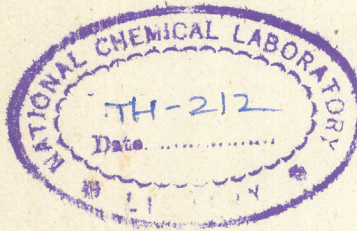


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Dr. K. VENKATRAMAN

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CONSTITUTION OF THE ELEMENTS OF LANTHANUM

A Thesis Submitted in
Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy

by



TH-212

A Thesis Submitted by
SATHYANARAYAN SATHYANARAYAN, M.Sc.

COMPUTERISED

to
THE UNIVERSITY OF TORONTO
for
The Degree of Ph.D.

CONSTITUTION OF THE PIGMENTS OF GARCINIA MORELLA

A New General Method for the Synthesis
of 2,2-Dimethyl chromanones

A Synthesis of DhydrojacareuBin



A Thesis Submitted by
HATTIANGADI BHASKER BHAT , M.Sc.

to

THE UNIVERCITY OF POONA

for

The Degree of Ph. D .

547.972.2(043)
BHA

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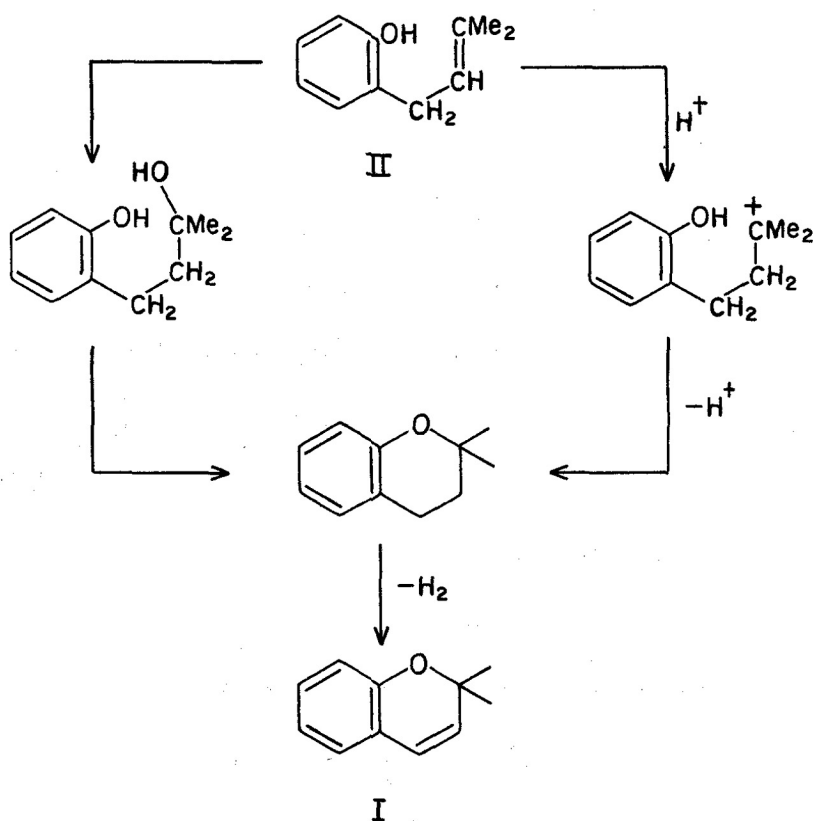
PART I

NATURALLY OCCURRING 2,2-DIMETHYLCHROMENES - A REVIEW

The 2,2-dimethylchromene ring system (I) is of common occurrence in plant products. The ring system occurs either as such in nature with hydroxyl and other substituents or is incorporated with other heterocyclic systems such as coumarin, flavone, isoflavone, xanthone and other complex ring systems as detailed in Chart I. Coumarins and isoflavones are the most commonly encountered natural products containing a 2,2-dimethylchromene nucleus; among the isoflavones may be included the closely related rotenoids such as toxicarol (XXII). Sericetin (XIII) is the only flavone and jacareubin (XVIII) is the only xanthone found so far to occur in nature which contains the 2,2-dimethylchromene. Morellin and other pigments, which are the main subject of this thesis, have now been shown to be complex xanthone derivatives containing a 2,2-dimethylchromene ring system.

