoartocarpin dimethyl ether, which contains no phenolic hydroxyl group, indicated that one of the two C₅ residues in isoartocarpin may be attached to the 2'-position. ^{occupied by a readily hydrolyzable alkoxy group.} ^{showing} ^E]

Alkali fusion of tetrahydroisoartocarpin gave β -resorcylic acid and a phenol (XVI), C₁₂H₁₈O₃, m.p. 88°, which contained one methoxyl group and one C-alkyl group, (E) When the phenol was coupled with diazotized aniline, the product was a bisazo dye, identified as 4,6-bisazo-2-^{phenyl} ^{the} TH isoamylphloroglucinol-1-methyl ether (XVII). The mixed melting point of the phenol and its bisazo dye respectively

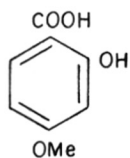
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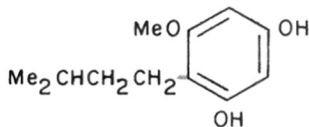
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with the phenol obtained from the alkali fusion of tetrahydroartocarpin and the corresponding bisphenylazo derivative remained undepressed. [These results indicate that one of the C₅ residues in isoartocarpin is attached to position 6- or 8-, probably in the 6-position on biogenetic grounds, since artocarpin carries an isopentenyl group in the 6-position of the flavone nucleus. The constitution of this phenol (XVI) was established by Dave by its synthesis. Phloroisovalerophenone was selectively acetylated to 2-hydroxy-4,6-diacetoxyisovalerophenone, which on methylation and deacetylation gave 2-methoxy-4,6-dihydroxyisovalerophenone. Reduction of the latter by Raney nickel in alcohol gave a mixture of compounds, and the hexane-soluble fraction was identified by Dave as C-isoamyl-phloroglucinol 2-methyl ether (XVI), m.p. 58-60°, by the mixed melting point with the phenol obtained from tetrahydroartocarpin by alkaline hydrolysis. The corresponding bisazo dye prepared by coupling with diazotized aniline was also identical. Vandewalle and Verzele²² have recently synthesized (XVI) by starting with 1-carbomethoxy-phloroglucinol-4-methyl ether (XVIII). The latter compound was monoalkylated by isoprenyl bromide to methyl 4-methoxy-2,6-dihydroxy-3-YY-

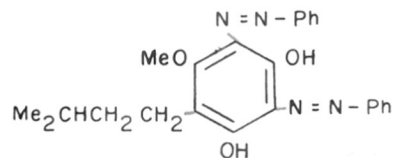
dimethylallylbenzoate (XIX). Hydrogenation and removal of the carbomethoxy group gave 1-isoamylphloroglucinol-2-methyl ether (XVI), m.p. 89-91°. The melting point recorded by Dave was not of the recrystallized product, because the quantity available to him was inadequate.



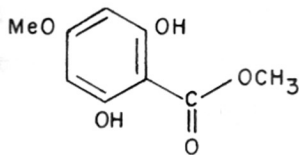
(XV)



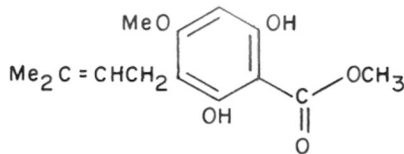
(XVI)



(XVII)

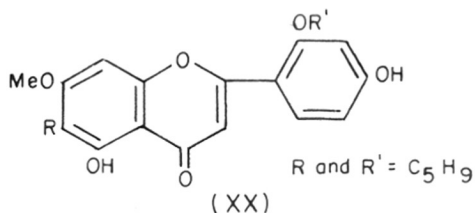


(XVIII)



(XIX)

The formation of 2-hydroxy-4-methoxybenzoic acid by the alkali fission of isoartocarpin dimethyl ether has shown that a C_5H_9 residue is probably present as an ether group in the 2'-position. Isoartocarpin may therefore be tentatively represented as (XX).

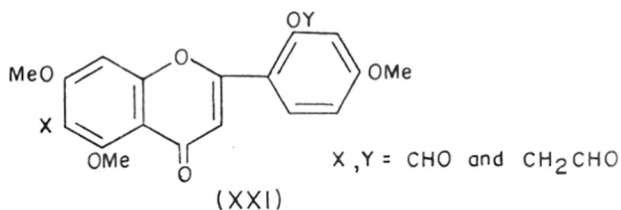


As mentioned earlier, isoartocarpin contains two olefinic bonds, one of which undergoes hydrogenation much more rapidly than the other. The structure of the side-chains in isoartocarpin has been established by ozonolysis of isoartocarpin dimethyl ether and dihydroisoartocarpin dimethyl ether. Isoartocarpin dimethyl ether was ozonized in ethyl acetate at -50° , and the ozonide decomposed by hydrogenation in presence of palladized carbon. The volatile products were removed by distillation of ethyl acetate, and converted to the dinitrophenylhydrazones, identified by paper chromatography as the dinitrophenylhydrazones of acetone and isobutyraldehyde. From the mixture of acetone and isobutyraldehyde dinitrophenylhydrazones in ethanol the latter crystallizes out first, and by repeated

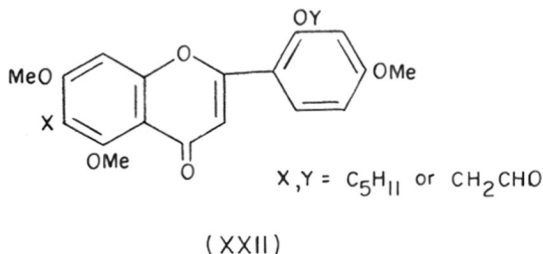
recrystallization from ethanol, isobutyraldehyde dinitrophenylhydrazone could be isolated in pure form and its identity further established by mixed melting point with an authentic sample. Concentration of the mother-liquors yielded acetone dinitrophenylhydrazone, obtained in pure form after several crystallizations and identified by mixed melting point with an authentic sample. The isolation of acetone and isobutyraldehyde indicates the unsymmetrical disposition of the double bonds in the side-chains. Artocarpin and its dimethyl and trimethyl ethers on ozonolysis yielded the same volatile products.⁵

9) [The nonvolatile product] was directly obtained in crystalline form and purified by repeated recrystallization from ethyl acetate. The substance [corresponded in its elementary analysis to the dialdehyde (XXI), but with one molecule of water of crystallization.] ^{III; R = CHO} The formation of this dialdehyde on ozonolysis proves that the two ethylenic bonds in isoartocarpin are present in two side-chains. The dialdehyde (XXI) was found to be stable to oxidation with potassium permanganate in acetone at 0° and at room temperature. However, when the oxidation was carried out at water-bath temperature, a small amount of 2-hydroxy-4-methoxybenzoic acid was isolated. The formation of the dialdehyde (XXI) in the ozonolysis of isoartocarpin

dimethyl ether, together with isobutyraldehyde and acetone, shows that R and R' are $\text{Me}_2\text{CH}-\text{CH}=\text{CH}-$ and $\text{Me}_2\text{C}=\text{CHCH}_2-$ in formula (XX) for isoartocarpin, and the remaining problem is to distinguish between them.



The ozonolysis of dihydroisoartocarpin dimethyl ether exclusively yielded acetone as the volatile product, as shown by paper chromatography of the dinitrophenylhydrazone. The identity of acetone dinitrophenylhydrazone was further established by mixed melting point with an authentic sample. [The nonvolatile component was a monoaldehyde, the elementary analysis of which corresponded to (XXII), ^(III; R=H) but with one molecule of water of crystallization as in the case of the dialdehyde ^(III) (XXI). It may be noted here that ^Pphenoxyacetaldehyde²³ crystallizes with one molecule of water of crystallization.]

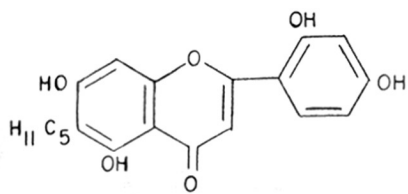


The monoaldehyde (XXII), like the dialdehyde (XXI), was stable to oxidation with potassium permanganate at 0° and at room temperature. Oxidation at water-bath temperature gave again a small amount of 2-hydroxy-4-methoxybenzoic acid. The same results were obtained when the oxidation was carried out on dihydroisoartocarpin dimethyl ether.

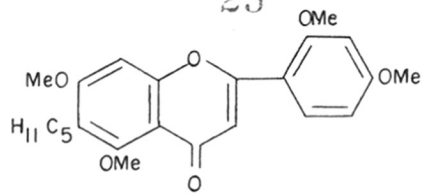
Because of the obvious structural similarity between artocarpin and isoartocarpin, indicated for instance by the similar behaviour towards catalytic hydrogenation, and on biogenetic grounds, the side-chain $-\text{CH}=\text{CH}-\text{CHMe}_2$ may be assumed to be in the 6-position, the double bond being in conjugation with the benzene ring. The side-chain occurring as an ether group in the 2'-position should then be $-\text{CH}_2-\text{CH}=\text{CMe}_2$.

In order to confirm the character of the 2'-ether group careful dealkylation studies were carried out. As a model, demethylation of tetrahydroartocarpin with hydriodic acid was studied, and 5,7,2',4'-tetrahydroxy-3,6-diisoamylflavone was isolated after chromatography. Demethylation of tetrahydroisoartocarpin under identical conditions yielded a compound (XXIII), the analysis of which corresponded to a tetrahydroxy-monoamylflavone;

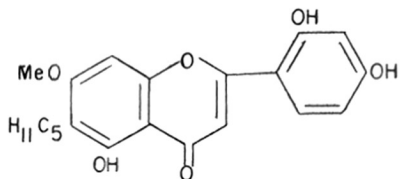
the action of hydriodic acid therefore resulted in the loss of one methyl and one amyl group. Methylation of this compound with dimethyl sulphate in acetone and potassium carbonate gave what seems to be 5,7,2',4'-tetramethoxy-6-isoamylflavone (XXIV). Attempted dealkylation of dihydroisoartocarpin with hydrobromic acid in acetic anhydride at water-bath temperature gave a product (XXV), which had lost a C_5 residue, but in which the methoxyl group was still intact. Methylation of this compound gave the same methyl ether as that obtained from the dealkylation and methylation of tetrahydroisoartocarpin. This clearly indicates that the second double bond is in the side-chain eliminated by treatment of dihydroisoartocarpin with hydrobromic acid. Dihydroisoartocarpin dimethyl ether on treatment with glacial acetic acid containing a trace of hydrochloric acid at water-bath temperature gave a compound which had a red ferric colour and corresponded in its elementary analysis to 5,2'-dihydroxy-7,4'-dimethoxy-6-isoamylflavone (XXVI). Geissman²⁴ has shown that the flavanone (XXVII), occurring in the bark of Melicope sarcococca, loses the C_5H_8 ($-CH_2CH=CMe_2$) fragment on treatment with a trace of mineral acid in hot acetic acid.



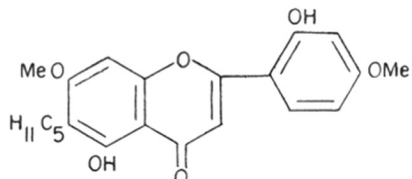
(XXIII)



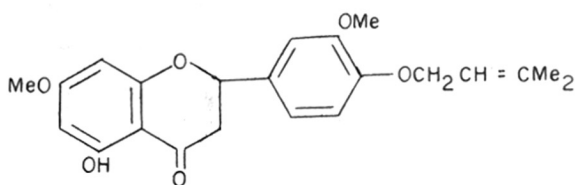
(XXIV)



(XXV)

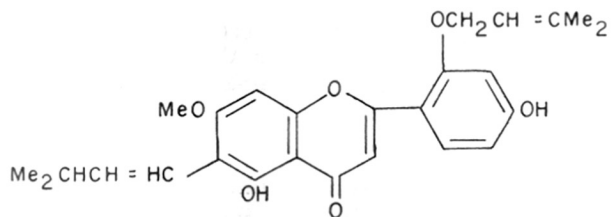


(XXVI)



(XXVII)

On the basis of the present experimental evidence isoartocarpin has the structure (XXVIII).



(XXVIII)

Ultraviolet absorption spectra

The spectra were recorded on a Beckman automatic recording spectrophotometer using 1 cm cells and were determined in ethanol solution. The spectra are suitably grouped in the Figures. The tables record the absorption maxima in $m\mu$ and intensities in ϵ .

TABLE 1. WAVELENGTHS AND INTENSITIES OF THE MAXIMA IN THE ULTRAVIOLET ABSORPTION SPECTRA OF THE CONSTITUENTS OF THE HEARTWOOD OF ARTOCARPUS INTEGRIFOLIA AND THEIR DERIVATIVES

Compound	λ_{\max}	ϵ	λ_{\max}	ϵ
Artocarpanone	288	21400	320- 330 (sh)	3990-3550
Artocarpanone trimethyl ether	284	28800	-	-
2,4,2',4',6'- Pentamethoxy- chalcone	-	-	305	17380
Artocarpetin	254 264 286	18200 19050 10200	355	26300
Artocarpetin trimethyl ether	242 262 286	19500 19500 12000	335	23000
Demethylated artocarpetin (5,7,2',4'- tetrahydroxy- flavone	252 265 286	19100 19100 12000	355	25100
Isoartocarpin	225 259 292	30200 23000 28200	370	27000

(Contd.)

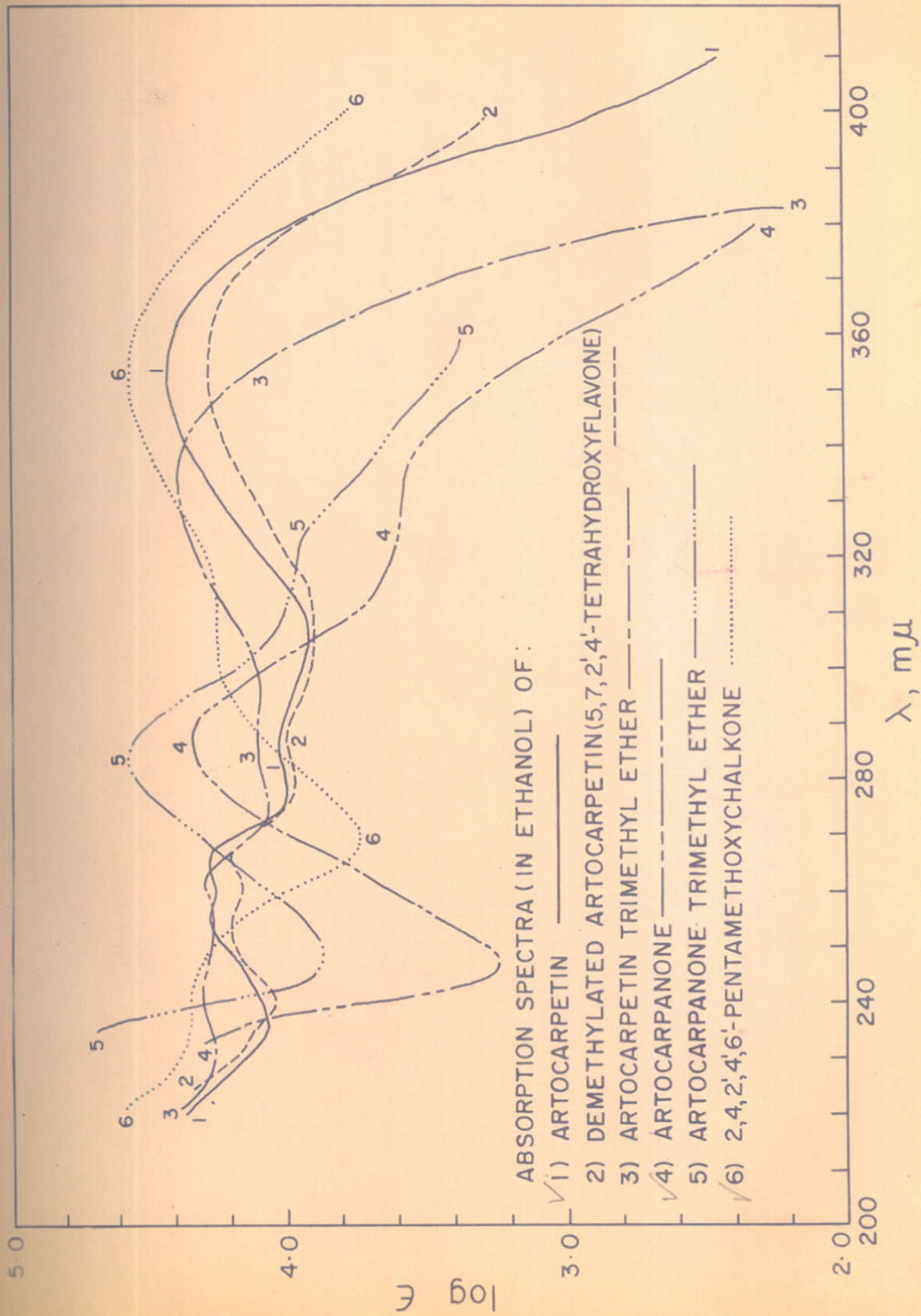


FIG. 1.

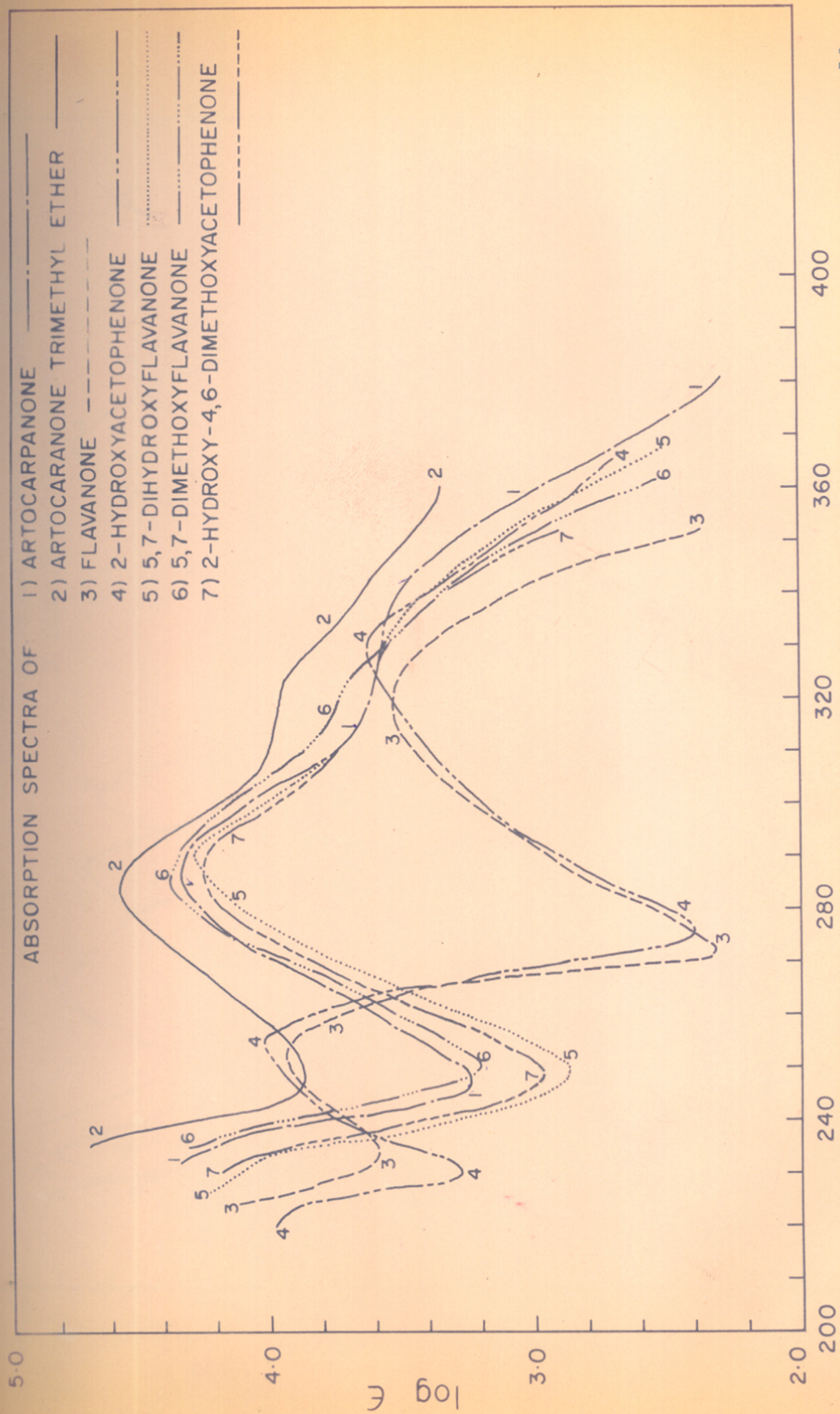
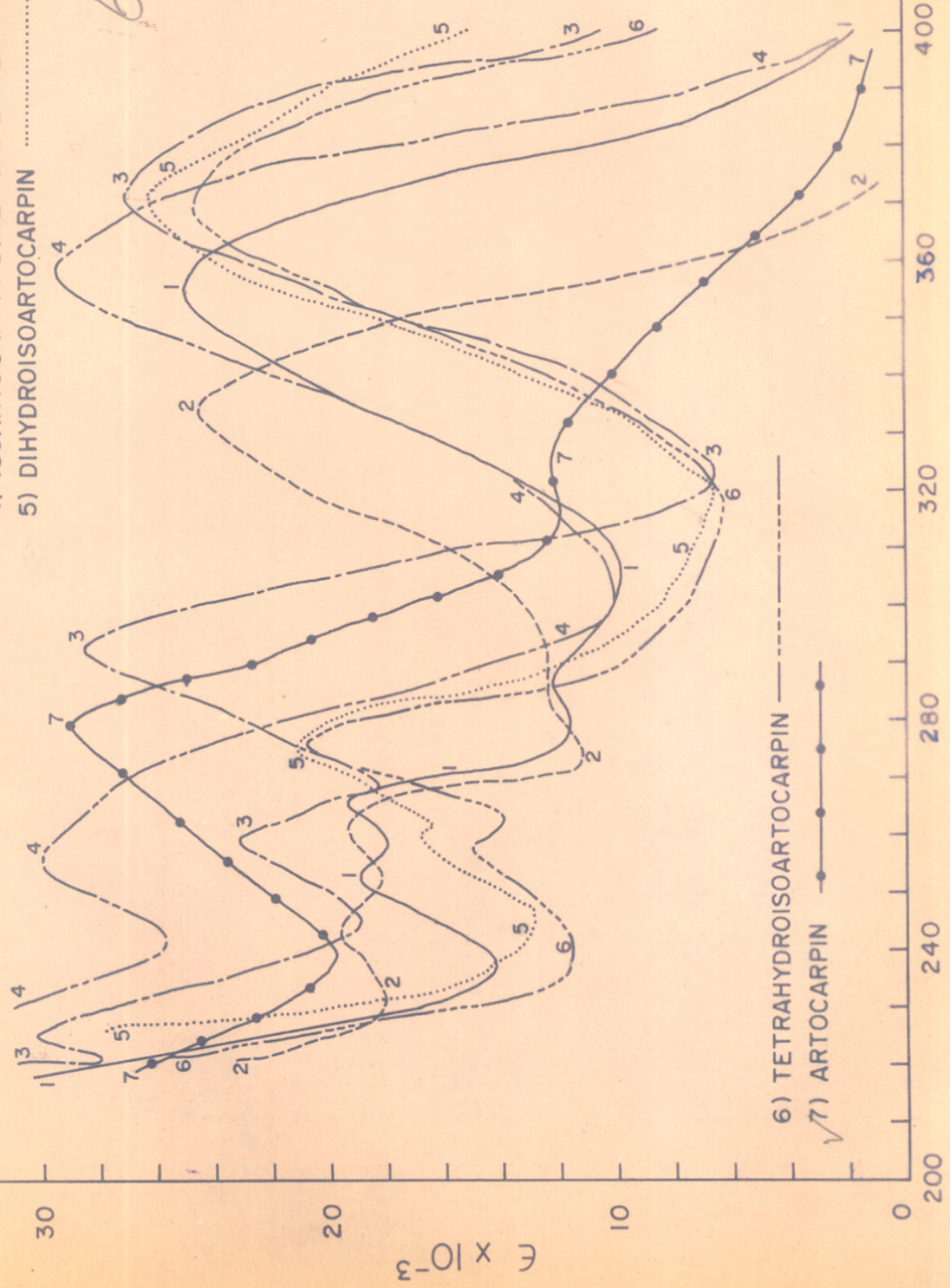


FIG. 2.

ABSORPTION SPECTRA OF: 1) ARTOCARPETIN ———
 2) ARTOCARPETIN TRIMETHYL ETHER - - - -
 3) ISOARTOCARPIN ———
 4) ISOARTOCARPIN DIMETHYL ETHER ———
 5) DIHYDROISOARTOCARPIN ······



6) TETRAHYDROISOARTOCARPIN ———
 7) ARTOCARPIN ———

$\lambda, m\mu$

FIG. 7

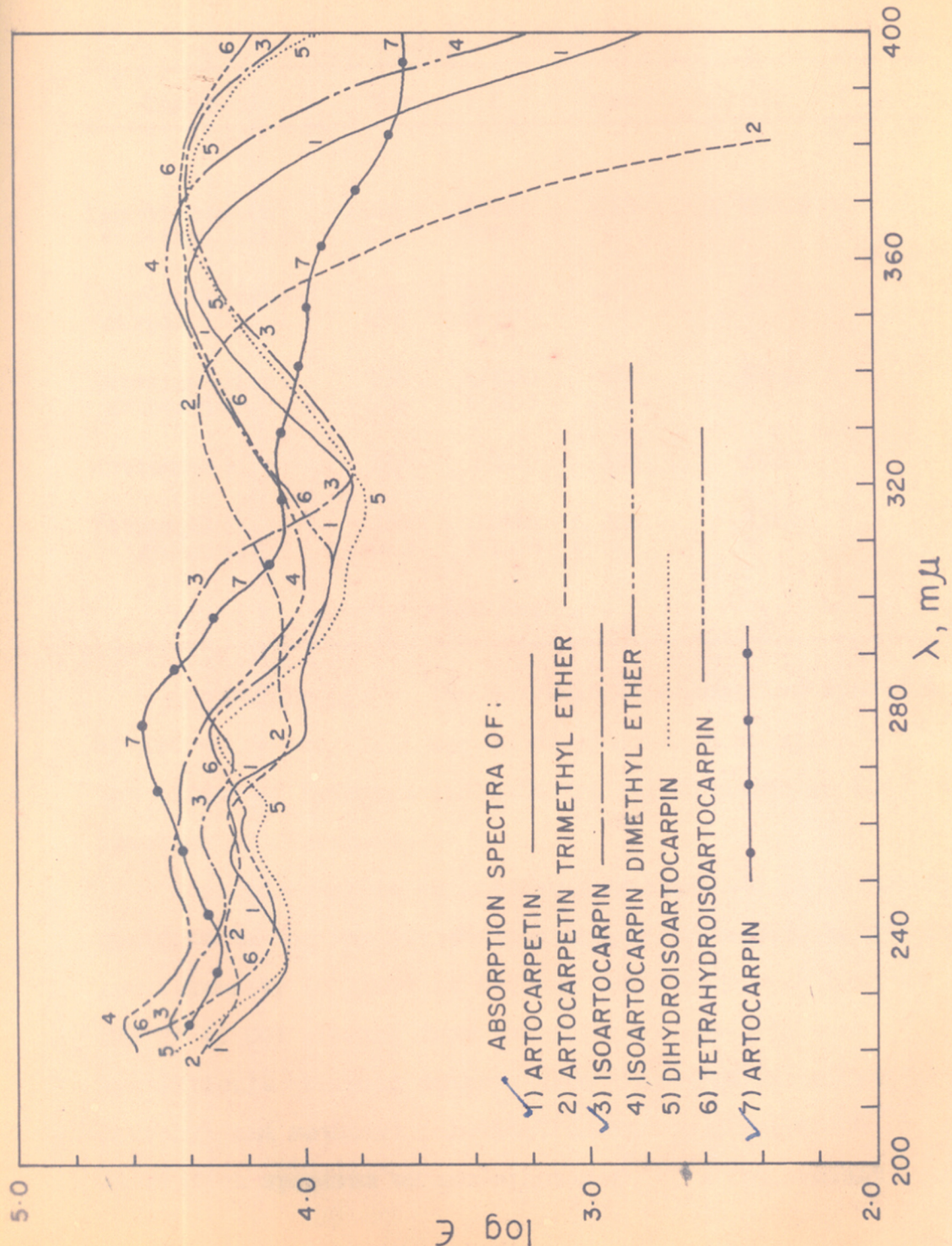


FIG. 4.

TABLE 1 (Contd.)

Compound	λ_{\max}	ϵ	λ_{\max}	ϵ
Isoartocarpin dimethyl ether	225	43700	358	29500
	255	30000		
Dihydroisoartocarpin	260	16600	370	25700
	276	21400		
Tetrahydroisoartocarpin	256	15200	370	24600
	276	20500		
Artocarpin	278	29200	324	12300
Tetrahydroartocarpin	235	22480	315	11600
	262	22300		

sh = shoulder

Artocarpanone. - The ultraviolet absorption spectrum of artocarpanone (XII) may be considered in relation to the effect of hydroxyl and methoxyl substitution on the spectrum of flavanone.

Acetophenone has an intense band near 240 $m\mu$ (ϵ 13000) assigned to the $\text{Ph}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}=\text{O}$ chromophore, a "benzenoid band" of low intensity (ϵ 1100) at 278 $m\mu$, and a very weak band at 319 $m\mu$ (ϵ 50) arising from the carbonyl group ($n \rightarrow \pi^*$ transition). Several authors have discussed the effect of hydroxyl and methoxyl substitution on the ultraviolet absorption spectrum of acetophenone.²⁵⁻²⁸ The present

interest is in phloroglucinol derivatives, and Table 2 records the spectra of some acetophenones substituted in the 2, 4 and 6-positions.²⁵⁻²⁸

TABLE 2. U.V. ABSORPTION SPECTRA OF ACETOPHENONES

Substitution in acetophenone	λ_{\max}	ϵ	λ_{\max}	ϵ
None ^(a)	240 278	13000 1100	319	50
2-Hydroxy ^(b)	256	10600	329	4300
2-Methoxy ^(b)	243	8000	300	3800
2,4-Dihydroxy ^(b)	270	13800	314	5754
2,6-Dihydroxy ^(b)	263	8318	334	2291
2,6-Dimethoxy ^(b)	240 279	2188 1660		
2-Hydroxy-4,6-dimethoxy ^(a)	288	17380	320 (sh)	3981
2,4,6-Trimethoxy ^(a)	274	5754	-	-

(a) = 95% ethanol (b) = cyclohexane
sh = shoulder

The spectra of flavanones are broadly similar to those of 2-hydroxy- and 2-methoxyacetophenones. Flavanone absorbs at 252 m μ (ϵ 8880) and 320 m μ (ϵ 3350). Hydroxyl or methoxyl substitution of flavanone in the 2-phenyl ring does not alter the character of the spectrum. The effect of a 7-hydroxyl is to produce

a bathochromic shift in the 256 $m\mu$ band, and the effect of a 5-hydroxyl to flatten the 320 $m\mu$ band to a shelf or shoulder. A remarkable feature in the spectrum of flavanone is the profound change which occurs on substitution by hydroxyl or methoxyl groups in the 5- and 7-positions. The flavanone spectrum closely resembles that of *o*-hydroxyacetophenone (see Fig. 2), exhibiting two bands in the 250 $m\mu$ and 320 $m\mu$ regions; but when hydroxyl or methoxyl groups are present in the 5,7-positions, the spectra are characterized by a single peak in the 280-290 $m\mu$ region. 5,7-Dihydroxyflavanone and its dimethyl ether have a band of about the same intensity (ϵ 17000-17800) in the 284-292 $m\mu$ region; but the shoulder at 320-330 $m\mu$ in the former spectrum has disappeared on methylation. The spectra of 5,7-dihydroxyflavanone and artocarpone are similar; and the same effect of methylation of the 5-hydroxyl group resulting in the disappearance of the shoulder in the 320 $m\mu$ region is noticed in the spectrum of artocarpone trimethyl ether (5,7,2',4'-tetramethoxyflavanone). When the spectra of 2-hydroxy-4,6-dimethoxyacetophenone and 2,4,6-trimethoxyacetophenone are compared, it is observed that methylation of the third hydroxyl group results in considerable lowering of the intensity of the long wavelength band.

TABLE 3. U.V. ABSORPTION SPECTRA OF FLAVANONES

Compound	λ_{\max}	ϵ	λ_{\max}	ϵ
Flavanone	252	8880	320	3350
2-Hydroxyflavanone	254 281 (sh)	8950 3400	322	3540
4'-Methoxyflavanone	252	12000	325	4100
5,7-Dihydroxyflavanone	292	17000	320-330 (sh)	4470-3700
5,7-Dimethoxyflavanone	284	17800	-	-
Artocarpinone	288	21400	320-330 (sh)	3990-3550
Artocarpinone trimethyl ether	284	28800	-	-

sh = shoulder

(A) Artocarpin and isoartocarpin. Flavones show two absorption bands in the near ultraviolet region: one near 250 $m\mu$ and the other in the 300-360 $m\mu$ region. Flavone, the parent member of the group, absorbs at 250 $m\mu$ (ϵ 12600) and 298 $m\mu$ (ϵ 15850). The 3-hydroxy derivative, flavonol, absorbs at 239, 305 and 348 $m\mu$, the additional band being associated with the additional possibility of tautomerism; etherification of the 3-hydroxyl restores the character of the flavone spectrum. (29) The present discussion is limited to the ultraviolet spectrum of

artocarpetin, artocarpin and isoartocarpin (and their ^{cyclic} related flavones. ~~but are not briefly discussed in relevant show~~ ^{in the long wave region} ~~the steric effect of substituents in the 3-position.~~ ~~(S)~~

Changes which occur in the spectrum of flavone

by hydroxyl and methoxyl substitution have been explained by Skarzynski (1939) on the basis of chromone as the main chromophore;²⁹ by Aronoff³⁰ in terms of resonance structures involving the carbonyl group; and by Chen³¹ on the analogy of the x and y bands of Lewis and Calvin, ascribed to polarisation along the main axis of the molecule and along the perpendicular axis, involving electronic transitions in the chalcone and γ -pyrone components of the flavone skeleton.

The effect of hydroxyl substitution on ultraviolet absorption maxima of flavone is shown in Table 4, the examples being chosen from the point of view of the Arto-carpus pigments. The intensities of the maxima are not available for most of the flavones. The profound effect of chelation in 5-hydroxyflavone is shown by large red shifts in both the flavone bands. The 7-hydroxyflavone spectrum on the other hand closely resembles the flavone spectrum, except for a small hypsochromic shift in the short wavelength band and a bathochromic shift of about 10 m μ in the long wavelength band. The absorption spectrum of 5,7-dihydroxyflavone (chrysin) combines the features of the spectra of 5- and 7-hydroxyflavones. The

spectra of 2'- and 4'-hydroxyflavone and of 2',4'- and 3',4'-dihydroxyflavones are very similar, but a closer study is not possible in the absence of intensity data.³¹ There is a disagreement on the positions of the maxima for 4'-hydroxyflavone as recorded by Hattori and by Skarzynski (marked H and S in Table 4).

TABLE 4. ABSORPTION MAXIMA OF SOME FLAVONES RELATED TO 5,7,2',4'-TETRAHYDROXYFLAVONE

Compound	λ_{\max}	ϵ	λ_{\max}	ϵ
Flavone	250	12600	297.5	15850
5-Hydroxyflavone	270.5	-	339	-
7-Hydroxyflavone	246	18200	308	20000
5,7-Dihydroxyflavone (chrysin)	269	28800	313	12000
2'-Hydroxyflavone	250 290	- -	333 -	- -
4'-Hydroxyflavone (S) (H)	248.5 245 286	- - -	328 323 -	- - -
2',4'-Dihydroxyflavone	250 290 (sh)	- - -	333 - -	- - -
3',4'-Dihydroxyflavone	250 290 (sh)	- - -	333 - -	- - -
5,7,4'-Trihydroxyflavone	265	17800	340	20400
5,7,2',4'-Tetrahydroxyflavone	252 265 286	19100 19100 12000	355 - -	25100 - -
Artocarpetin	254 264 286	18200 19050 10200	355 - -	26300 - -
5,7,3',4'-Tetrahydroxyflavone	258	16600	355	19050
3,5,7,2',4'-Pentahydroxyflavone (morin)	264	18310	370	18180
3,5,7,2',4'-Pentamethoxyflavone	256	20410	319	14000

(Contd.)

TABLE 4 (Contd.)

Compound	λ_{\max}	ϵ	λ_{\max}	ϵ
3,5,7,3',4'-Pentahydroxy-flavone (quercetin)	256	18300	373	20720
3,5,7,3',4'-Pentamethoxy-flavone	249 262	20100 19900	336 -	22100 -

S = Skarzynski²⁹ H = Hattori³²
sh = shoulder

The spectra of artocarpetin (IV), its trimethyl ether and demethylated artocarpetin (5,7,2',4'-tetrahydroxyflavone) are given in Fig. 1. Methylation of the 7-hydroxyl group has little effect on the spectrum, because 5,7,2',4'-tetrahydroxyflavone and artocarpetin have very similar spectra. Both show three principal regions of absorption. There are two bands at about 254 $m\mu$ (ϵ 18200) and about 264 $m\mu$ (ϵ 19050) and a stronger band at 355 $m\mu$ (ϵ 26300). In between these two regions there is a narrow inflexion near 286 $m\mu$ (ϵ 10200). The trimethyl ether of artocarpetin, like artocarpetin, shows bands at 242 $m\mu$ (ϵ 19500) and 262 $m\mu$ (ϵ 19500) and an inflexion at 286 $m\mu$ (ϵ 12000); but in the long wavelength band, as anticipated, there is a considerable hypsochromic shift (335 $m\mu$; ϵ 23000).

The spectra of morin and 5,7,2',4'-tetrahydroxyflavone are very similar in the longer wavelength region (355-370 $m\mu$), although morin shows a less intense peak. Morin has

only one peak in ^{the} short wavelength region at 264 $m\mu$, while 5,7,2',4'-tetrahydroxyflavone shows bands at 252 $m\mu$ and 265 $m\mu$ and an inflexion at 286 $m\mu$. Their respective methyl ethers show the expected hypsochromic shifts; in addition the morin ether exhibits a splitting of the short wavelength band into two bands, both hypsochromically shifted.

The spectra of isoartocarpin (XXVIII), its dimethyl ether and its di- and tetrahydro-derivatives are given in Fig. 3. Isoartocarpin shows four absorption bands: 225 $m\mu$ (ϵ 30200), 259 $m\mu$ (ϵ 23000), 292 $m\mu$ (ϵ 28200) and 370 $m\mu$ (ϵ 27000).

There are differences to be observed between the spectra of artocarpetin and isoartocarpin. The long wavelength band of artocarpetin (355 $m\mu$) shows a bathochromic shift of 15 $m\mu$ in isoartocarpin. The inflexion at 286 $m\mu$ in artocarpetin is replaced by a well-defined peak at 292 $m\mu$ in isoartocarpin. The 254 $m\mu$ and 264 $m\mu$ bands of artocarpetin are replaced by a single band of higher intensity at 259 $m\mu$ in isoartocarpin. The short-wavelength high-intensity band in the 210-220 $m\mu$ region exhibited by substituted flavones occurs at 225 $m\mu$ in isoartocarpin.

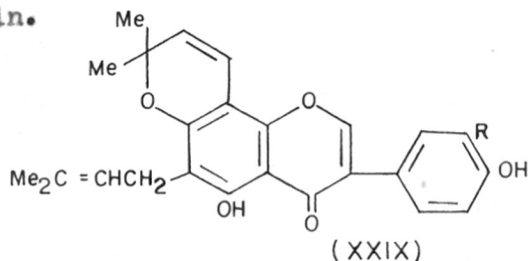
The changes which take place in the absorption

spectrum of isoartocarpin by progressive hydrogenation confirm the ozonization results, which showed that one ethylenic bond is conjugated with a benzene ring. The long wavelength band of isoartocarpin at $370\text{ m}\mu$ undergoes no shift by progressive hydrogenation, although there are small decreases in intensity. The characteristic change on hydrogenation to dihydroisoartocarpin is in the high intensity band of isoartocarpin at $292\text{ m}\mu$, which undergoes a hypsochromic shift to $276\text{ m}\mu$ together with a considerable decrease in intensity; further hydrogenation to tetrahydroisoartocarpin produces practically no change in the absorption spectrum, showing that the second stage of hydrogenation involves an isolated ethylenic bond. Similar changes were observed by Dave²¹ in the absorption spectra of artocarpin, dihydroartocarpin and tetrahydroartocarpin.

The reduction of a double bond in conjugation with an aromatic system is well known to produce a shift in the ultraviolet absorption (E band) towards shorter wavelength with a drop in the intensity,³³ e.g. the $244\text{ m}\mu$ (ϵ 12000) band of styrene shifts to $208\text{ m}\mu$ (ϵ 7800) in ethylbenzene. Osajin (XXIX; R = H) and pomiferin³⁴ (XXIX; R = OH), the yellow pigments of the osage orange, exhibit similar changes in the absorption spectra on

reduction to the dihydro- and tetrahydro-derivatives.

Thus the $275 \text{ m}\mu$ (ϵ 51300) band of osajin shifts to $272 \text{ m}\mu$ (ϵ 37200) and $271 \text{ m}\mu$ (ϵ 33900) respectively in the dihydro- and tetrahydro-osajin.



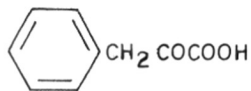
A comparison of the absorption spectra of artocarpetin, isoartocarpin and artocarpin in long wavelength region clearly shows the steric effect of the isopentenyl group in the 3-position of the flavone nucleus in artocarpin. [Artocarpetin and isoartocarpin have high intensity bands at 355 and $370 \text{ m}\mu$ respectively, but this band becomes a shoulder or inflexion of low intensity (ϵ 12300) at $324 \text{ m}\mu$ in artocarpin. The ^{more feature of the} spectrum of artocarpin therefore ^{is} mainly consists of a single high-intensity peak at $278 \text{ m}\mu$. The spectrum of artocarpin is somewhat similar to that of chrysin, ^(5, 7-dihydroxy) indicating that the bathochromic shift in the band in the ^{region} 300 - $360 \text{ m}\mu$, which should normally be produced by the hydroxyl substitution in the 2'- or 4'-positions, is eliminated by the steric effect of the 3-isopentenyl substituent, ^{wh.} such substitution in 3-position appears to prevent the complete coplanarity of the 2-phenyl and chromone ring systems.] This was confirmed by Dave²¹ by the synthesis of a series of 3-alkyl- and 3-arylflavones and the study of their ultraviolet spectra.

Biogenetic aspects

Among the numerous flavones isolated from plants prior to artocarpin, artocarpetin and isoartocarpin, morin was the only one in which the B-ring was a derivative of β -resorcylic acid. 'Lotoflavin,' which Dunstan and Henry¹⁵ isolated from Lotus arabicus and to which they assigned the structure 5,7,2',4'-tetrahydroxyflavone, has recently been shown¹⁰ to be a mixture of quercetin and kaempferol. It is a fact of considerable biogenetic interest that the four known flavones and the only flavanone (artocarpanone) with the hydroxylation pattern of resorcinol in the B-ring occur in the same plant, Artocarpus integrifolia. The A-ring in morin, artocarpin, artocarpetin, isoartocarpin and artocarpanone is derived from phloroglucinol. A fourth constituent of this wood, cyanomaclurin, has been formulated as a derivative of a 3-ketoflavan with similar hydroxyl substitution in both the A- and B-rings.³

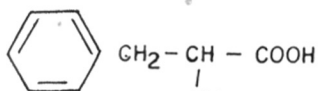
From the biogenetic point of view isoartocarpin is of extraordinary interest, because of the C₅ residues. One of the two C₅ residues is attached in the 6-position as in artocarpin, while the other is present as a 2'-ether group.

It has been shown that the phloroglucinol pattern of the A-ring of the flavonoid compounds arises from the

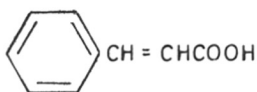


(XXX)

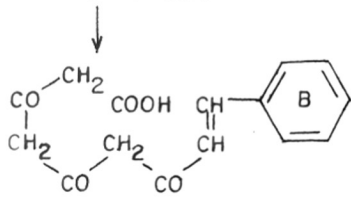
Phenyl pyruvic acid



Phenylalanine

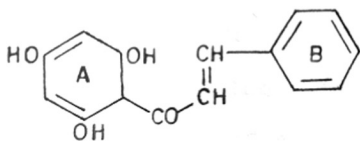


Cinnamic acid

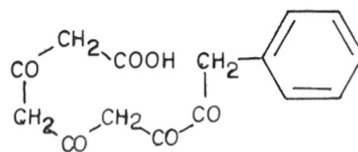


(XXXIV)

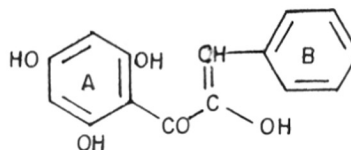
Cyclize



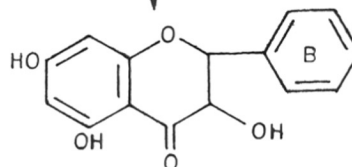
(XXXVII)



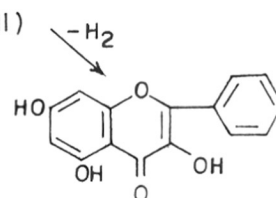
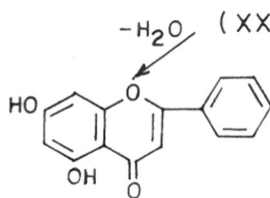
(XXXI)



(XXXII)

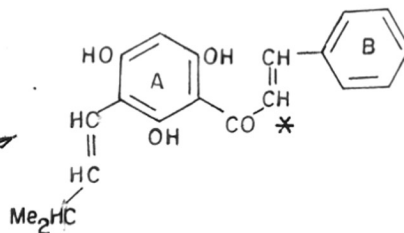


(XXXIII)



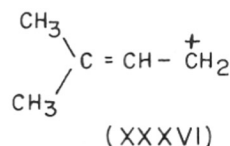
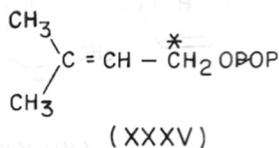
XXXVI; Cyclize
Rearrange

XXXVI, Cyclize



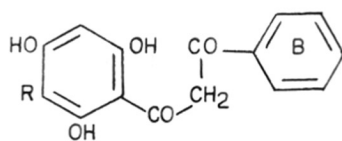
(XXXVIII)

condensation of three acetate units. As a source of ring B together with carbon atoms 2, 3 and 4 of flavone, phenylpyruvic acid or a hydroxylated derivative has been suggested by Neish³⁵ and Grisebach.³⁶ Grisebach has formulated a hypothetical scheme for the formation of quercetin in which phenylpyruvic acid (XXX) reacts with 3 moles of acetyl-coenzyme A to form (XXXI), the α -hydroxychalkone (XXXII) and the flavanone (XXXIII). An alternative route to the flavonoid framework through cinnamic acid and the triketo acid (XXXIV) was suggested by Birch,³⁷ and this route appeared more likely to Mani⁵ in the biosynthesis of artocarpin. The attachment of the isoprene unit in the 6-position of artocarpin was attributed by Mani to the attack of a 3,3-dimethylallyl pyrophosphate group (XXXV) or cation (XXXVI) on the triketo acid (XXXIV) or the phloroglucinol

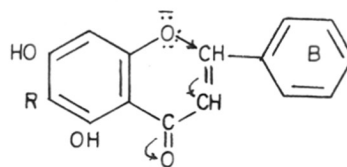


nucleus of the chalkone (XXXVII) followed by conjugation with the benzene ring to form (XXXVIII). The intervention of a second cation or "active isoprene unit" in several ways was suggested by him. (a) Isomerization

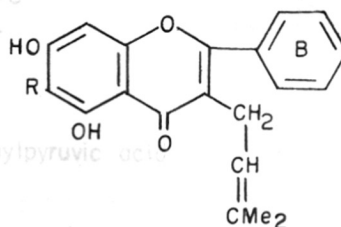
of chalcone (XXXVIII) to a flavanone, and attack of (XXXVI) on a reactive methylene group of flavanone followed by dehydrogenation and monomethylation to artocarpin. (b) The cation (XXXV) may attack the starred carbon atom in the chalcone (XXXVIII), the product then cyclizing to a flavanone and dehydrogenating to a flavone. Geissman has reported an enzyme carrying out a similar type of dehydrogenation in plant material (private communication). (c) The formation of the intermediate dibenzoylmethane has not been completely ruled out in the biogenetic scheme (XXXIX). (d) Ionisation of a phenolic hydroxyl group and the electron drift as shown in (XL), leading to a carbanion susceptible to attack by (XXXVI), which then yields (XLI) on cyclisation and dehydrogenation.



(XXXIX)

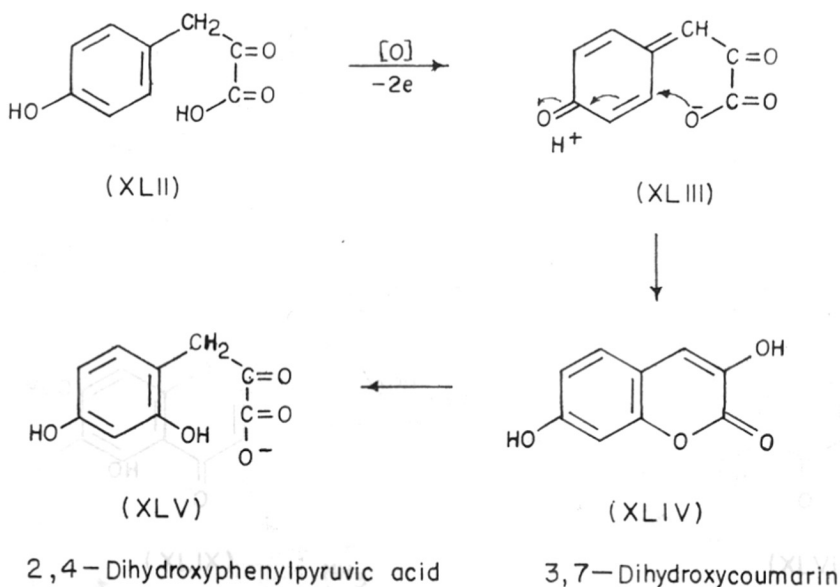


(XL)



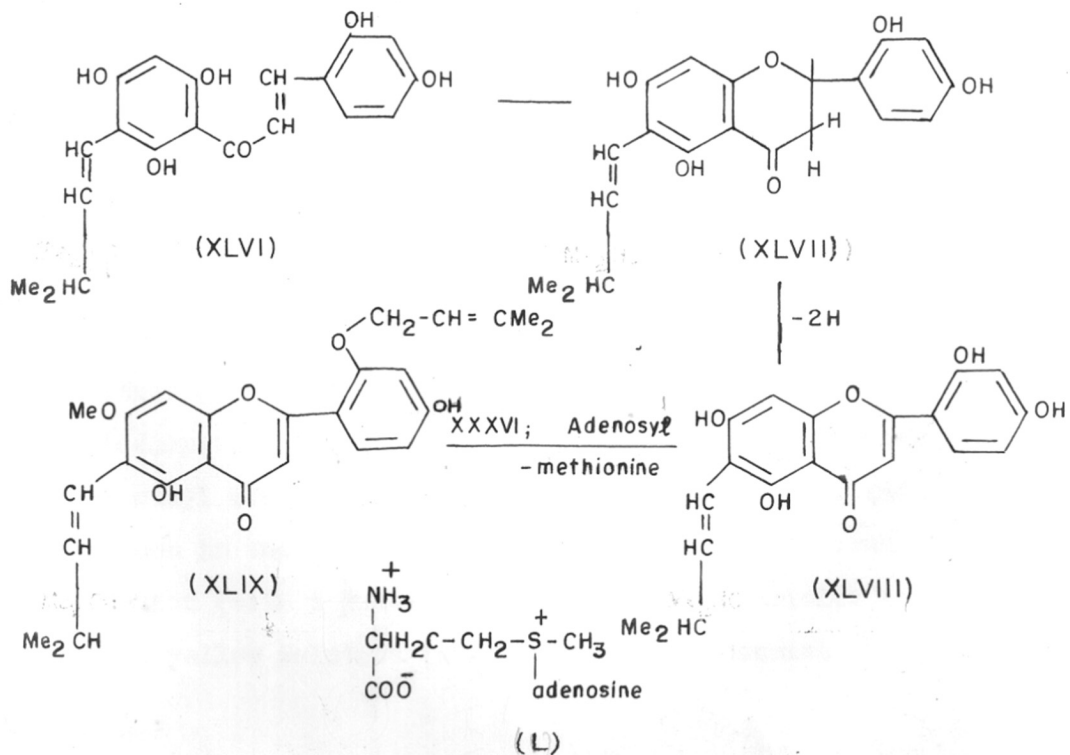
(XLI)

The nature of the intermediate involved in the actual formation of the ring B has not been determined so far. *p*-Hydroxyphenylpyruvic acid (XLII) may get oxidized to give (XLIII), which then cyclizes by an indirect quinonoid addition to give 3,7-dihydroxycoumarin (XLIV). The latter compound undergoes a base-catalysed ring opening to give 2,4-dihydroxyphenylpyruvic acid (XLV). The intramolecular hydroxylation step is suggested by the work of Senoh and Witkop on the catecholamines.³⁹ Further the biosynthesis of coumarin by the shikimic acid pathway involves *o*-hydroxylation of cinnamic acid.³⁵



In the formation of isoartocarpin the attachment of the first "active isoprene unit" may take place as suggested by Mani. The chalcone (XLVI) may then cyclize to the flavanone (XLVII) and dehydrogenate to the flavone (XLVIII). At this stage the second cation may attack the hydroxyl group in the 2'-position to give (XLIX).

S-adenosyl-methionine (L), which has been shown to be the reactive intermediate in transmethylation reactions in plants and animals, is probably involved in the methylation of the 7-hydroxyl group in artocarpin, isoartocarpin, artocarpetin and artocarpanone at some stage of biogenesis.



E X P E R I M E N T A L

Isolation of artocarpetin

(a) The coarsely powdered heartwood (2 kg) was extracted in a Soxhlet with benzene for 48 hr. Evaporation of the extract to dryness yielded a brown semi-solid mass, which was triturated with cold methanol. The yellow residue crystallized from glacial acetic acid in yellow needles (0.5 g), m.p. 310° . (Found: C, 63.7; H, 3.8; OMe, 10.0. $C_{16}H_{12}O_6$ requires: C, 64.0; H, 4.0; OMe, 10.3%). Artocarpin⁴ was recovered from the methanol mother liquor.

(b) The powdered heartwood (2 kg) was extracted with 95 per cent ethanol for 24 hr. Ethanol was then distilled off as far as possible. The syrupy mass was mixed with the alcohol-extracted wood (80 g), dried at 80° , and extracted in a Soxhlet with benzene. Treatment of the benzene extract as in (a) yielded yellow needles (0.4 g), m.p. 310° . The wood was then extracted with ether for 48 hr. The ether extract was shaken with saturated $NaHCO_3$ solution to remove a bicarbonate-soluble fraction, washed with water, dried, and evaporated. The residue on treatment with methanol as above yielded a further quantity of artocarpetin (1 g), m.p. 310° . Artocarpetin is sparingly soluble in methanol, ethanol and ethyl acetate, and readily soluble in acetone and dioxane in the cold. In conc H_2SO_4 it forms an orange solution (with a green fluorescence in ultraviolet light) and a yellow solution (with a green fluorescence in

ultraviolet light) in aqueous sodium hydroxide. The alcoholic solution gives an intense reddish brown ferric reaction, and with magnesium and HCL an orange colour. A purple colour is produced after acidification in the sodium amalgam reduction test. In Wilson's boric acid test the yellow solution becomes deeper in colour with a weak green fluorescence in ultraviolet light. In the Gibbs test a green colour is obtained. The o-dinitrobenzene and gossypetone tests are negative.

Acetylation of artocarpetin

A mixture of artocarpetin (0.5 g), acetic anhydride (5 ml) and dry pyridine (a few drops) was refluxed for 4 hr. The orange solution became pale yellow. Cooling and adding to crushed ice yielded a brown oil which slowly solidified, and crystallized from benzene-hexane in colourless needles (0.4 g), m.p. 120° . (Found: C, 62.4; H, 4.2; Ac, 30.4. $C_{22}H_{18}O_9$ requires: C, 62.0; H, 4.3; Ac, 30.3%).

Methylation of artocarpetin

A mixture of artocarpetin (0.5 g), acetone (50 ml), potassium carbonate (4 g) and dimethyl sulphate (2 ml) was refluxed for 36 hr. Distillation of acetone and treatment of the residue with water yielded a product which crystallized from benzene-hexane in yellow needles, m.p. 176° .

(Found: C, 66.8; H, 5.1; OMe, 36.3; mol. wt. by the Rast method, 331. $C_{19}H_{18}O_6$ requires: C, 66.7; H, 5.4; OMe, 36.2%; mol. wt. 342). The substance does not give a ferric colour.

Demethylation of artocarpetin

A solution of artocarpetin (0.2 g) in glacial acetic acid (4 ml) and hydriodic acid (d 1.7; 4 ml) was refluxed for 4 hr. After cooling, the mixture was poured into a saturated solution of sodium bisulphite. The product crystallized from dil acetic acid in brownish yellow needles (0.08 g), m.p. above 300° (decomp.). After running a methanolic solution through a short column of Florex and recrystallization of the substance recovered from the percolate, the m.p. was 330° (decomp), undepressed by mixing with 5,7,2',4'-tetrahydroxyflavone.⁶ (Found: C, 63.3; H, 4.0. $C_{15}H_{10}O_6$ requires: C, 63.0; H, 3.5%).

Alkaline hydrolysis of artocarpetin

(a) Artocarpetin (0.5 g) was heated at 100° under reflux with KOH (2.5 g) dissolved in water (5 ml) for 4 hr in a current of hydrogen. The solution was then diluted with water, saturated with carbon dioxide, filtered to remove a little silica, and extracted with ether (extract A). The aqueous layer was acidified with dil H_2SO_4 , saturated with ammonium sulphate and

extracted with ether. Evaporation of the ether gave a brown semi-solid substance; repeated crystallization from water yielded brown needles, m.p. 208-210° (decomp), identified as β -resorcylic acid by mixed m.p. and paper chromatography, using a 4:1:5 mixture of n-butanol, formic acid and water (R_f 0.90).

From the ether extract (A) a phenol was obtained which distilled at 118-120°/10⁻² mm. The substance gives a brown ferric colour, and its identity was established by coupling a NaHCO₃ solution with excess of diazotized aniline. The reddish brown dye was dissolved in benzene and chromatographed on alumina, using the same solvent for development and elution. The first fraction led to reddish brown needles, m.p. 128°, identified as 2,4-bis-benzeneazophenol. The second minor fraction was discarded, and the third fraction yielded bright red needles, m.p. 255° (m.p. 250-252°, Perkin and Allison⁷) after crystallizing from alcohol. (Found: C, 65.3; H, 4.5; N, 15.7. C₁₉H₁₆O₃N₄ requires: C, 65.5; H, 4.6; N, 16.1%). The m.p. was undepressed by mixing with the dye similarly obtained from authentic phloroglucinol monomethyl ether.

(b) A solution of artocarpetin (0.5 g) and KOH (2.5 g) in water (5 ml) was heated to gentle boiling for 90 min in a current of hydrogen. On working up as in (a),

a phenol was obtained, which distilled at 145-150°/0.5 mm and on cooling in an ice-salt mixture solidified to colourless needles, melting at 139° after crystallization from water. The mixed m.p. with 2,6-dihydroxy-4-methoxyacetophenone was undepressed.

2-Hydroxy-4,6-dimethoxyacetophenone³⁹

The following is an improved procedure for the preparation of this substance. A mixture of phloracetophenone (10.0 g; 1 mole), acetone (500 ml), anhydrous potassium carbonate (80 g), and dimethyl sulphate (12.4 ml; 2.2 moles) was refluxed for 12 hr. Distillation of the solvent and treatment of the residue with water resulted in a colourless precipitate, which was taken up in ether. The ether extract was washed with 2% aqueous NaOH, and the aqueous solution acidified with conc HCl at 15°. The colourless precipitate (10 g) crystallized from hexane in needles, m.p. 82° (lit,³⁹ 82-83°). The ether layer led to a product which crystallized from hexane in colourless needles (0.1 g), m.p. 104°, identified as 2,4,6-trimethoxyacetophenone.

2-Hydroxy 4,6-dimethoxyphenyl 2,4-dimethoxystyryl ketone

To a warm solution of 2-hydroxy-4,6-dimethoxyacetophenone (1 g) and 2,4-dimethoxybenzaldehyde (0.8 g)

in ethanol (10 ml), 50% NaOH solution (2 g) was added. After standing for 4 hr the mixture was neutralized with dil HCl. The yellow product crystallized from 95% alcohol in shining yellow needles (0.7 g), m.p. 152° (Kostanecki *et al.*¹⁷ m.p. 152°; Mitter and Saha,¹⁸ m.p. 124°). (Found: C, 66.4; H, 5.8. $C_{19}H_{20}O_6$ requires: C, 66.3; H, 5.8%). The substance gives a red ferric colour.

5,7,2',4'-Tetramethoxyflavone

The above chalcone (0.6 g) amyl alcohol (12 ml) and selenium dioxide (0.6 g) were refluxed at 140° for 24 hr. Selenium was filtered off, the filtrate steam-distilled, and the yellow sticky residue taken up in benzene and chromatographed on alumina. The major band was eluted with benzene-ethyl acetate (1:1) and led to yellow needles (0.13 g), m.p. 176°, not depressed by mixing with artocarpetin trimethyl ether (Doperto *et al.*,¹⁰ m.p. 179-180°; Gupta and Seshadri,¹² m.p. 184-186°). (Found: C, 66.7; H, 5.5. $C_{19}H_{18}O_6$ requires: C, 66.7; H, 5.4%). The substance does not give a ferric colour, and gives a reddish orange colour with magnesium and HCl.

5,4'-Dihydroxy-7,2'-dimethoxyflavone (VI)

(a) 5,7,2',4'-Tetramethoxyflavone (0.3 g) in acetic anhydride (6 ml) was heated with hydriodic acid (d 1.7;

6 ml) at 115° for 45 min. Worked up as usual, the product crystallized from glacial acetic acid in yellow needles, (0.1 g), m.p. 305°. (Found: C, 64.5; H, 4.8; OMe, 18.6. $C_{17}H_{14}O_6$ requires: C, 65.0; H, 4.5; OMe, 19.7%).

(b) A mixture of the tetramethoxyflavone (0.4 g), glacial acetic acid (4 ml) and 63% hydrobromic acid (4 ml) was refluxed for 4 hr. The product crystallized from glacial acetic acid in yellow needles (0.1 g), m.p. 305°, undepressed by mixing with the product obtained by method (a).

Alkaline hydrolysis of (VI)

Compound (VI) (0.5 g) was heated at 100° under reflux with KOH (2.5 g) in water (5 ml) for 4 hr in a current of hydrogen. Worked up as in the case of the alkaline hydrolysis of artocarpetin, a phenol and an acid were isolated. The phenol was identified as phloroglucinol monomethyl ether through its bisbenzeneazo derivative, m.p. 255°. The acid crystallized from water in colourless needles, m.p. 189°, and was identified as 4-hydroxy-2-methoxybenzoic acid, prepared as described below.

Methyl 4-benzyloxy-2-hydroxybenzoate

A mixture of methyl β -resorcylate (2 g), acetone

(100 ml), anhydrous potassium carbonate (10 g) and benzyl chloride (1.5 ml) was refluxed for 14 hr. The acetone solution led to a product which crystallized from benzene-hexane in colourless needles (1.8 g), m.p. 102°. (Found: C, 70.2; H, 5.3. $C_{15}H_{14}O_4$ requires: C, 69.8; H, 5.4%). The substance gives a reddish brown ferric colour.

Methyl 4-benzyloxy-2-methoxybenzoate

A mixture of methyl 4-benzyloxy-2-hydroxybenzoate (1.5 g), acetone (100 ml), potassium carbonate (10 g) and dimethyl sulphate (1 ml) was refluxed for 24 hr. The product, which was free from ferric colour, crystallized from benzene-hexane in colourless needles (1.2 g), m.p. 90°. (Found: C, 70.6; H, 5.7. $C_{16}H_{16}O_4$ requires: C, 70.6; H, 5.9%).

4-Benzyloxy-2-methoxybenzoic acid

Hydrolysis of the ester (1 g) with 5% alcoholic KOH gave an acid which crystallized from benzene-hexane in colourless needles (0.7 g), m.p. 112°. (Found: C, 70.0; H, 5.0. $C_{15}H_{14}O_4$ requires: C, 69.8; H, 5.4%).

4-Hydroxy-2-methoxybenzoic acid

4-Benzyloxy-2-methoxybenzoic acid (0.4 g) was added to a suspension of 12% palladized carbon (50 mg) in

ethanol (20 ml) after saturating the catalyst with hydrogen. In 30 min there was an absorption of 40 ml (slightly less than 1 mole) of hydrogen. The product crystallized from water in colourless needles (0.2 g), m.p. 190° (m.p. $187-189^{\circ}$, Bergmann and Dangschat¹⁴). (Found: C, 57.1; H, 4.3. $C_8H_8O_4$ requires: C, 57.1; H, 4.8%). The mixed m.p. with the acid obtained by the alkaline hydrolysis of (VI) remained undepressed.

2-Hydroxy-4,6-dimethoxyphenyl 2,4-dibenzoyloxystyryl ketone

A solution of 2-hydroxy-4,6-dimethoxyacetophenone (5 g) and 2,4-dibenzoyloxybenzaldehyde⁴⁰ (8 g) in alcohol (50 ml) and 50% aqueous NaOH (10 g) was heated on a water-bath in a nitrogen atm. for 30 min. After leaving at room temp for 4 hr and acidification, the product was crystallized from a large volume of methanol. The orange needles (4.6 g) had m.p. 118° . (Found: C, 74.6; H, 5.5. $C_{31}H_{28}O_6$ requires: C, 75.0; H, 5.6%). The substance gives a red ferric colour.

2',4'-Dibenzoyloxy-5,7-dimethoxyflavone (XI)

The chalkone described above (4.4 g), amyl alcohol (90 ml) and selenium dioxide (4.4 g) were heated under reflux for 24 hr. After filtering off selenium and removing amyl alcohol by steam distillation, the brownish

yellow residue was extracted with benzene, and the solution chromatographed on alumina. Elution with 1:1 benzene-ethyl acetate and crystallization from the same solvent gave yellow needles (2.2 g), m.p. 155°. (Found: C, 75.4; H, 5.2. $C_{31}H_{26}O_6$ requires: C, 75.3; H, 5.3%). The substance gives a red colour with magnesium and HCl, and absence of the chalcone is shown by a negative ferric test.

2',4'-Dihydroxy-5,7-dimethoxyflavone

The dibenzyl ether (XI; 1 g) was heated with acetic acid (10 ml) and conc HCl (10 ml) on a water-bath for 1 hr. The mixture was steam-distilled and the precipitate dissolved in 5% KOH solution, filtered and the clear filtrate acidified. The yellow precipitate crystallized from a large volume of ethanol in yellow needles (0.6 g), m.p. 321°. (Found: C, 61.2; H, 4.4; loss of water on heating at 200°, 5.4. $C_{17}H_{14}O_6 \cdot H_2O$ requires: C, 61.4; H, 4.8; H_2O , 5.4%). After drying at 200°/0.5 mm for 4 hr, the substance melted at 324-325°. (Found: C, 65.0; H, 4.5; OMe, 19.7. $C_{17}H_{14}O_6$ requires: C, 65.0; H, 4.5; OMe, 19.7%). The compound does not give a ferric colour.

5,2',4'-Trihydroxy-7-methoxyflavone (IV)

2',4'-Dihydroxy-5,7-dimethoxyflavone (0.4 g), acetic anhydride (12 ml) and hydriodic acid (d 1.7; 6 ml) were heated at 120° for 45 min. After working up as usual, an alcoholic solution of the product was run through a short column of Florex. Concentration of the percolate yielded yellow needles, m.p. 310°, not depressed by mixing with artocarpetin. (Found: C, 63.8; H, 3.7; OMe, 10.8. $C_{16}H_{12}O_6$ requires: C, 64.0; H, 4.0; OMe, 10.3%). The triacetate crystallized from benzene-hexane in colourless needles, m.p. 120°, not depressed by mixing with artocarpetin triacetate. (Found: C, 62.2; H, 4.7. $C_{22}H_{18}O_9$ requires: C, 62.0; H, 4.3%).

Isolation of artocarpanone

The powdered heartwood (2 kg) was extracted in a Soxhlet with benzene for 48 hr. Concentration of the extract to about 500 ml and cooling yielded a yellow product (3.5 g), which was filtered off and dissolved in the minimum quantity of methanol (20 ml) at room temp. Pale yellow needles (3 g) separated on cooling to 0°, and after recrystallization from ether-hexane melted at 210°. A further quantity (0.8 g) was recovered from the original methanol mother liquor. (Found: C, 64.0; H, 5.1; OMe, 9.9; mol. wt. by the Rast method, 310. $C_{16}H_{14}O_6$

requires: C, 63.6; H, 4.7; OMe, 10.3%; mol. wt. 302).

Artocarpanone dissolves in conc H_2SO_4 with a crimson colour. An intense purple colour is produced with conc HNO_3 . In aqueous NaOH the colour changes from yellow to red; in aqueous Na_2CO_3 artocarpanone gives a red colour. The alcoholic solution gives an intense reddish brown colour with alcoholic ferric chloride, a deep magenta colour with magnesium and HCl, and a wine-red colour with sodium amalgam and subsequent acidification. In the Gibbs test with 2,6-dichlorobenzoquinone-4-chloroimide a greenish blue colour is obtained. The *o*-dinitrobenzene and gossypetone tests for *o*- and *p*-dihydroxy groups are negative.

Acetylation of artocarpanone

A mixture of artocarpanone (0.4 g), acetic anhydride (4 ml) and dry pyridine (a few drops) was refluxed for 4 hr. Cooling and adding to crushed ice yielded a brown oil which slowly solidified and crystallized from methanol in colourless needles, m.p. 143° . (Found: C, 61.7; H, 5.0; Ac, 28.6. $C_{22}H_{20}O_9$ requires: C, 61.7; H, 4.7; Ac, 30.1%).

Methylation of artocarpone

(a) A mixture of artocarpone (0.5 g), acetone (50 ml), potassium carbonate (4 g) and dimethyl sulphate (0.5 ml) was refluxed for 12 hr. Distillation of acetone and treatment of the residue with water yielded a yellowish semi-solid mass which gave negative ferric colour and gave a magenta colour with magnesium and HCl. It was dissolved in benzene, and run through a column of alumina. The yellow percolate led to a product which crystallized from methanol in pale yellow prisms (0.4 g), m.p. 166° . (Found: C, 66.4; H, 6.0; OMe, 35.6; mol. wt. by the Rast method, 320. $C_{19}H_{20}O_6$ requires: C, 66.3; H, 5.8; OMe, 36.0% mol. wt. 344).

(b) When the reaction was repeated, using 2.5 ml of dimethyl sulphate and increasing the time of treatment to 48 hr, the product (0.45 g) crystallized from methanol in yellow needles, m.p. 128° , not depressed by mixing with 2,4,2',4',6'-pentamethoxychalkone, m.p. 128° (lit.,¹⁸ m.p. 124°). (Found: C, 67.0; H, 6.3; OMe, 43.8. $C_{20}H_{22}O_6$ requires: C, 67.0; H, 6.2; OMe, 43.3%). The compound does not give a ferric colour or a colour with magnesium and HCl.

(c) A solution of artocarpanone (0.5 g) in dry ether (10 ml) was mixed with diazomethane (0.6 g) in ether, and kept at 5° for 24 hr. Excess of diazomethane was destroyed with acetic acid, and after the removal of solvent the residue crystallized from methanol in yellow needles (0.4 g), m.p. 121°.

(Found: C, 65.7; H, 5.1; OMe, 26.0. $C_{18}H_{18}O_6$ requires: C, 65.4; H, 5.4; OMe, 28.2%). The substance gives a reddish brown ferric colour and a magenta colour with magnesium and HCl.

(d) A solution of artocarpanone (0.2 g) in dry methanol (5 ml) was mixed with diazomethane (0.3 g; about 10 moles) in dry ether. Working up as in (c), the product crystallized from methanol in yellow needles (0.15 g), m.p. 166°, not depressed by mixing with the compound obtained in (a). (Found: C, 66.2; H, 5.7. $C_{19}H_{20}O_6$ requires: C, 66.3; H, 5.8%).

Artocarpanone 2,4-dinitrophenylhydrazone

Prepared in the usual manner with the Brady reagent, the dinitrophenylhydrazone crystallized from ethanol in red needles, m.p. 245° (decomp). (Found: C, 55.2; H, 3.9; N, 11.0. $C_{22}H_{18}O_9N_4$ requires: C, 54.8; H, 3.7; N, 11.6%).

Alkaline hydrolysis of artocarpanone

A solution of artocarpanone (0.5 g) and KOH (2.5 g) in water (5 ml) was refluxed for 4 hr in an atm. of hydrogen. The solution was then diluted with water, saturated with carbon dioxide, and extracted with ether (A). The aqueous layer was acidified with dil H_2SO_4 , saturated with ammonium sulphate and extracted with ether (B). Evaporation of extract (B) gave a brown semi-solid substance, from which β -resorcylic acid was isolated and identified by paper chromatography. On evaporation of extract (A), a phenol was obtained which was distilled at $120^\circ/10^{-2}$ mm. It was identified as phloroglucinol monomethyl ether by coupling with diazotized aniline as described earlier.

5,7,2',4'-Tetramethoxyflavanone was prepared according to Kostanecki, Lampe and Tambor¹⁷ from 2'-hydroxy-2,4,4',6'-tetramethoxychalkone (0.5 g), ethanol (100 ml), HCl (3 ml) and water (9 ml) by refluxing the mixture for 24 hr. On cooling to room temp the orange-coloured chalkone (0.3 g), m.p. 152° , was recovered. Concentration and dilution of the filtrate gave a product which was dissolved in benzene, and chromatographed on alumina. A dark orange band remained at the top of the column, and elution with benzene gave a yellow percolate which led to yellow

needles (0.02 g), m.p. 166° , from methanol (lit,¹⁷ m.p. $167-168^{\circ}$); the mixed m.p. with artocarpanone trimethyl ether was undepressed. (Found: C, 66.1; H, 6.0. $C_{19}H_{20}O_6$ requires: C, 66.3; H, 5.8%).

Isolation of isoartocarpin

(a) The coarsely powdered heartwood (2 kg) was extracted in a Soxhlet with pet ether ($60-80^{\circ}$) for 48 hr. Evaporation of the extract to dryness yielded a brown mass, which was triturated with cold methanol. The yellow residue crystallized from glacial acetic acid in yellow needles (0.45 g), m.p. 270° . (Found: C, 71.2; 71.3; H, 5.9, 6.2; OMe, 7.51, 7.1; mol. wt. by the Rast method, 420, 425. $C_{26}H_{28}O_6$ requires: C, 71.5; H, 6.5; OMe, 7.1%; mol. wt., 436). Artocarpin was recovered from the methanol mother liquor.

(b) The coarsely powdered heartwood (2 kg) was extracted in a Soxhlet with benzene for 48 hr. Treatment of the benzene extract as in (a) yielded isoartocarpin in yellow needles (0.47 g), m.p. 270° , while artocarpin and artocarpanone remained in methanol. Evaporation of the methanol mother liquor to dryness, extraction of the residue with benzene (40 ml) and filtration of the hot solution gave artocarpanone as insoluble part (0.8 g),

m.p. 210°, while artocarpin (4.0 g), m.p. 174°, was isolated from benzene solution on cooling. Isoartocarpin is sparingly soluble in methanol, ethanol and ethyl acetate, and readily soluble in acetone and dioxane in the cold. In conc H_2SO_4 it forms a deep red solution (with a pale green fluorescence) and an orange solution (with a green fluorescence in ultraviolet light) in aqueous NaOH. It is insoluble in saturated solution of $NaHCO_3$. The alcoholic solution gives an intense greenish brown ferric reaction, and with magnesium and HCl a pink colour. A pale pink colour is produced after acidification in the sodium amalgam reduction test. In Wilson's boric acid test the yellow solution becomes deeper in colour with a weak green fluorescence in ultraviolet light. In the Gibbs test a greenish brown colour is obtained. The o-dinitrobenzene and gossypetone tests are negative.

Acetylation of isoartocarpin

(a) A mixture of isoartocarpin (0.2 g), acetic anhydride (4 ml) and dry pyridine (a few drops) was refluxed for 4 hr. The orange solution became pale yellow. Cooling and adding to crushed ice yielded a brown oil, which slowly solidified. It crystallized from methanol in very pale yellow needles (0.15 g), m.p. 215°. (Found;

C, 69.8, 69.8; H, 5.9, 5.7; Ac, 14.0, 14.4; mol. wt. by the Rast method, 475, 489. $C_{30}H_{32}O_6$ requires: C, 69.2%; H, 6.2; Ac, 16.5%; mol. wt. 520). The substance does not give a ferric colour.

(b) A mixture of isoartocarpin (0.1 g), acetic anhydride (1 ml) and fused sodium acetate (1 g) was refluxed for 3 hr. The reaction mixture became very pale yellow. Worked up as usual, the product crystallized from methanol in very pale yellow needles (0.05 g), m.p. 215° , which was undepressed when mixed with the sample prepared according to method (a).

Methylation of isoartocarpin

(a) Isoartocarpin (0.2 g) was suspended in dry ether (50 ml) and an ethereal solution of diazomethane (about 10 moles) added and kept at $0-5^{\circ}$ for 48 hr. Excess of diazomethane was destroyed with acetic acid, and after the removal of solvent the residue was crystallized from methanol in yellow needles (0.14 g), m.p. 214° . (Found: C, 71.6; H, 6.7; OMe, 13.9. $C_{27}H_{30}O_6$ requires: C, 71.9; H, 6.7; OMe, 13.8%). The substance gives a greenish brown ferric colour and a pink colour with magnesium and HCl.

(b) Isoartocarpin (0.2 g) in anhydrous acetone (40 ml) was refluxed with freshly ignited potassium carbonate (4 g) and freshly distilled dimethyl sulphate (2 ml) added in two lots during 48 hr. At the end of the reaction, when a sample of the reaction mixture gave no ferric colour, the acetone was distilled off, and the residue was treated with water, when a pale yellow precipitate separated. Crystallization from methanol gave yellow needles (1.6 g), m.p. 185°. (Found: C, 72.3, 72.6, 72.7; H, 6.7, 6.5, 6.7; OMe, 20.0, 19.2. $C_{28}H_{32}O_6$ requires: C, 72.4; H, 6.9; OMe, 20.0%). The substance does not give a ferric colour, and a pink colour in magnesium and HCl.

(c) The same dimethyl ether of isoartocarpin was obtained when the methylation was carried out for 48 hr with dimethyl sulphate and potassium carbonate in methyl ethyl ketone.

p-Toluene sulphonyl ester of isoartocarpin

Isoartocarpin (0.2 g) in acetone (20 ml) was refluxed with p-toluenesulphonyl chloride (0.6 g) and anhydrous potassium carbonate (1 g) for 3 hr. The orange solution became very pale yellow in colour. The solvent was removed on a water-bath and the product

worked up as usual crystallized from ethanol in colourless needles (0.19 g), m.p. 235° . (Found: C, 64.5; H, 5.5, 5.3; S, 8.6, 8.8. $C_{40}H_{40}O_{10}S_2$ requires: C, 64.5; H, 5.3; S, 8.6%). The substance does not give a ferric colour.

Catalytic hydrogenation

Dihydroisoartocarpin. Dihydroisoartocarpin was prepared by hydrogenating isoartocarpin (0.2 g) in presence of 12% palladized carbon (0.1 g) at 25° , using cellosolve as solvent (10 ml). The hydrogenation was stopped after absorption 12 ml of hydrogen (1 mol) which took place within 45 min. The solution became pale yellow in colour. The catalyst was filtered through Hyflo Super-Cel and the filtrate concentrated under reduced pressure to about 2 ml. On cooling and dilution with water a yellow amorphous substance separated (0.155 g). Crystallization from methanol gave pale yellow needles, m.p. 255° . (Found: C, 70.9, 71.5; H, 6.6, 6.9. $C_{26}H_{30}O_6$ requires: C, 71.2; H, 6.9%). The compound gives a reddish brown ferric colour and a pink colour with magnesium and HCl.

Tetrahydroisoartocarpin. Isoartocarpin (0.25 g) in cellosolve (15 ml) was hydrogenated, using 12%

palladized carbon (0.2 g) at 25°. One mol. of hydrogen (15 ml) was absorbed within 45 min, but the absorption of the second mol. (15 ml) took about 20 hr. The catalyst was filtered through Hyflo Super-Cel and the filtrate, after concentration under vacuum, dilution with water and cooling, gave a yellow precipitate. Crystallization from methanol yielded yellow needles (0.14 g), m.p. 240°. (Found: C, 71.4, 71.4; H, 6.9, 7.0. $C_{26}H_{32}O_6$ requires: C, 70.8; H, 7.3%). The substance gives a reddish brown ferric colour and a pink colour with magnesium and HCl.

Mozingo reduction on isoartocarpin

Isoartocarpin (0.1 g) was dissolved in warm ethanol (10 ml) and refluxed with Raney nickel (1 g) for 6 hr, at the end of which the solution had become pale yellow. Nickel was filtered, and the alcoholic solution on concentration and cooling gave yellow needles (0.07 g), m.p. 240°, undepressed when mixed with tetrahydroisoartocarpin obtained in the previous experiment.

Alkaline hydrolysis of isoartocarpin dimethyl ether

A solution of isoartocarpin dimethyl ether (0.1 g) in alcoholic KOH (1 g KOH in 10 ml ethanol) was refluxed on a water-bath for 14 hr. The colour of the reaction mixture changed from yellow to reddish orange.

At the end of the reaction the alcohol was distilled off as far as possible and an equal quantity of water was added. The solution was then saturated with carbon dioxide and extracted with ether (extract A). The aqueous layer was acidified with dil H_2SO_4 and extracted with ether. Evaporation of the ether gave brownish yellow needles, which on crystallization from water yielded colourless needles (0.02 g), m.p. 154° . (Found: C, 57.3; H, 4.6; OMe, 18.0. $C_8H_8O_4$ requires: C, 57.1; H, 4.8; OMe, 18.4%). The substance gives a red-violet ferric reaction and the mixed m.p. with 2-hydroxy-4-methoxybenzoic acid does not show any depression.

A residue from the ether extract (A) was difficult to crystallize.

Alkali fusion of tetrahydroartocarpin

Tetrahydroartocarpin was prepared by hydrogenating artocarpin (1.5 g) in presence of 12% palladized carbon (0.5 g) at 25° , using cellosolve as solvent (50 ml). One mol. of hydrogen was absorbed within 20 min, but the absorption of the second mol. took about 12 hr. The hydrogenation was stopped after absorption of 179 ml of hydrogen (2 mol.), the catalyst filtered off, and the filtrate concentrated under reduced pressure

to about 10 ml. On cooling and dilution with water a pale yellow precipitate was obtained which was crystallized from dil methanol in very pale yellow needles (1.1 g), m.p. 116° . The substance gives an intense violet ferric colour and orange colour with magnesium and HCl.

A mixture of tetrahydroartocarpin (1 g), powdered KOH (5 g) and water (2 ml) was heated in a pyrex tube at $230-240^{\circ}$ for 30 min in nitrogen atm. Vigorous mechanical agitation was employed throughout the reaction time. The melt was extracted with water (50 ml), acidified with dil H_2SO_4 and extracted with ether after saturating with ammonium sulphate. A sodium bicarbonate wash of the ether extract was acidified with dil H_2SO_4 . The precipitate isolated by ether was a brownish semi-solid mass (35 mg) which crystallized from water in pale brown needles, m.p. 210° (decomp). The acid gives a dark violet ferric colour and mixed m.p. with β -resorcylic acid remained undepressed. After the removal of the bicarbonate soluble part, the ether extract was washed with 5% aqueous NaOH. The alkaline extract was acidified with dil H_2SO_4 and extracted with ether. The ethereal layer was dried over sodium sulphate, filtered and evaporated to dryness, when an

oil was obtained. The oil was crystallized from a large volume of pet ether in colourless plates (0.3 g), m.p. 88°. (Found: C, 63.2; H, 8.9; OMe, 13.6. $C_{12}H_{18}O_3, H_2O$ requires: C, 63.1; H, 8.7; OMe, 13.6%). After drying at 110°/0.5 mm for 6 hr, the substance melted at 89° (lit, ²² 89-91°). (Found: C, 68.0; H, 8.1; OMe, 14.0. $C_{12}H_{18}O_3$ requires: C, 68.5; H, 8.6; OMe, 14.8%). The substance does not give a colour with ferric chloride. This phenol was coupled with excess of diazotized aniline. A benzene solution of the azo dye was chromatographed on alumina. On evaporation of the benzene percolate a dark red substance was obtained which crystallized from methanol in needles (45 mg), m.p. 146°. (Found: C, 69.2; H, 6.1; N, 14.0. $C_{24}H_{26}O_3N_4$, bisbenzeneazo-C-amyphloroglucinol monomethyl ether, requires: C, 68.9; H, 6.2; N, 13.4%).

Alkali fusion of tetrahydroisoartocarpin

Powdered tetrahydroisoartocarpin (0.5 g) was mixed with powdered KOH (2.5 g) and water (1 ml) was added to form a paste. The mixture was heated under vigorous mechanical agitation for 30 min at 265° in nitrogen atm. The melt was extracted with water (30 ml), acidified with 20% H_2SO_4 and extracted with

ether after saturating with ammonium sulphate. A sodium bicarbonate wash of the ether extract gave a brown precipitate on acidification with 20% H_2SO_4 . Ether extraction of the precipitate and crystallization of the residue, after evaporation of ether from water, yielded pale brown needles, m.p. 210° (decomp). The substance gives a dark violet ferric colour and mixed m.p. with β -resorcylic acid remains undepressed. After the removal of the bicarbonate soluble part, the ether extract was washed with 5% aqueous NaOH. The alkaline extract was acidified with 10% H_2SO_4 and extracted with ether. The ethereal layer was dried over sodium sulphate, filtered and evaporated to dryness, when an oil was obtained. It was crystallized from pet ether in colourless plates (0.12 g), m.p. 88° (lit, ²² $89-91^\circ$). (Found: C, 63.0; H, 8.5; OMe, 13.4. $C_{12}H_{18}O_3, H_2O$ requires: C, 63.1; H, 8.7; OMe, 13.6%). After drying at $110^\circ/0.5$ mm for 6 hr, the substance melted at 89° . (Found: C, 68.3; H, 8.4. $C_{12}H_{18}O_3$ requires: C, 68.5; H, 8.6%). The substance does not give colour with ferric chloride and mixed m.p. with the phenol obtained in the previous experiment remains undepressed. The phenol on coupling with excess of diazotized aniline and working up as above, gave the identical product as obtained in the previous experiment.

Ozonolysis of isoartocarpin dimethyl ether

Through a solution of isoartocarpin dimethyl ether (0.5 g) in ethyl acetate (50 ml) cooled to -50° a slow stream of ozonized oxygen was passed till the ozonization was complete (2 hr) as indicated by starch-iodide paper. The residual ozone was removed by flushing the reaction with oxygen for a few min. The ozonide was decomposed by hydrogenation at 28° in presence of 12% palladized carbon (0.08 g), when hydrogen (55 ml) was absorbed (approx 2 mol.). The catalyst was filtered off and washed with hot ethyl acetate (20 ml). The ethyl acetate filtrate was distilled, using ice-cold water in the condenser, and the volatile components were carefully collected in a solution of 2,4-dinitrophenylhydrazine (0.5 g) in 10% H_2SO_4 (250 ml). After the removal of ethyl acetate by distillation the dinitrophenylhydrazone was extracted with benzene and the benzene extract washed with 10% H_2SO_4 to remove most of the unconverted dinitrophenylhydrazine. The dried benzene solution was chromatographed over alumina, when traces of dinitrophenylhydrazine were retained on the column; the benzene eluate on removal of the solvent yielded orange-red crystals (0.35 g) which consisted of a mixture of acetone and isobutyraldehyde dinitrophenylhydrazones

as shown by paper chromatography. On recrystallization of the mixed dinitrophenylhydrazones twice from ethanol, orange needles were obtained, m.p. 186° . (Found: C, 47.7; H, 5.0; N, 21.8. $C_{10}H_{12}N_4O_4$ requires: C, 47.6; H, 4.8; N, 22.2%), undepressed when mixed with an authentic sample of isobutyraldehyde dinitrophenylhydrazone, m.p. 187° . Careful crystallization (six times) of the residue obtained by evaporation of the above mother-liquor from ethanol yielded orange-yellow plates, m.p. 126° . (Found: C, 45.6; H, 3.7; N, 23.6. $C_9H_{10}N_4O_4$ requires: C, 45.3; H, 4.2; N, 23.5%), undepressed when mixed with an authentic sample of acetone dinitrophenylhydrazone, m.p. 126° .

The nonvolatile constituent, after the removal of ethyl acetate, was crystallized from a large volume of ethyl acetate in colourless needles (0.15 g), m.p. 285° . (Found: C, 61.1; 60.6; H, 4.7, 4.7. $C_{21}H_{18}O_8$ corresponding to the dialdehyde with loss of seven carbon atoms from isoartocarpin dimethyl ether requires: C, 63.3; H, 4.5 With water of crystallization $C_{21}H_{18}O_8 \cdot H_2O$ requires: C, 60.6; H, 4.7%). The substance does not give ferric colour but an orange colour with magnesium and HCl. It is not soluble in saturated solution of $NaHCO_3$ and does not give hydroxamic acid

and iodide-iodate test for carboxylic acid. The substance forms dinitrophenylhydrazone very easily, but is difficult to crystallize.

Permanganate oxidation of the nonvolatile ozonolysis product (XXI) from isoartocarpin dimethyl ether

(a) To a solution of dialdehyde (0.1 g) in acetone (10 ml) powdered potassium permanganate (0.05 g) was added portionwise with mechanical agitation at 0° during the course of 1 hr. The mixture was stirred at 0-5° for 3 hr. The acetone was removed under reduced pressure at room temp and the residue suspended in water (10 ml) and sulphur dioxide passed, when a pale yellow solid was obtained which was ether extracted. The ether extract was then washed with 5% aqueous NaHCO₃ solution. The bicarbonate extract on acidification gave no precipitate, and therefore it was extracted with ether. The ethereal layer was dried over sodium sulphate, filtered and evaporated to dryness, but no product could be isolated. The ethereal layer, after bicarbonate extraction, was washed with water, dried over sodium sulphate, filtered and evaporated to dryness, when a colourless product was obtained, identified as the starting material, m.p. 285°.

(b) This oxidation, when carried out at room temp, gave the same result.

(c) To a refluxing solution of dialdehyde (0.180 g) in acetone (15 ml), powdered potassium permanganate (0.8 g) was added portionwise during the course of 1 hr. The first 0.1 g of potassium permanganate was rapidly consumed. After the completion of the addition the reaction mixture was refluxed for a further period of 4 hr. The acetone was distilled, and the residue suspended in water (20 ml) and saturated with sulphur dioxide, when a yellow product was obtained which was ether extracted. The ether extract was then washed with a saturated solution of NaHCO_3 . The bicarbonate extract on acidification gave a pale yellow substance which was extracted with ether. The ethereal layer was dried over sodium sulphate, filtered and evaporated to dryness, when a colourless product was obtained. Crystallization from water gave colourless needles (0.02 g), m.p. 154° . The substance gives red-violet ferric colour and the mixed m.p. with 2-hydroxy-4-methoxybenzoic acid remains undepressed. The ethereal layer, after bicarbonate extraction, was washed with water, dried over sodium sulphate, filtered and evaporated to dryness. As in (a) the product was the starting material, m.p. 285° .

Dihydroisoartocarpin dimethyl ether

Isoartocarpin dimethyl ether (1.0 g) was hydrogenated in presence of 12% palladized carbon (0.2 g) at 28°, using cellosolve as solvent (40 ml). The hydrogenation was stopped after absorption of 55 ml of hydrogen (1 mol.), which took place within 45 min, the catalyst filtered off, and the filtrate concentrated under reduced pressure to about 2 ml. On cooling and dilution with water a pale yellow precipitate separated out. The substance was collected and crystallized from methanol in yellow needles (0.86 g), m.p. 150°. (Found: C, 72.2, 72.2; H, 6.8, 7.1; OMe, 19.3, 19.1. $C_{28}H_{34}O_6$ requires: C, 72.1; H, 7.4; OMe, 20.0%). The substance does not give ferric colour but a pink colour with magnesium and HCl.

Ozonolysis of dihydroisoartocarpin dimethyl ether

A solution of dihydroisoartocarpin dimethyl ether (0.7 g) in ethyl acetate (50 ml) was ozonized at -50°. The ozonization was complete within 2 hr and the excess of ozone was removed by flushing the reaction mixture with oxygen for a few min. The ozonide was decomposed by hydrogenation in presence of 12% palladized carbon (0.5 g). The volume of hydrogen absorbed at 28° was 35 ml (approx. 1 mol.). On working up as usual, the

volatile component yielded the dinitrophenylhydrazone, which on chromatography over alumina yielded orange-yellow plates (0.2 g), m.p. 126° . (Found: C, 45.4; H, 3.9; N, 24.0. $C_9H_{10}N_4O_4$ requires: C, 45.3; H, 4.2; N, 23.5%), undepressed when mixed with an authentic sample of acetone dinitrophenylhydrazone, m.p. 126° .

The nonvolatile constituent crystallized from ethyl acetate in needles (0.42 g), m.p. 250° . (Found: C, 66.0; H, 6.0. $C_{25}H_{28}O_7$ corresponding to the monoaldehyde formed by the loss of 3 carbon atoms from dihydroisoartocarpin dimethyl ether requires: C, 68.2; H, 6.3, with water of crystallization. $C_{25}H_{28}O_7 \cdot H_2O$ requires: C, 65.5; H, 6.5%). The substance does not give a ferric colour but a pale orange colour with magnesium and HCl. It is not soluble in saturated solution of $NaHCO_3$ and does not give hydroxamic acid and iodide-iodate tests for carboxylic acid.

Permanganate oxidation of the nonvolatile ozonolysis product (XXII) from dihydroisoartocarpin dimethyl ether

(a) Powdered potassium permanganate (0.04 g) was added portionwise to a solution of the aldehyde (0.1 g) in acetone (5 ml) with mechanical agitation at 0° during 4 hr. Acetone was distilled off, the residue suspended in water (10 ml) and saturated with sulphur dioxide, when a pale yellow precipitate separated out which was

ether extracted. The ether extract was washed with a saturated solution of NaHCO_3 . The bicarbonate extract was acidified and extracted with ether. Evaporation of ether to dryness gave no product. The ethereal layer, after bicarbonate extraction, was washed with water, dried over sodium sulphate, filtered and evaporated to dryness, when a colourless product was obtained, identified as starting material, m.p. 250° .

(b) The same result was obtained when the oxidation was carried out at room temp.

(c) Powdered potassium permanganate (0.5 g) was added portionwise to a refluxing solution of monoaldehyde (0.1 g) in acetone (10 ml). The reaction mixture was heated on a water-bath for 4 hr. Working up as above, the bicarbonate soluble part was identified as 4-methoxy-2-hydroxybenzoic acid, m.p. 154° , and the compound gives red-violet ferric colour. As observed above the ethereal layer, after bicarbonate wash yielded the starting material, m.p. 250° .

Permanganate oxidation of dihydroisoartocarpin dimethyl ether

(a) Addition of powdered potassium permanganate (0.04 g) to a solution of dihydroisoartocarpin dimethyl ether (0.1 g) in acetone (5 ml) at 0° , and working up as above, gave the starting material.

(b) When the reaction was carried out at room temp, the same result was obtained.

Demethylation of tetrahydroartocarpin

A mixture of tetrahydroartocarpin (0.5 g), acetic anhydride (5 ml) and hydriodic acid (d 1.7; 5 ml) was refluxed for 4 hr. After cooling, the mixture was poured into saturated sodium bisulphite solution. The yellowish brown precipitate was collected, washed thoroughly with water, dried and dissolved in ethyl acetate. After running the ethyl acetate solution through a short column of Florex, a yellow coloured percolate was obtained. Evaporation of ethyl acetate to dryness and crystallization of the substance from ethyl acetate-benzene yielded yellow needles (0.2 g), m.p. 234° . (Found: C, 70.1; H, 6.8. $C_{25}H_{30}O_6$ requires: C, 70.4; H, 7.0%). The substance gives a green colour with ferric chloride and orange colour with magnesium and HCl.

Dealkylation of tetrahydroisoartocarpin

Tetrahydroisoartocarpin (0.3 g) in acetic anhydride (3 ml) was refluxed with hydriodic acid (d 1.7; 3 ml) for 4 hr. After cooling, the saturated sodium bisulphite solution. The yellow coloured precipitate was collected,

washed thoroughly with water, dried and dissolved in ethyl acetate. After running the ethyl acetate solution through a short column of Florex, a yellow coloured percolate was obtained, which on evaporation to dryness and crystallization of the residue from ethyl acetate-benzene yielded a yellow crystalline product (XXII; 0.15 g), m.p. 285° . (Found: C, 67.0; 67.9; H, 6.2; 5.7. $C_{20}H_{20}O_6$ requires: C, 67.4; H, 5.6%). The substance gives reddish brown ferric colour and orange colour with magnesium and HCl.

Methylation of (XXIII)

A mixture of (XXIII) (0.1 g), acetone (20 ml), potassium carbonate (2 g) and dimethyl sulphate (2 ml) was refluxed for 36 hr. Distillation of acetone and treatment of the residue with water yielded a pale yellow coloured mass which gave negative ferric colour and orange colour with magnesium and HCl. It was dissolved in benzene and run through a short column of alumina. The yellow percolate led to a product which crystallized from methanol in pale yellow needles (0.8 g), m.p. 191° . (Found: C, 70.1, 70.2; H, 6.5, 6.1; OMe, 22.3, 22.6. $C_{20}H_{16}O_2(OCH_3)_4$ requires: C, 69.9; H, 6.7; OMe, 30.0. $C_{20}H_{17}O_3(OCH_3)_3$ requires: C, 69.3; H, 6.5; OMe, 23.0%).

Dealkylation of dihydroisoartocarpin

Dihydroisoartocarpin (0.4 g) in acetic anhydride (4 ml) was heated on a water-bath with hydrobromic acid (48%) for 1 hr. After cooling, the reaction mixture was poured on saturated solution of sodium bisulphite. The yellow coloured precipitate was collected, washed with water and crystallized from methanol in yellow needles (XXV; 0.2g), m.p. 180°. (Found: C, 68.5; H, 6.2. $C_{20}H_{19}O_5(OCH_3)$ requires: C, 68.1; H, 6.0%). The substance gives red ferric colour and orange colour with magnesium and HCl.

Methylation of (XXV)

Methylation of (XXV) with dimethyl sulphate in acetone and potassium carbonate and working up as usual gave the same methyl ether as obtained by the methylation of (XXIII).

Dealkylation of dihydroisoartocarpin dimethyl ether

A mixture of dihydroisoartocarpin dimethyl ether (0.5 g), acetic acid (7 ml) and HCl (0.6 ml) was heated on a water-bath for 1 hr. After cooling, the mixture was poured into a large volume of water. The yellow coloured precipitate was collected and crystallized from

methanol in yellow needles (XXVI; 0.2 g), m.p. 166°. (Found: C, 69.4; H, 6.8; OMe, 13.8. $C_{20}H_{18}O_4(OCH_3)_2$ requires: C, 68.8; H, 6.3; OMe, 16.0%). The substance gives red colour with ferric chloride and orange colour with magnesium and HCl.

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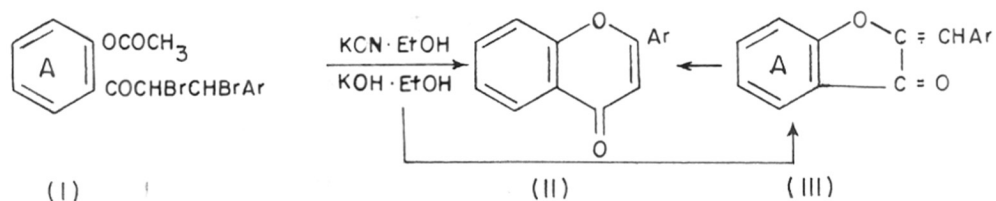
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PART II

**THE BAKER-VENKATARAMAN TRANSFORMATION
AS A PRACTICAL METHOD FOR THE SYNTHESIS
OF NATURALLY OCCURRING FLAVONES**

Introduction

Flavone was first synthesized by Kostanecki¹ by the action of ethanolic potassium hydroxide on 2'-acetoxy-chalkone dibromides (I; Ar = aryl); but this reaction was found to be of limited application. He showed that with chalkones, derived for instance from p-alkoxybenzaldehyde² and phloracetophenone,³ the reaction took an alternative course leading to 2-benzylidene-3-coumaranones (III).



Wheeler and his collaborators,⁴ while studying the methods to extend the application of the Kostanecki synthesis, showed that 2-p-alkoxybenzylidene-3-coumaranones undergo a ring expansion to form the corresponding 4'-alkoxyflavone (II; Ar = p-alkoxyaryl), when refluxed with excess of potassium cyanide. Coumaranones of the type obtained by Kostanecki were obtained from the corresponding dibromides when limited quantities of potassium cyanide were employed, and were therefore intermediates in the reaction. Use of excess of potassium cyanide did not help when ring A was derived

from phloroglucinol.

A second method, also due to Kostanecki,¹ was a reversal of the hydrolytic fission of flavones. Thus he obtained chrysin (5,7-dihydroxyflavone) by condensing phloracetophenone trimethyl ether with ethyl benzoate and treating the resultant 1,3-diketone with hydriodic acid. Mentzer⁵ has recently described a variation of this method in which phloroglucinol is condensed with ethyl benzoylacetate at 240-250°. Several flavones have been synthesized by this route, but the yields are very poor.

Tahara⁶ observed that the prolonged action of boiling acetic anhydride and sodium acetate on resacetophenone led to 7-acetoxy-3-acetyl-2-methylchromone, which was then hydrolysed to 7-hydroxy-2-methylchromone. The application of this reaction to the synthesis of flavones by using aromatic acid anhydrides was realized over thirty years later by Allan and Robinson.⁷ They obtained 7-hydroxy-3-methoxyflavone in about 87 per cent yield (crude) by the action of benzoic anhydride and sodium benzoate on *o*-methoxyresacetophenone at 180-185°, followed by treatment with ethanolic potassium hydroxide to hydrolyse the *o*-benzoyl

derivative of the flavone. Applying the same reaction to ω -methoxyphloracetophenone, followed by demethylation with hydriodic acid, Robinson and his collaborators prepared various 3-hydroxyflavones (flavonols). Quercetin (3,5,7,3',4'-pentahydroxyflavone) was thus synthesized by heating ω -methoxyphloracetophenone with veratric anhydride and sodium veratrate at 180°; after alkaline hydrolysis to remove Q-aroyl groups, the product was quercetin-3,3',4'-trimethyl ether, which was then demethylated to quercetin. Chrysin and other flavones unsubstituted in the 3-position could be similarly prepared; but the flavones may be accompanied by the 3-aroyl derivatives. Normally this Q-aroyl group is removed during the alkaline hydrolysis of Q-aroyl groups; but Bhullar and Venkataraman⁸ reported that some 3-aroyl derivatives resist hydrolysis under conditions in which the γ -pyrone ring remains intact or, with increased concentration of alkali and time of heating, the pyrone ring is broken down. Thus the scope of the Allan-Robinson reaction is limited by some disadvantages, such as the high reaction temperature, difficulty in preparing some of the anhydrides which were always used in large excess, and the formation of 3-acyl derivatives.

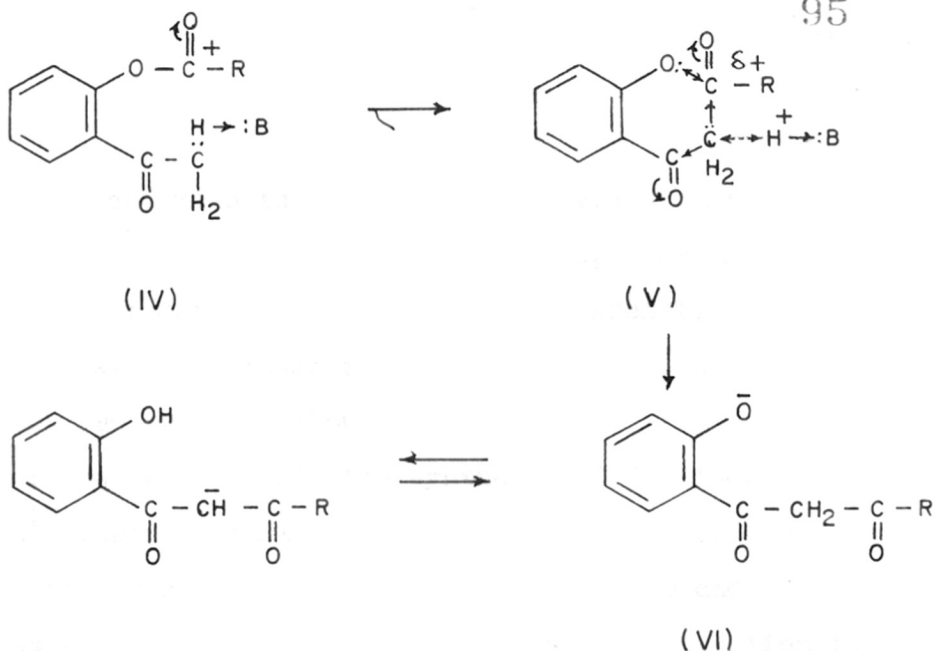
A milder method, substantially free from the first two of the defects mentioned above, was reported by Baker⁹ and Venkataraman¹⁰ independently and at the same time, while studying the mechanism of the Allan-Robinson reaction. In an attempt to prepare the benzyl ether of 4-benzoyloxyresacetophenone Baker⁹ heated the compound in benzene with benzyl chloride and anhydrous potassium carbonate; the product however was ω ,4-dibenzoylresacetophenone which gave 7-hydroxyflavone on treatment with cold concentrated sulphuric acid. Benzyl chloride played no essential part in the reaction for ω ,4-dibenzoylresacetophenone could be obtained from 4-benzoyloxyresacetophenone and resacetophenone itself by the action of one and two moles of benzoyl chloride respectively. Since acetophenone itself did not react with benzoyl chloride under these conditions, it was concluded that ω -benzoylation had not taken place by direct attack on the reactive methylene group. Resacetophenone dibenzoate was found to rearrange to ω ,4-dibenzoylresacetophenone by the action of potassium carbonate in boiling toluene. When the esterifying acid groups were different, only the ortho acyl group migrated. The reaction of benzoyl chloride with

p-hydroxyacetophenone did not yield a diketone. Baker therefore concluded that the migration took place only from the ortho position and that it was intramolecular. Jurd¹¹ has recently shown that p-aroyloxyacetophenones, having a free o-hydroxyl group, undergo this rearrangement. Thus he has achieved the rearrangement of 4-o-benzoylresacetophenone and 4-o-anisoylresacetophenone to the corresponding ω ,4-dibenzoylresacetophenone and ω ,4-dianisoylresacetophenone. The presence of a free hydroxyl group in the ortho position is essential, because p-benzoyloxyacetophenone and 2-o-benzyl-4-o-benzoylresacetophenone were recovered unchanged after many hours of heating. Cyclization of o-hydroxydibenzoylmethanes, obtained by the Baker-Venkataraman rearrangement can be effected by concentrated sulphuric acid or with boiling acetic acid and sodium acetate. The general application of the new rearrangement was illustrated by Baker by the synthesis of a large number of flavones and chromones through the corresponding diketones.

Simultaneously with Baker, the mechanism of the Allan-Robinson reaction was examined by Venkataraman. Chada and Venkataraman¹² found that 2-acetyl-1-naphthyl benzoate could not be converted to the

corresponding α -naphthaflavone under the action of dehydrating agents, such as phosphorus oxychloride in chloroform, sodium acetate, and acetic anhydride-sodium acetate. Continuing these studies, Mahal and Venkataraman¹⁰ found that 2-acetyl-1-naphthyl benzoate was transformed into ω -benzoyl-2-acetyl-1-naphthol by the action of sodamide in ether below 16°, followed by decomposition of the sodio-derivative with acid. The diketone was then cyclized to α -naphthaflavone in the usual manner with cold concentrated sulphuric acid. A smooth synthesis of a flavone was thus accomplished below 16°.

This base-catalysed rearrangement of 2-aryloxyacetophenones to 2-hydroxydiaroylmethanes is known as the Baker-Venkataraman transformation, and it has been widely used for the synthesis of flavones, because the procedure via the diketone is often more convenient than the Allan-Robinson reaction. Wheeler and his collaborators¹³ have made an extensive study of this transformation and have shown that it is an intramolecular Claisen condensation proceeding by the following mechanism.



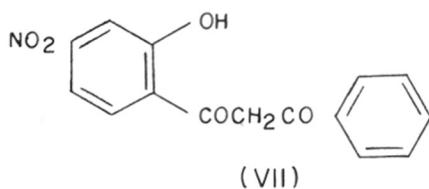
The carbanion produced by the action of base on the methyl group of the acetophenone attacks the positively polarized carbon atom of the ester carbonyl group, and the resulting cyclic intermediate opens up to the diketone, which separates from the reaction mixture as its alkali salt. This probably irreversible conversion can be catalysed by a wide variety of bases, including potassium hydroxide in pyridine and triphenylmethyl anion.¹⁴

Schmid and Banholzer¹⁵ have proved the intramolecular nature of the transformation of (IV) to (VI) by using benzoyl chloride with ¹⁴C in the carbonyl group.

Ollis and Weight¹⁶ extended the Baker-Venkataraman transformation to the synthesis of 3-substituted

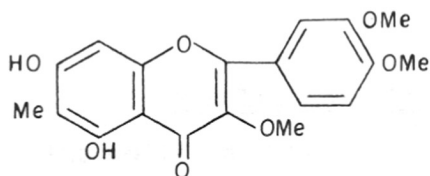
flavones, and made the interesting observation that the diketones of the ω -substituted type, where ω -substitution may be methyl, methoxy or phenyl, are colourless, while those in which no ω -substitution is present are bright yellow.

In connection with the synthesis of 7-aminoflavone, Bapat¹⁷ reported that when 2-hydroxy-4-nitroacetophenone in acetone was treated with benzoyl chloride and potassium carbonate, α -aroylation and transformation to the diketone occurred in one step, giving the corresponding diketone (VII) in about 72 per cent yield. It may be recalled here that the preparation of 2-hydroxy-dibenzoylmethanes from acetophenones, using the Baker-Venkataraman transformation by the original procedure, involves two steps.

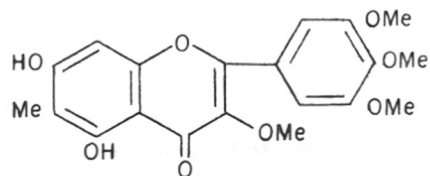


During the synthesis of pinoquercetin-3,3',4'-trimethyl ether (VIII) and pinomyricetin-3,3',4',5'-tetramethyl ether (IX), Mani *et al.*¹⁸ showed that similar treatment of ω -methoxy- α -methylphloracetophenone with veratroyl chloride or trimethylgalloyl chloride

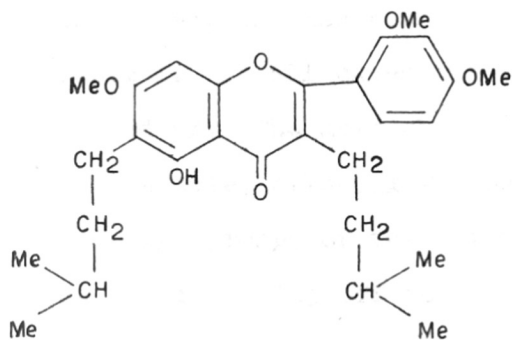
afforded the corresponding flavones directly. He made a similar observation while synthesizing tetrahydroartocarpin dimethyl ether (X)¹⁹ from 3-isoamyl-2,4,6-trihydroxyisoeptophenone (XI) and 2,4'-dimethoxybenzoyl chloride.



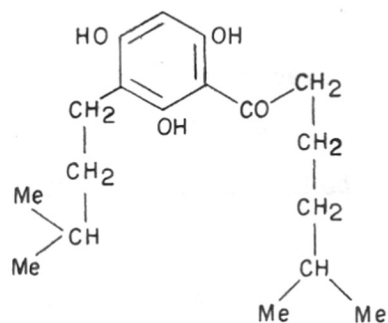
(VIII)



(IX)



(X)



(XI)

The present work was carried out in order to examine the scope and limitations of this method, in which acetone is used as solvent and o-arylation of an o-hydroxyacetophenone and the Baker-Venkataraman transformation are effected in one operation, as a

practicable procedure for the synthesis of flavones. Several naturally occurring and other flavones have thus been synthesized; the experimental results have also led to a better understanding of the mechanism of the Baker-Venkataraman transformation.

Results and Discussion

The modified Baker-Venkataraman transformation was carried out, using various acetophenones and acid chlorides, and the results obtained are presented in Table 1. In all cases the reaction mixture was refluxed for 24 hr. The acid chloride was employed in an excess of one mole, allowing for esterification of all the hydroxyl groups of the ketone. The products were worked up by distilling off acetone and treating the residue with ice-cold water. The resulting mixture was then saturated with carbon dioxide, when the diketone or flavone formed in the reaction precipitated out.

Treatment of the diketones with cold concentrated sulphuric acid for about 10 min and pouring the solution into ice-water gave the flavones in yields of 80 to 90 per cent. It was observed that the ester groups were hydrolysed by the acid treatment. The products and the yields before and after the sulphuric acid treatment,

TABLE 1

Sr. No.	Substitution in 2-hydroxy-acetophenones	Substitution in benzoyl chloride	Product and yield per cent		Flavone obtained after sulphuric acid treatment and yield	Over-all yield of flavone %
			Dibenzoyl-methane	Flavone		
1.	None	None	2-Hydroxy (72)	-	Unsubstituted (88)	63
2.	6-Methoxy	"	2-Hydroxy-6-methoxy (65)	-	5-Methoxy (78)	51
3.	6-Hydroxy	"	-	3-Benzoyl-5-hydroxy (56)	-	56
4.	4-Hydroxy	"	2-Hydroxy-4-benzoyloxy (70)	-	7-Hydroxy (85)	60
5.	4,6-Dimethoxy	"	2-Hydroxy-4,6-dimethoxy (50)	-	5,7-Dimethoxy (85)	43
6.	4,6-Dihydroxy	"	-	3-Benzoyl-7-benzoyloxy-5-hydroxy (42)	-	42

TABLE I (Contd.)

Sr. No.	Substitution in 2-hydroxyacetophenones	Substitution in benzoyl chloride	Product and yield per cent		Flavone obtained after sulphuric acid treatment and yield	Over-all yield of flavone %
			Dibenzoyl-methane	Flavone		
7.	4,6-Dihydroxy	3,4,5-Trime-thoxy	-	3-Trimethyl-galloyl-5,7-dihydroxy-3',4',5'-trime-thoxy (30)	-	30
8.	None	2,4-Dimethoxy	2-Hydroxy-2',4'-dime-thoxy (40)	-	2',4'-Dime-thoxy (85)	34
9.	4,6-Dihydroxy	"	-	5,7-Dihydroxy-2',4'-di-methoxy	-	35
10.	5,7-Dimethoxy	4-Nitro	2-Hydroxy-4,6-dimethoxy-4'-nitro (40)	-	5,7-Dime-thoxy-4'-nitro (90)	36
11.	4,6-Dihydroxy-5-methyl	None	-	5,7-Dihydroxy-6-methyl (20)	-	1) 20
				5,7-Dihydroxy-8-methyl (10)	-	2) 10

TABLE I (Contd.)

Sr. No.	Substitution in 2-hydroxyacetophenones	Substitution in benzoyl chloride	Product and yield per cent		Flavone obtained after sulphuric acid treatment and yield	Over-all yield of flavone %
			Dibenzoyl-methane	Flavone		
12.	4,6- ω -Trime-thoxy	None	4,6- ω -Trime-thoxy (45)	-	3,5,7-Tri-methoxy (78)	35
13.	4,6-Dihydroxy- ω -methoxy	"	-	7-Benzoyloxy-5-hydroxy-3-methoxy (36)	-	36
14.	"	3,4,5-Trime-thoxy	-	5,7-Dihydroxy-3,3',4',5'-tetramethoxy (36)	-	36
15.	4,6-Dimethoxy- ω -methyl	None	4,6-Dimethoxy- ω -methyl (45)	-	5,7-Dimethoxy-3-methyl (80)	36
16.	4,6-Dihydroxy- ω -methyl	"	-	5,7-Dihydroxy-3-methyl (40)	-	40
17.	4,6-Dihydroxy- ω -methoxy-5-methyl	"	-	7-Benzoyloxy-5-hydroxy-3-methoxy-6-methyl (35)	-	35

as well as the overall yields, are mentioned in Table 1. All the yields recorded in the Table are of the pure crystalline products.

The main feature of the results presented in Table 1 is that acetophenones containing hydroxyl groups in the 2- and 6-positions invariably yield a flavone; in all other cases which were investigated, diketones are obtained. Before considering the implications of this interesting fact, the value of the results for the synthesis of flavones may first be discussed.

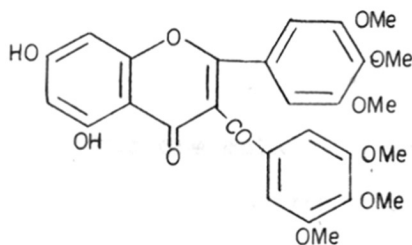
Baker⁹ has reported that the rearrangement of o-benzoyloxyacetophenone and resacetophenone dibenzoate to 2-hydroxydibenzoylmethane and 2-hydroxy-4-benzoyloxydibenzoylmethane, using toluene and potassium carbonate, takes place in 32 per cent and 80 per cent yield respectively. The two diketones were obtained in yields of 72 per cent and 70 per cent in the present work (expt. 1 and 4 in Table 1). Unfortunately these are the only two compounds for which a direct comparison can be made with Baker's results. The yields reported by Baker, with few exceptions, were in the range of 20 to 40 per cent, whereas the majority of the experiments in Table 1 gave yields of 40 per cent or more. The

esterification reaction, involved in going from *o*-hydroxyacetophenones to Baker's starting materials for rearrangement, has been ignored in this comparison. The advantage of the revised procedure is therefore obvious. The overall yield of 7-hydroxyflavone obtained by Baker was 40 per cent, whereas the overall yield obtained in expt. 4 (Table 1) was nearly 60 per cent. In the case of flavone itself the comparison is more favourable to the revised procedure. Virkar and Shah²⁰ have reported the synthesis of 7-methoxyflavone by the Baker-Venkataraman method, but the yields of the diketone and flavone were not mentioned. 2-Benzoyloxy-6-methoxyacetophenone was converted to 2-hydroxy-6-methoxydibenzoylmethane in unspecified yield by Rajagopalan and Seshadri,²¹ and they were unable to isolate the diketone in crystalline form. 2-Hydroxy-6-methoxydibenzoylmethane was obtained in crystalline form yellow coloured plates, m.p. 102^o, in expt. 2 (Table 1) in a yield of 65 per cent. Wheeler and Toole²² have recorded a yield of 16 per cent in the Baker-Venkataraman rearrangement of *o*-methoxyphloracetophenone tribenzoate to 2-hydroxy-4,6-dibenzoyloxy-*o*-methoxydibenzoylmethane. The diketone was then cyclized to 5,7-dihydroxy-3-methoxyflavone (galangin monomethyl

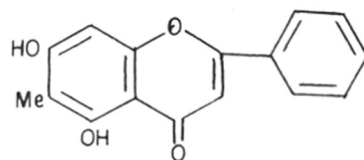
ether). The latter compound has now been prepared (expt. 13) by the hydrolysis of 7-benzoyloxy-5-hydroxy-3-methoxyflavone, which was obtained in 36 per cent yield in one step.

The Allan-Robinson method may now be taken up for comparison. 5-Hydroxyflavone (primuletin) was thus obtained in 16 per cent yield by Sugasawa.²³ Trivedi and others²⁴ confirmed the above low yield, and they isolated 3-benzoyl-5-benzoyloxyflavone. 3-Benzoyl-5-hydroxyflavone was obtained in 56 per cent yield in expt. 3 of this study. Although the yields mentioned above in the Allan-Robinson reaction are low, Robinson and co-workers have reported excellent yields for 7-hydroxy-,²⁵ 5,7-dihydroxy-,²⁵ 5,7-dihydroxy-2',4'-dimethoxy-,²⁶ 5,7-dihydroxy-3-methoxy-,²⁷ and 5,7-dihydroxy-3,3',4',5'-tetramethoxy-²⁷ derivatives of flavone by the same procedure. The yields were 70, 99, 99, 93, and 98 per cent respectively. Although the yields were of the crude products, they demonstrate the superiority of the method for the preparation of these compounds. The yields by the present method for the same compounds or their derivatives were 60, 42, 35, 36 and 36 per cent in experiments 4, 6, 9, 13 and 14. Gulati and Venkataraman²⁸ synthesized 5,7,4'-trihydroxy-3',5'-dimethoxyflavone (tricin) in poor yield, using the

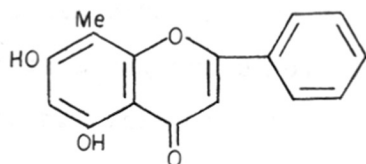
Allan-Robinson reaction. In expt. 7 the synthesis of tricrin was attempted. The yield of the intermediate product, 3-trimethylgalloyl-5,7-dihydroxy-3',4',5'-trimethoxyflavone (XII) was 30 per cent. Mukerjee and Seshadri²⁹ have reported 6-methyl-5,7-dihydroxyflavone (XIII) in 19 per cent yield and its 8-methyl isomer (XIV) in 21 per cent yield in the Allan-Robinson reaction between o-methylphloracetophenone, benzoic anhydride and sodium benzoate. In expt. 11 admixture of the 6- and 8-methyl isomers was obtained in 30 per cent yield. The former compound (XIII) was separated from the mixture in pure form by fractional crystallization. The amount thus isolated corresponded to 20 per cent. The remaining part was presumably 8-methylchrysin (XIV) contaminated with the 6-methyl isomer. Carrying out the Allan-Robinson reaction on o-methoxy-o-methylphloracetophenone, benzoic anhydride and sodium benzoate, Jain and Seshadri³⁰ obtained 5,7-dihydroxy-3-methoxy-8-methylflavone in 43 per cent yield together with the 6-methyl isomer in 14 per cent yield. In expt. 17 only the 7-benzoyl ester of the 6-methyl isomer was obtained in 30 per cent yield. This was readily hydrolysed to 5,7-dihydroxy-3-methoxy-6-methylflavone (XV).



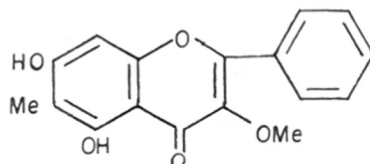
(XII)



(XIII)



(XIV)



(XV)

As mentioned earlier, the main disadvantage of the Allan-Robinson method lies in the necessity for using a large excess of the acid anhydride and the sodium salt of the acid; for instance, in the preparation of 5,7-dihydroxy-3,3',4'-trimethoxyflavone⁷ 2.5 moles of potassium veratrate and 4.8 moles of veratric anhydride were used per mole of ω -methoxyphloracetophenone. Similarly, in the synthesis of 5,7-dihydroxy-3-methoxyflavone²⁷ one mole of ω -methoxyphloracetophenone required about two moles of sodium benzoate and about three moles of benzoic anhydride.

Thus one mole of a phenolic ketone required 8-12 moles of an aromatic acid for conversion to a flavone. Although a molar excess of the acid chloride was employed in the experiments recorded in Table 1, it will be seen from Table 2 that 2-acetylresorcinol reacts with 2, 3 or 5 moles of benzoyl chloride to give 3-benzoylprimuletin in the same yield of 56 per cent. This aspect of the problem is being further studied.

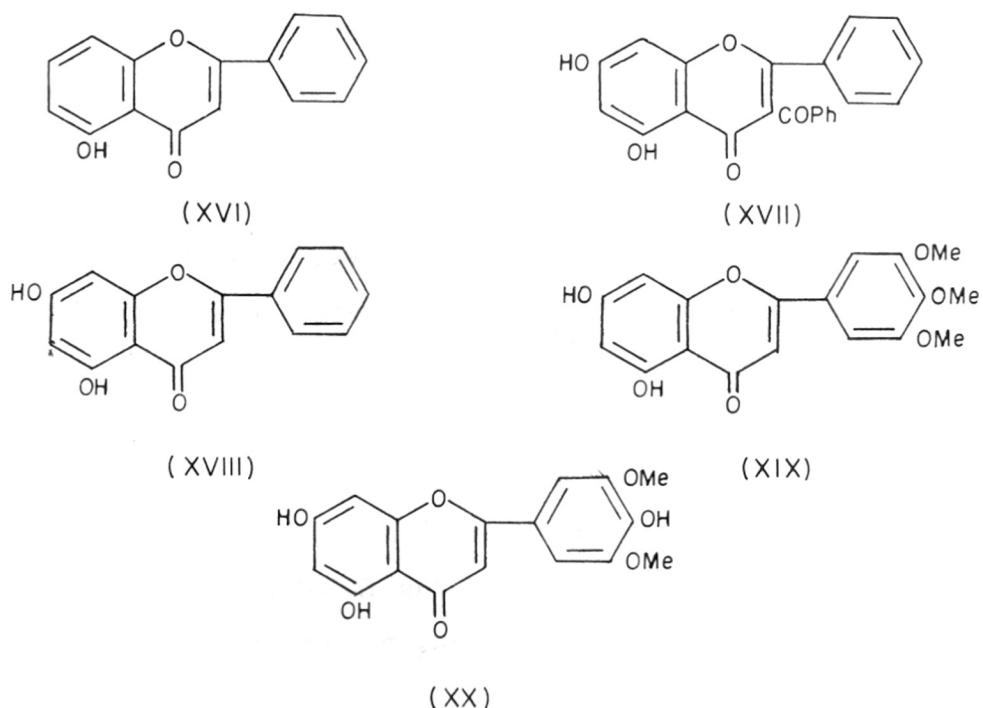
The products mentioned in Table 1 are either known flavones or their simple derivatives which can be easily transformed into the parent compound.

The 3-benzoyl derivative of 5-hydroxyflavone (XVI) obtained in expt. 3 resisted debenzoylation by 5 per cent sodium carbonate, but the hydrolysis proceeded smoothly in 5 per cent ethanolic potassium hydroxide. When phloracetophenone was treated with benzoyl chloride as in expt. 6, the product, which gave a red ferric colour and an orange colour with magnesium and hydrochloric acid, could not be crystallized. Its m.p. at about 220° showed that it was neither chrysin nor its 3-benzoyl derivative, but probably 3-benzoyl-7-benzoyloxy-5-hydroxyflavone; treatment with cold concentrated sulphuric acid gave 3-benzoylchrysin (XVII)

and treatment with boiling 5 per cent aqueous potassium carbonate gave chrysin (XVIII). Chrysin was also obtained by refluxing the mixture of 5,7-dimethoxyflavone with hydriodic acid for 2 hours. Selective demethylation of the 5-methoxyl group occurred when 5,7-dimethoxyflavone was heated with 48 per cent hydrobromic acid and glacial acetic acid for 2 hours. The use of hydrobromic acid at room temperature for preferential demethylation of 5-methoxy group in presence of 3-methoxy group was reported by Shah *et al.* during the course of work on the constitution of calycopterin.³¹ The 3-methoxyl group gets demethylated only when the reaction mixture is heated on a water-bath at 100° for 2 hours.

One object of the present work was to synthesize hydroxyflavones and their methyl ethers required for conversion into glycollic acid derivatives and Mannich bases in connection with another investigation on potential chemotherapeutic agents. 5,7-Dihydroxy-3',4',5'-trimethoxyflavone (XIX) and triclin (XX) were two compounds in which there was interest, and which were needed in quantity. The interaction of phloracetophenone and trimethylgalloyl chloride (expt. 7, Table 1) gave 3-trimethylgalloyl derivative of (XIX), readily hydrolysed to (XIX) on treatment with 5 per cent

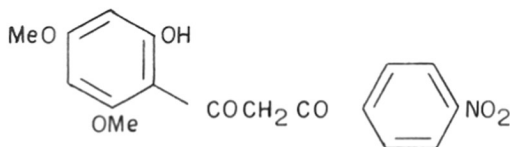
ethanolic potassium hydroxide. Preferential demethylation in the 4'-position with hydrobromic acid, according to the method employed by Horning *et al.*³² for the synthesis of syringic acid from trimethylgallic acid, presented difficulties, and alternative demethylation procedures and the use of *o*-benzyl or *o*-tosyl syringoyl chloride are under examination.



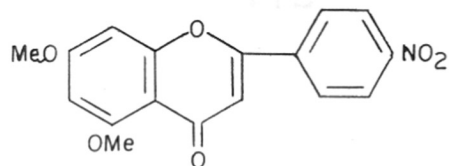
2',4'-Dimethoxyflavone was obtained in 34 per cent yield in expt. 8. In the next experiment phloracetophenone was heated with 2,4-dimethoxybenzoyl chloride. The sticky product obtained on working up as usual gave an orange colour with magnesium and hydrochloric

acid and a reddish brown ferric colour. Alcoholic alkaline hydrolysis gave 5,7-dihydroxy-2,4'-dimethoxyflavone, which on further methylation gave 5,7,2',4'-tetramethoxyflavone, identical with artocarpetin trimethyl ether.

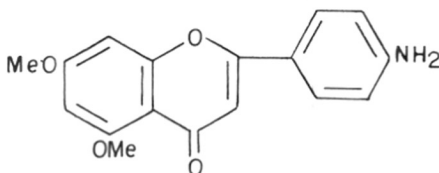
A new synthesis of 5,4'-dihydroxy-7-methoxyflavone (genkwanin; XXV) was achieved, starting from phloracetophenone dimethyl ether and p-nitrobenzoyl chloride. The product was 2-hydroxy-4,6-dimethoxy-4'-nitrodibenzoylmethane (XXI), which on cyclization gave 5,7-dimethoxy-4'-nitroflavone (XXII) (expt. 18) in 36 per cent overall yield. Reduction to the amine (XXIII) by zinc and glacial acetic acid and hydrolysis of the diazonium salt with boiling 48 per cent sulphuric acid gave 5,7-dimethoxy-4'-hydroxyflavone (XXIV). Genkwanin (XXV) was then obtained by treatment of (XXIV) with hydriodic acid at 125° for 45 minutes. Genkwanin was synthesized by Mahal and Venkataraman³³ as follows. 2'-Hydroxy-4-benzoyloxy-4',6'-dimethoxychalkone was oxidized with selenium dioxide to flavone. Debonylation with hydrochloric acid and glacial acetic acid gave genkwanin 5-methyl ether (XXIV), which was then converted to genkwanin (XXV) by partial demethylation.



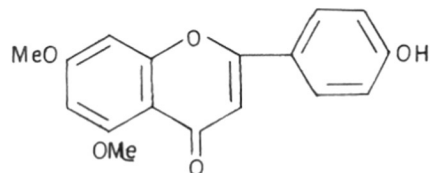
(XXI)



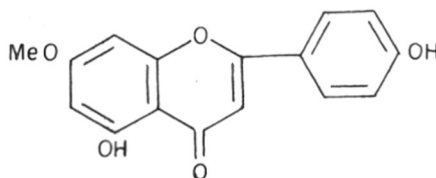
(XXII)



(XXIII)



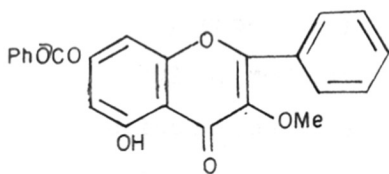
(XXIV)



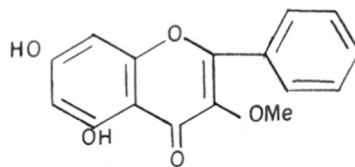
(XXV)

Galangin monomethyl ether (XXVII) was obtained by the alcoholic alkaline hydrolysis of 7-benzoyloxy-5-hydroxy-3-methoxyflavone (XXVI) (expt. 13). 3-Methylchrysin (XXVIII) was isolated directly from the reaction products in expt. 16. A sample of myricetin (3,5,7,3',4'-pentahydroxyflavone (XXXII) was desired in connection with the further examination of the colouring matters of Ponderosa pine bark, from which Kurth *et al.*³⁴ have already isolated quercetin, pinoquercetin (XXIX), pinomyricetin (XXX), and taxifolin

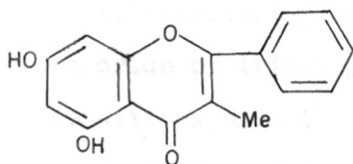
(dihydroquercetin). Myricetin (XXXII) is readily obtained by demethylation of 5,7-dihydroxy-3,3',4',5'-tetramethoxyflavone (XXXI) prepared in expt. 14.



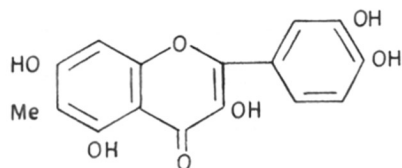
(XXVI)



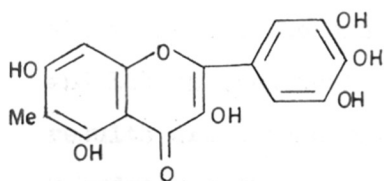
(XXVII)



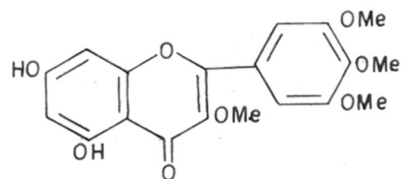
(XXVIII)



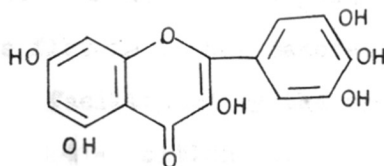
(XXIX)



(XXX)



(XXXI)



(XXXII)

Substituent effects

It will be seen from Table 1 that the overall yields of flavones are decreased by an increase in nuclear methoxyl or hydroxyl substitution in the acetophenone or the acid chloride. Substitution by a methyl or methoxyl group in the α -position of the acetophenone does not seem to produce a significant difference in the yield. Mani *et al.*¹⁸ showed that flavones were obtained directly when ω -methoxy- \underline{C} -methylphloracetophenone was treated with veratroyl chloride or trimethylgalloyl chloride under the conditions used in the present experiments under discussion. It was believed that the direct formation of flavones was perhaps the result of ω -substitution. However, ω -methoxy- and ω -methyl-2-hydroxy-4,6-dimethoxyacetophenones gave only diketones (expt. 12 and 15) on treatment with benzoyl chloride. These results are consistent with the observation that 2-hydroxyacetophenones, not having an additional free hydroxyl group in the 6-position, give only diketones and not flavones. Wheeler³⁵ has postulated that cyclization to a flavone in the Baker-Venkataraman transformation is facilitated by the presence of a nitro group in the 4'-position, since this would promote

enolization of the diketone. However, the reaction between 2-hydroxy-4,6-dimethoxyacetophenone and p-nitrobenzoyl chloride gave the corresponding diketones which required treatment with acid for cyclization. The absence of a free hydroxyl group at position 6 is apparently responsible for the formation of the diketone.

The effect of alkyl substitution on the course of the reaction was the chief interest in expts. 11 and 17. C-Methylphloracetophenone and benzoyl chloride, as mentioned earlier, gave a mixture of 6- (XIII) and 8-methylchrysin (XIV) in yields of 20 and 10 per cent respectively. The formation of the 6-methyl isomer seems to be more favoured, probably because of a steric factor. The product of the reaction of ω -methoxy-C-methylphloracetophenone and benzoyl chloride, followed by hydrolysis, was 5,7-dihydroxy-3-methoxy-6-methylflavone (XV). The results reported in the Allan-Robinson reaction on C-methylphloracetophenone and its ω -methoxy derivative do not confirm the above observations. 6- and 8-Methylchrysin were obtained in nearly equal yields by Mukerjee and Seshadri;²⁹ the 8- and 6-methyl derivatives of galangin 3-methyl ether were obtained in yields of 43 and 14 per cent respectively by Jain and Seshadri.³⁰ The direction of cyclization in the Baker-Venkataraman transformation of C-alkyl phloracetophenone is being studied further.

Mechanism

It has been already observed that the results given in Table 1 show that the modified Baker-Venkataraman transformation gives flavones directly whenever the starting acetophenone has hydroxyl groups in both the 6- and the 2-positions. When one of the hydroxyl groups is methylated or when the 6-position is unsubstituted, only diketones are formed in the reaction. Bapat¹⁷ has reported that 2-hydroxy-4-nitroacetophenone, like 2-hydroxyacetophenone in expt 1 (Table 1), gave the corresponding diketone (2-hydroxy-4-nitrodibenzoylmethane) on treatment with benzoyl chloride under the same conditions. The available data show that other changes in substitution in the acetophenone or acid chloride do not have any such effect on the course of the reaction.

In all the experiments listed in Table 1 a molar excess of the acid chloride has been employed. However, in all the cases where flavones were obtained directly, they had a free hydroxyl group at position 5. These flavones were invariably benzoylated in the 3-position unless an ω -substituent was present in the acetophenone.

A few additional experiments were performed using 2-acetylresorcinol and benzoyl chloride to get

some idea of the role of the 6-hydroxyl group in the reaction, and the results are given in Table 2. All the reactions were carried out for 24 hours; the product was dibenzoate when the time of reaction was cut down to 30 minutes. In expt. 8 *p*-nitrobenzoyl chloride was used in place of benzoyl chloride. In the first four experiments the ratio of 2-acetylresorcinol to benzoyl chloride was varied from 1:1 to 1:5. It was found that the product was always 3-benzoyl-5-hydroxyflavone irrespective of the amount of benzoyl chloride used. The yield is not improved by using more than two moles of benzoyl chloride per mole of the acetophenone.

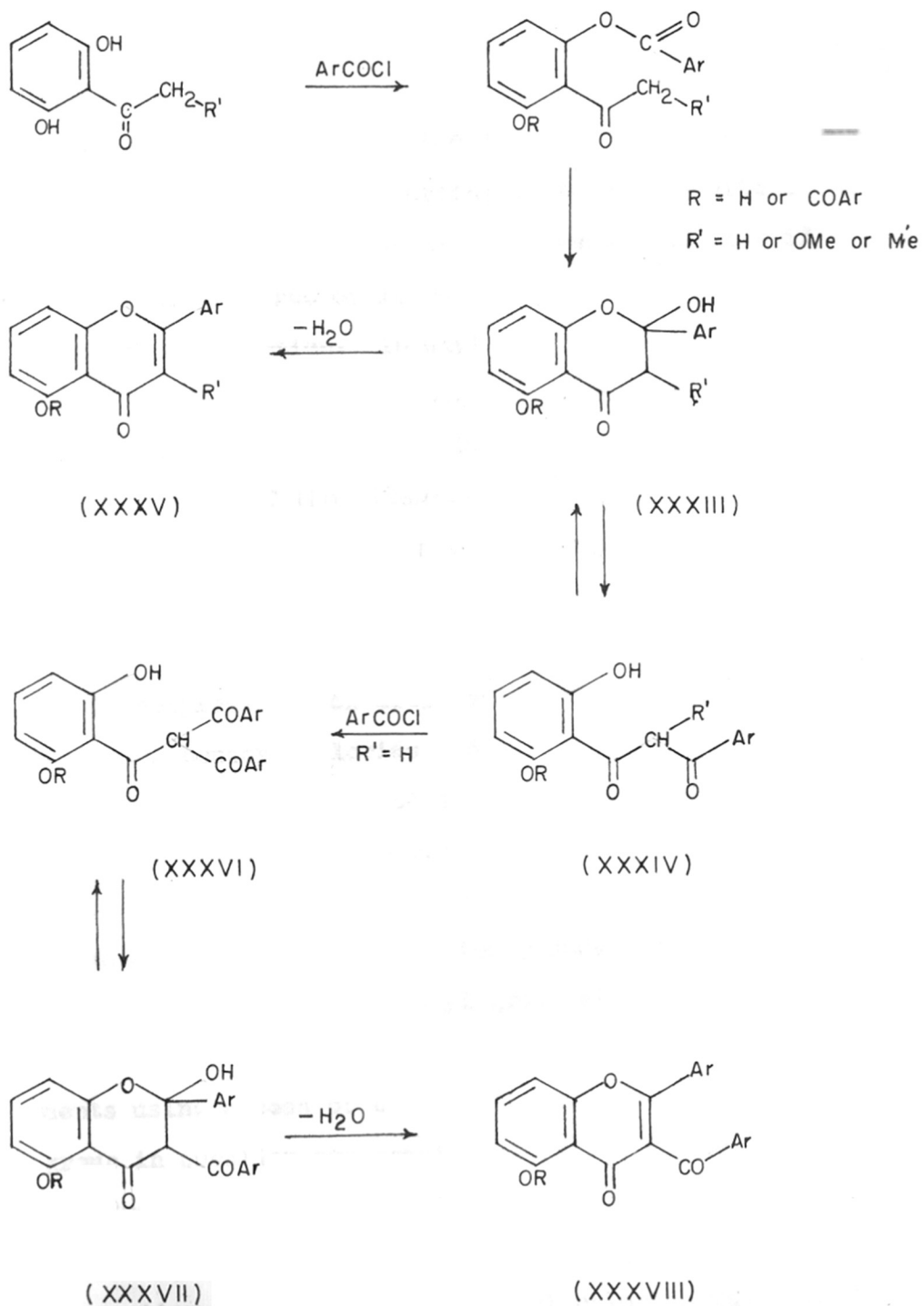
The probable sequence of reactions taking place in the system under consideration is outlined in Chart I. The available data indicate that when $R' = H$, the conversion of (XXXIII) into the triketone (XXXVI) takes place faster than dehydration to (XXXV). The formation of 3-benzoyl-5-hydroxyflavone rather than 5-hydroxyflavone in expt. 1 (Table 2) would mean that the first step of the reaction involving esterification of second hydroxyl group is slower than the accompanying rearrangement and C_2 -acylation to the triketone. The result of the experiment can also be explained in terms of intermolecular transfer of

benzoyl groups. The latter possibility has been realized in expt 5 (Table 2) in which 3-benzoyl-5-hydroxyflavone was obtained as the product when 2-acetylresorcinol monobenzoate was refluxed with acetone and potassium carbonate. In this experiment the benzoyl group is evidently being transferred to a molecule of the diketone from another molecule of the same species or of the starting ester to give the triketone.

TABLE 2.

Expts No.:	Ketone	Moles of acid chloride	Product	Yield %
1.	2-Acetylresorcinol	1	3-Benzoyl-5-hydroxyflavone	40
2.	"	2	"	56
3.	"	3	"	"
4.	"	5	"	"
5.	2-Acetylresorcinol monobenzoate	-	"	-
6.	2-Acetylresorcinol dibenzoate	-	"	-
7.	3-Benzoyl-5-hydroxyflavone	2	3-Benzoyl-5-benzoyloxyflavone	-
8.	"	p-Nitrobenzoyl Chloride (2)	3-Benzoyl-5-p-nitrobenzoyloxyflavone	-

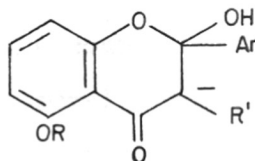
Chart - I



In order to understand the manner in which the 6-hydroxyl group of the starting acetophenone alters the course of the reaction it is necessary to know if it is remaining free or is esterified in the critical steps of the reaction. In expts. 1 and 5 (Table 2) one of the two hydroxyl groups has to remain free during the entire course of the reaction. In expt. 2 (Table 2) even if the dibenzoate of 2-acetylresorcinol is formed initially, by the time intermediate (XXXVII) is formed it should contain a free hydroxyl group in position 5 (XXXVII; R = H). An authentic sample of the 2-acetylresorcinol dibenzoate prepared by the action of benzoyl chloride and pyridine on 2-acetylresorcinol was transformed into 3-benzoyl-5-hydroxyflavone in refluxing acetone and potassium carbonate (expt. 6, Table 2). These experiments show that intermediate (XXXVII) undoubtedly undergoes dehydration when there is a free hydroxyl group at position 5. It is not clear if the same situation holds for experiments using excess of benzoyl chloride. The hydroxyl group in question may remain esterified during the dehydration and may be hydrolysed later. The dibenzoate of 2-acetylresorcinol was isolated in good yield when a reaction using excess of benzoyl chloride was worked

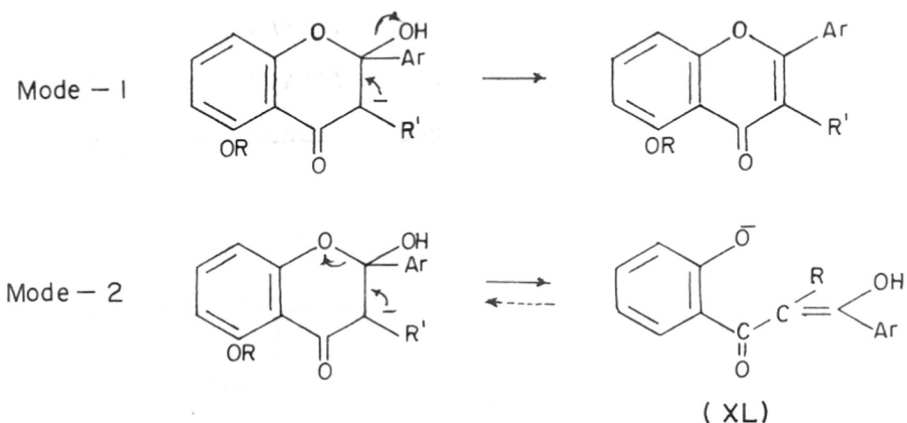
up after 30 minutes. It is evident from what has already been mentioned in connection with expt. 6 that this fact in itself is of no help in deciding whether the 5-hydroxyl group of the intermediate (XXXVII) is esterified or not during the dehydration. 3-Benzoyl-5-hydroxyflavone itself is readily esterified when treated with benzoyl chloride or its p-nitro derivative under the reaction conditions (expts. 7 and 8, Table 2). The esters are hydrolysed back to the hydroxyflavones on refluxing for 24 hours with one molecule of water in acetone and potassium carbonate. On the basis of the data available now, the possibility that the dehydration of intermediates (XXXIII) and (XXXVII) might proceed even when the 5-hydroxyl is esterified cannot be ruled out.

Now the conversion of intermediates (XXXIII) and (XXXVII) into flavones is a retrogression of an addition of the Michael type taking place under the influence of mild base. Loss of a proton from position 3 of the intermediate 2-hydroxyflavanone (XXXIII or XXXVII) to a base would give the anion (XXXIX).



(XXXIX)

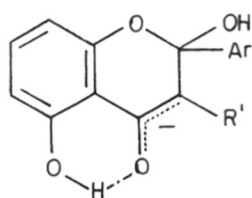
This anion can decompose in two ways. It can eliminate a hydroxyl group to give a flavone or the bond connecting the 1 and 2 positions of the flavanone can break to give (XL).



The latter cleavage itself may be reversible. In any case it is part of an equilibrium because (XL) is rapidly transformed into the diketone (XXXIV) which is in equilibrium with intermediate (XXXIX). The first mode of decomposition on the other hand may be nearly irreversible under the conditions of the reaction. The anion produced when base attacks the proton of the hydroxyl group at position 2 can decompose to give only the diketone or the ester formed initially.

The change in the course of the reaction caused by the presence of a hydroxyl group (and possibly also an acyloxy group) in the 5-position of the flavanone intermediate may be accounted for on the basis of the effect

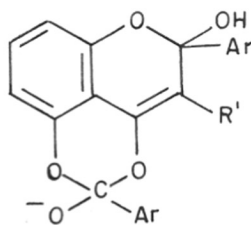
of these groups on the stability of the anion (XXXIX). Ordinarily this anion may be too unstable to be available at a high enough concentration for reaction to take place to any appreciable extent. But when $R = H$, the anion is stabilized by hydrogen bonding as shown in (XLI). In such case it will be available in larger concentrations, permitting the transformation to the flavone to take place at measurable rates.



(XLI)

..... delocalized electron pair.
 - - - - - hydrogen bond.

When $R = \text{ArCO}-$ the enolate ion can add to the carbonyl of the 5-acyloxy group giving intermediate (XLII), which in the form of the anion or in its protonated form may be more stable than anion (XXXIX) without any such interaction. Further experiments designed to give an unambiguous answer to the question of participation of the 5-acyloxy group are in progress.



(XLII)

Reichel and Henning³⁶ have observed that alkali salts of several 2-hydroxydibenzoylmethanes without any substituent in the 6-position cyclize to the corresponding flavones in aqueous solution in the pH range 7 to 9. This observation does not in any way affect the above discussion since the two systems are not comparable.

E X P E R I M E N T A L

2-Hydroxydibenzoylmethane

A mixture of o-hydroxyacetophenone (4 g), benzoyl chloride (7 ml; 2 moles), anhydrous potassium carbonate (20 g; 5 moles), and dry acetone (50 ml) was refluxed for 24 hr. The colour of the reaction mixture became dark yellow. The solvent was removed by distillation. After cooling the yellow residue was treated with water (100 ml) and saturated with carbon dioxide. The precipitate was collected and crystallized from benzene in long yellow needles (5.0 g; yield 72%), m.p. 121° (lit.⁹ m.p. 121°). (Found: C, 75.2; H, 4.5. $C_{15}H_{12}O_3$ requires: C, 75.0; H, 5.0%). The substance gives a cherry red colour with ferric chloride and negative magnesium and HCl test.

Flavone

2-Hydroxydibenzoylmethane (1.0 g) was cyclized to flavone by treatment with cold conc H_2SO_4 (1 ml). The clear yellow solution (green fluorescence) was left at room temp for 10 min and poured on crushed ice. The colourless precipitate was collected and crystallized from hexane in colourless needles (0.8 g; yield 88%), m.p. 98° (lit.⁹ m.p. 96-97°). (Found: C, 80.7; H, 4.6. $C_{15}H_{10}O_2$ requires: C, 81.1; H, 4.6%). The substance does not give colour with ferric chloride and gives an

orange colour with magnesium and HCl.

2-Acetylresorcinol monomethyl ether

The compound was prepared from 2-acetylresorcinol (1 mole) and dimethyl sulphate (1.1 mole) in presence of acetone and anhydrous potassium carbonate.

2-Hydroxy-6-methoxydibenzoylmethane

2-Acetylresorcinol monomethyl ether (2.5 g) in acetone (100 ml) was treated with benzoyl chloride (3.5 ml; 2 moles) and anhydrous potassium carbonate (20 g; 10 moles). After refluxing for 24 hr, the solvent was completely removed and the residue thus obtained was suspended in water and saturated with carbon dioxide. The yellow coloured precipitate was collected, dried and crystallized from methanol in yellow coloured plates (2.6 g; yield 65%), m.p. 102°. (Found: C, 71.4; H, 5.3. $C_{16}H_{14}O_4$ requires: C, 71.1; H, 5.2%). The substance gives a cherry red colour with ferric chloride.

5-Methoxyflavone

The above diketone (1 g) was dissolved in cold conc H_2SO_4 (4 ml) and allowed to stand for 10 min. The reaction mixture was then poured over crushed ice, when an oily precipitate separated out, which solidified to a white product (0.7 g; yield 78%). The product crystallized from aqueous methanol in white needles, m.p. 132°. (Found: C, 76.1; H, 4.6. $C_{16}H_{12}O_3$ requires:

C, 76.2; H, 4.8%). The substance gives an orange colour with magnesium and HCl.

5-Hydroxyflavone (XVI)

The methoxyflavone (0.5 g) was dissolved in acetic acid (5 ml) and refluxed with 40% hydrobromic acid (5 ml) for 2 hr. On cooling the solution was poured into a saturated solution of sodium bisulphite. The precipitate was collected, washed with water and crystallized from methanol in pale yellow needles (0.3 g), m.p. 156°. (Found: C, 75.3; H, 4.3. $C_{15}H_{10}O_3$ requires: C, 75.6; H, 4.2%). The substance gives a red ferric colour and an orange colour with magnesium and HCl. Acetyl derivative was prepared by the usual method of acetic anhydride and a few drops of pyridine. Working up as usual the product crystallized from methanol in colourless needles, m.p. 145°.

3-Benzoyl-5-hydroxyflavone

(a) A mixture of 2-acetylresorcinol (10 g), benzoyl chloride (23 ml; 3 moles), anhydrous potassium carbonate (100 g; ca. 10 moles) and acetone (200 ml) was refluxed for 24 hr. The colour of the reaction mixture turned yellow. After removing the acetone by distillation, the yellow residue was suspended in water and saturated with carbon dioxide. The product was collected, washed with

water and crystallized from ethanol in pale yellow needles (9.0 g; yield 56%), m.p. 175-176° (lit.²⁴ m.p. 174-175°). (Found: C, 77.0; H, 4.3. $C_{22}H_{14}O_4$ requires: C, 77.2; H, 4.1%). The substance gives a red colour with ferric chloride and a reddish orange colour with magnesium and HCl.

(b) 3-Benzoyl-5-hydroxyflavone was obtained in yield as in (a), when the reaction was carried out using 2 or 5 moles of benzoyl chloride.

(c) When 1 mole of benzoyl chloride was used, the product was the same as in (a) and (b), but the yield was 40%.

(d) 2-Benzoyloxy-6-hydroxyacetophenone, m.p. 159°, prepared according to the method of Baker,⁹ gave on treatment for 24 hr with acetone and anhydrous potassium carbonate the same flavone as in the above cases.

(e) 2-Acetylresorcinol dibenzoate, m.p. 105°, when treated with acetone and anhydrous potassium carbonate for 24 hr also gave the same flavone.

3-Benzoyl-5-p-nitrobenzoyloxyflavone

A mixture of 3-benzoyl-5-hydroxyflavone (1 g), p-nitrobenzoyl chloride (2 g), anhydrous potassium carbonate (10 g) and acetone (50 ml) was refluxed for 24 hr. After the complete distillation of acetone, water was added to the residue and the resultant

precipitate was collected. After saturating with carbon dioxide the product was collected and crystallized from gl acetic acid in colourless needles (0.9 g), m.p. 204°. (Found: C, 70.9; H, 3.4; N, 2.8. $C_{29}H_{17}O_7N$ requires: C, 70.8; H, 3.5; N, 2.8%). The substance does not give ferric colour.

3-Benzoyl-5-hydroxyflavone

The above nitroflavone (0.5 g) in acetone (25 ml) was refluxed with anhydrous potassium carbonate (2 g) and water (0.02 ml; ca. 1 mole) for 24 hr. At the end of the reaction acetone was distilled off completely, water was added to the residue and then saturated with carbon dioxide. The resulting precipitate was collected and crystallized from alcohol, m.p. 175°. Mixed m.p. with authentic 3-benzoyl-5-hydroxyflavone remained undepressed. The substance gives a red colour with alcoholic ferric chloride.

5-Hydroxyflavone

3-Benzoyl-5-hydroxyflavone (0.5 g) was debenzoylated by boiling with 5% alcoholic KOH for 30 min. Alcohol was distilled off and an equal amount of water was added. On cooling and acidifying, the precipitate was collected and crystallized from ethanol in yellow needles, m.p. 156°. Mixed m.p. with the above sample remained

undepressed.

Resacetophenone

(a) A mixture of resorcinol (2 g), boron fluoride-acetic acid complex (10 g) was kept at room temp (28-30°) for 18 hr and poured over crushed ice (200 g). The product crystallized from hot water in colourless needles (1.7 g), m.p. 147°. The substance gives a red colour with ferric chloride.

(b) A mixture of resorcinol (2 g), boron fluoride-acetic acid complex (10 g) was heated at 100° for 4 hr. The mixture was poured into water and boiled for 10 min. The product obtained on cooling, crystallized from hot water in colourless needles (1.4 g), m.p. 147°.

2-Hydroxy-4-benzoyloxydibenzoylmethane

Resacetophenone (1.0 g) in acetone (50 ml) was refluxed with benzoyl chloride (2.9 ml; 3 moles) and anhydrous potassium carbonate (10 g; ca. 10 moles) for 24 hr. The colour of the reaction mixture changed from pale yellow to deep yellow. On working up as usual the yellow coloured product was collected and crystallized first from benzene in yellow plates and further purified by crystallization from ethanol (1.5 g; yield 70%), m.p. 167° (lit.⁹ m.p. 167°). (Found:

C, 72.8; H, 4.6. $C_{22}H_{16}O_5$ requires: C, 73.3; H, 4.4%.

The substance gives a red colour with ferric chloride and negative test with magnesium and HCl.

7-Hydroxyflavone

The above diketone (0.5 g) was cyclised to flavone by treating with cold conc H_2SO_4 for 10 min. The reaction mixture was then poured over crushed ice. The yellow precipitate was collected, and crystallized from ethanol in long yellow needles (0.28 g; yield 85%), m.p. 240° (lit.^{9,25} m.p. 240°). (Found: C, 75.3; H, 4.1. $C_{15}H_{10}O_3$ requires: C, 75.6; H, 4.2%). The substance does not give colour with ferric chloride but gives an orange colour with magnesium and HCl; acetyl derivative, m.p. 130° (lit.^{9,25} m.p. $129-130^\circ$).

2-Hydroxy-4,6-dimethoxydibenzoylmethane

2-Hydroxy-4,6-dimethoxyacetophenone (5 g) in acetone (200 ml) was refluxed with benzoyl chloride (5.8 ml; 2 moles) and anhydrous potassium carbonate (35 g; about 10 moles) for 24 hr. The colour of the reaction mixture turned from pale yellow to orange. Working up of the reaction mixture as in other cases gave the semi-solid mass, which was collected and crystallized from hexane in prisms (3.9 g; yield 50%),

m.p. 120° . (Found: C, 67.7; H, 5.2. $C_{17}H_{16}O_5$ requires: C, 68.0; H, 5.3%). The substance gives a crimson red colour with ferric chloride and negative test with magnesium and HCl.

5,7-Dimethoxyflavone

The above diketone (0.5 g) was cyclised to 5,7-dimethoxyflavone by treatment with cold conc H_2SO_4 . On pouring the H_2SO_4 solution over crushed ice a sticky precipitate was obtained, which was crystallized from 50% ethanol in colourless needles (0.4 g; yield 85%), m.p. 145° (lit.³⁷ m.p. 143°). (Found: C, 72.3; H, 5.0. $C_{17}H_{14}O_4$ requires: C, 72.3; H, 3%). The substance does not give colour with ferric chloride, but gives an orange colour with magnesium and HCl.

7-Methoxy-5-hydroxyflavone (tectochrysin)

A solution of 5,7-dimethoxyflavone (0.5 g) in gl acetic acid (5 ml) and 48% hydrobromic acid (5 ml) was refluxed for 2 hr. After cooling the mixture was poured into a saturated solution of sodium bisulphite. The product crystallized from ethanol in needles (0.4 g), m.p. 163° (lit.²⁵ m.p. 163°). (Found: C, 71.2; H, 4.3; OMe, 11.0. $C_{16}H_{12}O_4$ requires: C, 71.6; H, 4.5, OMe, 11.6%). The substance gives a red colour with ferric

chloride and an orange colour with magnesium and HCl.

5,7-Dihydroxyflavone (chrysin) (XVIII)

A solution of 5,7-dimethoxyflavone (0.5 g), gl acetic acid (4 ml) and hydriodic acid (d, 1.7; 4 ml) was refluxed for 3 hr. Working up as above the product crystallized from ethanol in pale yellow needles (0.3 g), m.p. 286° (lit.²⁵ m.p. 275°). (Found: C, 70.6; H, 3.9. $C_{15}H_{10}O_4$ requires: C, 70.9; H, 4.0%). The substance gives a reddish brown ferric colour and an orange colour with magnesium and HCl; acetyl derivative, m.p. 192° (lit.²⁵ m.p. 192°).

Chrysin (XVIII)

A mixture of phloracetophenone (4 g), benzoyl chloride (10 ml; 4 moles), anhydrous potassium carbonate (30 g, ca. 10 moles) and anhydrous acetone (100 ml) was refluxed as usual for 24 hr. The colour of the reaction mixture changed from pale yellow to red. The product obtained, on working up as usual, was collected, but difficult to crystallize (4.2 g; yield 42%), m.p. ca. 220° . The substance gives a red colour with ferric chloride and a reddish orange colour with magnesium and HCl.

The above product was dissolved in 5% Na_2CO_3 solution and heated to boiling for 2 hr. The solution was then cooled and filtered to remove a small amount of undissolved matter. Acidification of filtrate with ice-cold HCl yielded a yellow precipitate, which on crystallization from ethanol gave pale yellow needles, m.p. 286° , identical with chrysin obtained by the previous method.

2b 3-Benzoyl-5,7-dihydroxyflavone (XVII)

The crude product (0.5 g) obtained in the above experiment was dissolved in cold conc H_2SO_4 , left at room temp for 10 min and poured over crushed ice. The yellow coloured precipitate was collected, washed with water and crystallized from ethanol in yellow needles (0.3 g), m.p. 145° (lit.²⁴ m.p. $145-146^\circ$). (Found: C, 73.7; H, 4.1. $\text{C}_{22}\text{H}_{14}\text{O}_5$ requires: C, 73.7; H, 3.9%).

2c 3-Trimethylgalloyl-5,7-dihydroxy-3',4',5'-trimethoxyflavone (XII)

Phloracetophenone (1 g) in acetone (50 ml) was treated with trimethylgalloyl chloride (5.6 g; 4 moles) and anhydrous potassium carbonate (8 g; ca. 10 moles). Carrying out the reaction for 24 hr. and working up as usual, the orange coloured precipitate was obtained, which crystallized from alcohol in brownish yellow

needles (0.9 g; 30%), m.p. 203-204°. (Found: C, 62.3; H, 4.7. $C_{28}H_{26}O_{11}$ requires: C, 62.5; H, 4.9%). The substance gives a reddish brown colour with ferric chloride and red colour with magnesium and HCl.

5,7-Dihydroxy-3',4',5'-trimethoxyflavone (XIX)

The above flavone (0.5 g) was dissolved in 5% alcoholic KOH and refluxed for 30 min. Alcohol was then distilled off and an equal quantity of water was added. After acidification the precipitate was collected and crystallized from ethanol in yellow needles (0.25 g), m.p. 269°. (Found: C, 63.0; H, 5.0. $C_{18}H_{16}O_7$ requires: C, 62.8; H, 4.6%).

2-Hydroxy-2',4'-dimethoxydibenzoylmethane

o-Hydroxyacetophenone (2.5 g) dissolved in acetone (100 ml) was refluxed with 2,4-dimethoxybenzoyl chloride (7.0 g; ca. 2 moles) and anhydrous potassium carbonate (25 g; ca. 10 moles) for 24 hr. The precipitate was collected, after working up as usual, washed with water and crystallized from ethanol (3.7 g; yield 40%), m.p. 114-115°. (Found: C, 68.2; H, 5.6. $C_{17}H_{16}O_5$ requires: C, 68.0; H, 5.3%). The substance gives a reddish brown colour with ferric chloride.

2',4'-Dimethoxyflavone

The above diketone (0.5 g) was dissolved in cold conc H_2SO_4 , left at room temp for 10 min and poured over crushed ice. The yellow precipitate was collected and crystallized from ethanol in yellow microscopic needles (0.4 g; 85%), m.p. 277-278°. (Found: C, 72.1; H, 4.6. $C_{17}H_{14}O_4$ requires: C, 72.3; H, 5.0%). The substance gives an orange colour with magnesium and HCl.

5,7-Dihydroxy-2',4'-dimethoxyflavone

A mixture of phloracetophenone (1 g), 2,4-dimethoxybenzoyl chloride (5 g; ca. 4 moles), anhydrous potassium carbonate (8 g; ca. 10 moles) and acetone (50 ml) was refluxed for 24 hr. Working of the reaction mixture as usual gave a reddish brown sticky residue, which was collected and hydrolysed with 5% alcoholic KOH. The product, obtained on hydrolysis, was crystallized from alcohol in yellow needles (0.6 g; yield 35%), m.p. 265° (lit.²⁶ m.p. 258-259). (Found: C, 65.5; H, 5.0. $C_{17}H_{14}O_6$ requires: C, 65.0; H, 4.5%). The substance gives a reddish brown colour with ferric chloride and an orange colour with magnesium and HCl.

5,7,2',4'-Tetramethoxyflavone

5,7-Dihydroxy-2',4'-dimethoxyflavone (100 mg) was

refluxed with dimethyl sulphate (1 ml), anhydrous potassium carbonate (2 g) and acetone (20 ml) for 48 hr. After evaporation of the solvent, water was added to the residue. The yellow coloured precipitate, free from ferric colour, crystallized from ethanol in yellow needles, m.p. 175° , not lowered on admixture with artocarpetin trimethyl ether.

2-Hydroxy-4,6-dimethoxy-4'-nitrodibenzoylmethane (XXI)

A mixture of 2-hydroxy-4,6-dimethoxyacetophenone (4 g), p-nitrobenzoyl chloride (7.6 g; 2 moles), dry acetone (100 ml) and anhydrous potassium carbonate (25 g; ca. 10 moles) was refluxed for 24 hr. The colour of the reaction mixture changed from pale yellow to red. Acetone was then distilled off completely and the red coloured residue was suspended in water and saturated with carbon dioxide. The product was collected and crystallized from benzene in yellow needles (3.0 g; yield 40%), m.p. 200° . (Found: C, 58.7; H, 4.3; N, 3.9. $C_{17}H_{15}NO_7$ requires: C, 59.1; H, 4.3; N, 4.0%). The substance gives a crimson-red colour with alcoholic ferric chloride.

5,7-Dimethoxy-4'-nitroflavone (XXII)

The above diketone (1.2 g) was dissolved in cold

conc H_2SO_4 (5 ml) and left at room temp for 10 min. On pouring over crushed ice a yellow coloured precipitate was obtained, which crystallized from acetic acid in long yellow needles (1.0 g; yield 90%), m.p. 255° . (Found: C, 62.7; H, 4.5; N, 4.2. $C_{17}H_{13}NO_6$ requires: C, 62.4; H, 4.0; N, 4.2%). The substance gives a reddish-orange colour with magnesium and HCl.

5,7-Dimethoxy-4'-aminoflavone (XXIII)

The nitroflavone (500 mg) and zinc dust (1.5 g) were suspended in alcohol (100 ml), refluxed and gl acetic acid (6 ml) was added in four portions at interval of 15 min. After refluxing for 15 min more, the orange coloured solution, having blue fluorescence, was filtered and concentrated to 15 ml. On dilution with water the aminoflavone was precipitated. It was crystallized from benzene in pale yellow needles (300 mg), m.p. 229° . (Found: C, 68.4; H, 4.9; N, 5.1. $C_{17}H_{15}NO_4$ requires: C, 68.7; H, 5.0; N, 4.7%).

5,7-Dimethoxy-4'-hydroxyflavone (XXIV)

The aminoflavone (200 mg) was suspended in water (8 ml) and H_2SO_4 (1.6 ml) was added. The mixture was cooled in ice and treated with cooled aqueous solution of sodium nitrite (60 mg). After allowing to stand for 30 min at 0° the excess of nitrous acid was destroyed

by addition of urea and the diazonium solution was gradually poured into a boiling mixture of water (16 ml) and conc H_2SO_4 (8 ml). The solution was boiled till no colouration was obtained with β -naphthol in aqueous alkali. The solution was diluted with water and the precipitate thus obtained was crystallized from ethanol in pale yellow needles (160 mg), m.p. 296° . (Found: C, 68.6; H, 4.7; OMe, 19.3. $C_{17}H_{14}O_5$ requires: C, 68.4; H, 4.7; OMe, 20.8%). The substance does not give ferric colour.

5,4'-Dihydroxy-7-methoxyflavone (genkwanin) (XXV)

The hydroxyflavone (100 mg) was dissolved in gl acetic acid (1.7 ml) and treated with hydriodic acid (d, 1.7; 1.7 ml). The reaction mixture was heated on an oil bath at 125° for 45 min and poured into a saturated solution of sodium bisulphite. The precipitate thus obtained was collected and crystallized from aqueous acetone in yellow needles (50 mg), m.p. 285° , (lit.³³ m.p. 285-286). (Found: C, 67.6; H, 4.4; OMe, 10.4. $C_{16}H_{12}O_5$ requires: C, 67.6; H, 4.2; OMe, 10.9%). The substance gives a brownish red colour with ferric chloride.

Acetyl derivative crystallized from ethanol in colourless needles, m.p. 197° . (Found: C, 65.3; H, 4.4. $C_{20}H_{16}O_7$ requires: C, 65.2; H, 4.3%).

6- and 8-Methylchrysin (XIII) and (XIV)

3-Methylphloracetophenone (2 g) was dissolved in dry acetone (100 ml) and treated with benzoyl chloride (6.6 ml; 5 moles) and freshly ignited potassium carbonate (17 g; ca. 10 moles). After refluxing for 24 hr acetone was distilled off. The yellow residue was then suspended in water and saturated with carbon dioxide. The brownish sticky mass was collected and tried to crystallize from a number of solvents. The substance gives a greenish brown colour with ferric chloride and an orange colour with magnesium and HCl. The residue was dissolved in 5% alcoholic KOH and refluxed for half an hr on a water-bath. Alcohol was then distilled off as far as possible and an equal volume of water was added. The solution was then cooled and acidified with ice-cold HCl. The resulting precipitate was collected and subjected to fractional crystallization from ethanol. The sparingly soluble fraction was 6-methylchrysin obtained in the form of pale yellow needles (0.6 g; yield 20%), m.p. 305° (lit.²⁹ m.p. 308-310°). (Found: C, 72.0; H, 4.6. $C_{16}H_{12}O_4$ requires: C, 71.6; H, 4.6%). The substance gives an orange colour with magnesium and HCl and a greenish brown colour with alcoholic ferric chloride; acetyl derivative, m.p. 197°.

(Found: C, 68.4; H, 4.5. $C_{20}H_{16}O_6$ requires: C, 68.2; H, 4.6%).

The more soluble fraction, 8-methylchrysin, separated on dilution with water as yellow needles (0.31 g; yield 10%), m.p. 240° (lit.²⁹ m.p. $255-260^{\circ}$).

7-Benzoyloxy-5-hydroxy-3-methoxyflavone (XXVI)

A mixture of α -methoxyphloracetophenone (5 g), benzoyl chloride (9.0 ml; 4 moles), acetone (100 ml) and anhydrous potassium carbonate (30 g; ca. 10 moles) was refluxed for 24 hr. The colour of the reaction mixture turned red. The precipitate obtained by the usual working up procedure was collected, washed with water and crystallized from benzene-hexane in very pale yellow needles (3.5 g; yield 36%), m.p. 152° . (Found: C, 70.7; H, 4.3. $C_{23}H_{16}O_6$ requires: C, 71.1; H, 4.1%). The substance gives a cherry-red colour with ferric chloride and red colour with magnesium and HCl.

5,7-Dihydroxy-3-methoxyflavone (XVII)

7-Benzoyloxy-5-hydroxy-3-methoxyflavone (0.5 g) was hydrolysed by boiling with 5% alcoholic KOH for 20 min. Alcohol was distilled off as far as possible and an equal quantity of water added. On cooling and acidifying a pale yellow precipitate separated, which was crystallized from ethanol in colourless needles (0.38 g), m.p. 297° ,

(lit.²² m.p. 297°). (Found: C, 67.4; H, 4.6.

$C_{16}H_{12}O_5$ requires: C, 67.6; H, 4.2%). Acetyl derivative crystallized from ethanol in colourless needles, m.p. 176° (lit.²⁶ m.p. 175-176°).

2-Hydroxy-4,6- ω -trimethoxydibenzoylmethane

2-Hydroxy-4,6, ω -trimethoxyacetophenone (4 g) in acetone (100 ml) was refluxed with benzoyl chloride (4 ml; 2 moles) and anhydrous potassium carbonate (25 g; ca. 10 moles) for 24 hr. Acetone was then distilled off and the residue was suspended in water. After saturating with carbon dioxide, an oil (2.5 g) (yield 45%) separated out, which was difficult to crystallize. The substance gives a cherry red colour with ferric chloride and negative test with magnesium and HCl.

3,5,7-Trimethoxyflavone

The above diketone (0.5 g) was dissolved in ice-cold H_2SO_4 , left at room temp for 10 min and poured over crushed ice. The precipitate was collected and crystallized from alcohol in colourless needles (0.36 g; yield 78%), m.p. 196° (lit.³⁸ m.p. 199-200°). (Found: C, 69.2; H, 4.8. $C_{18}H_{16}O_5$ requires: C, 69.2; H, 5.1%). The substance does not give colour with ferric chloride and gives a red colour with magnesium and HCl.

5,7-Dihydroxy-3,3',4',5'-tetramethoxyflavone (XXXI)

A mixture of *o*-methoxyphloracetophenone (1.0 g), acetone (50 ml), *o*-trimethylgalloyl chloride (3.5 g; ca. 3 moles) and anhydrous potassium carbonate was refluxed for 24 hr. The precipitate obtained by the usual procedure was collected and crystallized from ethanol (0.7 g; yield 36%), m.p. 277-278° (lit.²⁷ m.p. 276-277°). (Found: C, 60.6; H, 4.8. $C_{19}H_{18}O_8$ requires: C, 61.0; H, 4.8%). The substance gives a red colour with alcoholic ferric chloride and a red colour with magnesium and HCl.

3,5,7,3',4',5'-Hexahydroxyflavone (myricetin) (XXXII)

A mixture of the above flavone (0.5 g), acetic anhydride (5 ml) and hydriodic acid (*d*, 1.7; 5 ml) was refluxed for 4 hr. The reaction mixture on cooling was poured into a saturated solution of sodium bisulphite. The yellow coloured precipitate was collected and crystallized from dil ethanol in pale yellow needles (0.2 g), m.p. 360° (dec). (Found: C, 56.1; H, 3.4. $C_{15}H_{10}O_8$ requires: C, 56.6; H, 3.1%). The substance gives a red colour with ferric chloride and reddish orange colour with magnesium and HCl. Acetyl derivative, m.p. 215° (lit.²⁶ m.p. 214-215°).

5,7-Dihydroxy-3-methylflavone (XXVIII)

Phlorepropiophenone (5 g) in acetone (200 ml) was

refluxed with benzoyl chloride (9.1 ml; 3 moles) and anhydrous potassium carbonate (35 g; ca. 10 moles) for 24 hr. On working up as usual the precipitate was collected and crystallized from ethanol in colourless needles (2.8 g; yield 40%), m.p. 262 (lit.³⁹ m.p. 262). (Found: C, 71.5; H, 4.3. $C_{16}H_{12}O_4$ requires: C, 71.6; H, 4.5%). The substance gives a red colour with ferric chloride and a reddish orange colour with magnesium and HCl. Acetyl derivative, m.p. 133° (lit.³⁷ m.p. 132°).

2-Hydroxy-4,6-dimethoxy- α -methyldibenzoylmethane

A mixture of 2-hydroxy-4,6-dimethoxyphloroacetylphenone (5 g), acetone (200 ml), benzoyl chloride (5 ml; 2 moles) and potassium carbonate (30 g; ca. 10 moles) was refluxed for 24 hr. The colour of the reaction mixture became dark yellow. After working up of the reaction mixture as usual the pale yellow coloured precipitate was collected and crystallized from benzene-hexane in colourless needles (3.3 g; yield 45%), m.p. 152°. (Found: C, 68.6; H, 5.8. $C_{18}H_{18}O_5$ requires: C, 68.8; H, 5.7%). The substance gives a red colour with ferric chloride and negative colour with magnesium and HCl.

5,7-Dimethoxy-3-methylflavone

The above diketone (0.5 g) was cyclized to flavone by treatment with ice-cold H_2SO_4 . Pouring of H_2SO_4

solution on water gave the precipitate which was collected and crystallized from benzene-hexane in very pale yellow needles (0.38 g; yield 80%), m.p. 181° . (Found: C, 73.0; H, 5.4. $C_{18}H_{16}O_4$ requires: C, 73.0; H, 5.9%). The substance gives a reddish orange colour with magnesium and HCl and does not give colour with ferric chloride.

7-Benzoyloxy-5-hydroxy-6-methyl-3-methoxyflavone

A mixture of C-methyl- α -methoxyphloracetophenone (1 g), acetone (50 ml), benzoyl chloride (1.6 ml; 3 moles) and anhydrous potassium carbonate (6 g; ca. 10 moles) was refluxed for 24 hr. The colour of the reaction mixture became dark red. After working up as usual, the yellow coloured precipitate was collected and crystallized from alcohol in yellow needles (0.7 g; yield 35%), m.p. 146° . (Found: C, 71.5; H, 4.5. $C_{24}H_{18}O_6$ requires: C, 71.6; H, 4.5%). The substance gives a red colour with ferric chloride and a red colour with magnesium and HCl.

5,7-Dihydroxy-6-methyl-3-methoxyflavone (XV)

The above flavone (0.5 g) was dissolved in 5% alcoholic KOH (5 ml) and refluxed for 20 min. The product obtained after the usual working up procedure was crystallized from ethanol in yellow needles (0.3 g), m.p. 275° (lit.³⁰ m.p. $273-274^{\circ}$). (Found: C, 68.3; H, 4.4. $C_{17}H_{14}O_5$ requires: C, 68.5; H, 4.7%). Acetyl derivative, m.p. 168° (lit.³⁰ m.p. $167-168^{\circ}$).

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S U M M A R Y

Part I

Three new flavonoid pigments named artocarpetin, artocarpanone and isoartocarpin have been isolated from the heartwood of Artocarpus integrifolia, from which A. G. Perkin isolated morin (I) and cyanomaclurin (II), and Dave isolated artocarpin (III).

The elementary analysis of artocarpetin and its derivatives and the molecular weight of its trimethyl ether determined by the Rast method agree with the molecular formula $C_{16}H_{12}O_6$. Artocarpetin contains one methoxyl and three hydroxyl groups, and the colour reactions indicate that it is probably a flavone containing a hydroxyl group in the 5-position. Artocarpetin yielded a trimethyl ether which was identical with synthetic 5,7,2',4'-tetramethoxyflavone. Demethylation of artocarpetin by hydriodic acid gave 5,7,2',4'-tetrahydroxyflavone. Alkaline hydrolysis of artocarpetin yielded phloroglucinol monomethyl ether, characterized as its bisbenzeneazo derivative obtained by coupling with diazotized aniline, together with β -resorcylic acid. The ultraviolet absorption spectrum of artocarpetin is very similar to that of 5,7,2',4'-tetrahydroxyflavone. The constitution of artocarpetin is therefore 5,2',4'-trihydroxy-7-methoxyflavone (IV). An attempt to synthesize artocarpetin by the selective demethylation of 5,7,2',4'-tetramethoxyflavone was made,

but the product was 5,4'-dihydroxy-7,2'-dimethoxyflavone. Alkaline hydrolysis of 5,4'-dihydroxy-7,2'-dimethoxyflavone gave phloroglucinol monomethyl ether and 4-hydroxy-2-methoxybenzoic acid. The identity of the latter was established by the negative ferric reaction and direct comparison with the synthetic acid. Artocarpetin was then synthesized from 2-hydroxy-4,6-dimethoxyphenyl 2,4-dibenzoyloxystyryl ketone, which was cyclized with selenium dioxide to 5,7-dimethoxy-2',4'-dibenzoyloxyflavone. Debonylation and subsequent partial demethylation by means of hydriodic acid gave 5,2',4'-trihydroxy-7-methoxyflavone, which was identical in all its properties with artocarpetin.

Artocarpanone, $C_{16}H_{14}O_6$, like artocarpetin contains one methoxyl and three phenolic hydroxyl groups. It forms a dinitrophenylhydrazone very readily. The strong colours in the magnesium-hydrochloric acid (magenta) and sodium amalgam (red) tests indicate a flavanone structure. This was confirmed by the characteristic ultraviolet absorption spectrum and by the formation of two methyl ethers on treatment with dimethyl sulphate and potassium carbonate in acetone. One was identified as 5,7,2',4'-tetramethoxyflavanone and the other as 2,4,2',4',6'-pentamethoxychalkone. Methylation of artocarpanone with diazomethane in methanol-

ether gave 5,7,2',4'-tetramethoxyflavanone, while the use of diazomethane in ether yielded 5-hydroxy-7,2',4'-trimethoxyflavanone (red-brown ferric colour). A purple colour is given with conc nitric acid showing that the 7-position in artocarpanone is probably occupied by a methoxyl group. Alkaline hydrolysis of artocarpanone yielded the same phenol and acid as artocarpetin. Artocarpanone is therefore 5,2',4'-trihydroxy-7-methoxyflavanone (XII).

Analytical results for isoartocarpin, the third new colouring matter, and its derivatives and the molecular weight of its derivatives determined by the Rast method agree with the molecular formula $C_{26}H_{28}O_6$. Magnesium-hydrochloric acid and sodium amalgam tests indicate γ -pyrone character. Isoartocarpin contains one methoxyl and two phenolic hydroxyl groups, one less than artocarpin. Catalytic hydrogenation in presence of palladium-charcoal afforded a dihydro as well as tetrahydro derivative. Alcoholic alkaline hydrolysis of isoartocarpin dimethyl ether gave 2-hydroxy-4-methoxybenzoic acid. The formation of 2-hydroxy-4-methoxybenzoic acid from isoartocarpin dimethyl ether, which contains no phenolic hydroxyl group, indicates that one of the two C_5 residues in isoartocarpin, to which reference is made later, may be attached to the

2'-position. Alkali fusion of tetrahydroisoartocarpin led to the formation of isoamyphloreoglucinol monomethyl ether and β -resorcylic acid. Ozonolysis of isoartocarpin dimethyl ether gave isobutyraldehyde and acetone, together with a dialdehyde which analysed for a hydroxytrimethoxyflavone containing a CHO and a CH_2CHO group and one molecule of water of crystallization. Since isobutyraldehyde and acetone were obtained by ozonization it was clear that $\text{Me}_2\text{C}=\text{CC}$ and $\text{Me}_2\text{CH}-\text{CH}=\text{C}$ groups were present in isoartocarpin. Ozonization of dihydroisoartocarpin dimethyl ether gave acetone and a flavone monoaldehyde. Demethylation of tetrahydroisoartocarpin with hydriodic acid yielded a product, the analysis of which showed the loss of six carbon atoms. Treatment of dihydroisoartocarpin with hydrobromic acid in acetic anhydride at water-bath temperature gave a product with five carbon atoms less. The above dealkylated compounds gave the same methyl ether on methylation with dimethyl sulphate. Dihydroisoartocarpin dimethyl ether on treatment with hydrochloric acid at water-bath temperature gave a product which had a positive ferric chloride test and six carbon atoms less. The above data, in conjunction with the known constitution of artocarpin, suggest the structure of isoartocarpin as (XXVIII).

The ultraviolet absorption spectra of artocarpetin, artocarpanone and isoartocarpin and their derivatives

have been determined. The spectrum of artocarpanone has been compared with the spectra of acetophenones and related flavanones. The spectra of artocarpetin, isoartocarpin and artocarpin have been discussed.

A biogenetic scheme for the hydroxylation of the B-ring in artocarpin, artocarpanone, artocarpetin, isoartocarpin and morin has been suggested.

Part II

The direct formation of 2-hydroxydibenzoylmethanes and flavones in the reaction of various 2-hydroxyacetophenones with acid chlorides in refluxing acetone in presence of anhydrous potassium carbonate (a modified Baker-Venkataraman transformation) has been studied in detail, one object being to use it as a practicable method for flavone synthesis. It was observed that whenever the starting *o*-hydroxyacetophenone had an additional hydroxyl group in the 6-position the reaction product was a flavone. If the acetophenone did not have any ω -substituent, the flavone obtained was invariably benzoylated in the 3-position. Thus, for example, 2-acetylresorcinol, phloracetophenone and ω -methoxyphloracetophenone gave 3-benzoyl-5-hydroxyflavone, 3-benzoyl-5,7-dihydroxyflavone and 5,7-dihydroxy-3-methoxyflavone respectively with benzoyl chloride. On the other hand, when the 6-position of the starting *o*-hydroxyacetophenone carried an alkoxy group or did not have any substituent, the product

of the reaction was a 2-hydroxydibenzoylmethane. Thus 2-hydroxyacetophenone, resacetophenone, the monomethyl ether of 2-acetylresorcinol and the dimethyl ether of phloracetophenone, when heated with benzoyl chloride, gave the corresponding 2-hydroxydibenzoylmethanes. These and various other dibenzoylmethanes obtained similarly were cyclized to flavones by the usual method of treatment with sulphuric acid.

Methoxyl or hydroxyl substitution in the acetophenone or acid chloride tended to lower the yields in the reaction. The yields were not affected by methoxyl or methyl substitution in the ω -position. It was observed that the formation of 6-methylflavones was favoured in preference to the 8-methyl isomer in the reactions of C-methylphloracetophenone and its ω -methoxy derivative with benzoyl chloride.

The mechanism of the reaction has been studied briefly in order to ascertain the role of the 6-hydroxyl group. The direct formation of flavones from 2,6-dihydroxyacetophenones has been rationalized on the basis of the increase in stability due to hydrogen bonding in the enolate from the 2-hydroxyflavanone intermediate formed in the reaction.

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