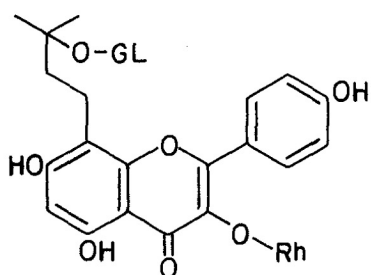
The gem-dimethyl group and the 5-carbon chain in the pyran nucleus of the 2,2-dimethylchromenes listed in Chart I indicate their biogenesis from a phenol and an isoprene unit through an o-YY-dimethylallyl phenol (II). Phenols, especially resorcinol and phloroglucinol, have nucleophilic activity and can therefore be readily

attacked by "active isoprene" ($\text{Me}_2\text{C}=\text{CH}-\text{C}^+\text{H}_2$) postulated by CORNFORTH and POPJAK.^{1a} The formation of I from II may proceed through one of several mechanisms, such as those indicated below, and a choice can be made only by specific biosynthetic experimentation.

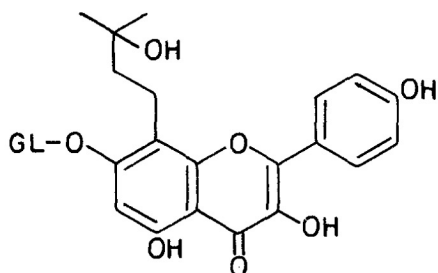


The dehydrogenation of 2,2-dimethylchromanes to 2,2-dimethylchromenes has analogies in well-established biological dehydrogenations, but may involve a specific dehydrogenase. Hydration of the ethylenic bond in II

finds support in the structures of icarin³ (III) and amurensin⁴ (IV), which have been isolated from the leaves of Epimedium macranthum and Phellodendron amurense. Amurensin is accompanied by the corresponding flavanoneol, phellamurin.

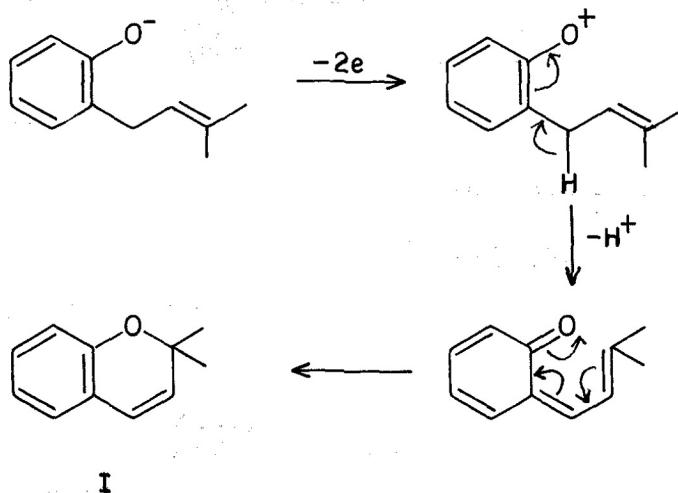


III GL = D - Glucose
Rh = L - rhamnose



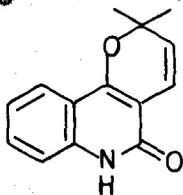
IV

OLLIS² has suggested the following mechanism, in which the phenol anion is initially oxidized, followed by the loss of the benzylic proton to form an *o*-methylene-quinone intermediate, which subsequently cyclizes to the 2,2-dimethylchromene. This mechanism appears to have greater validity for the conversion of *o*-dimethylallyl phenols to benzofurans, such as the widely occurring rotenoids.



Distribution

The simple substituted 2,2-dimethylchromenes, their coumarin derivatives and a few alkaloidal compounds are mainly distributed in the natural orders Rutaceae and Compositae, and are contained in the essential oil fractions. Seselin (XII), which belongs to this class, also occurs in a plant belonging to the Umbelliferae. Flindersine¹ (IV), an alkaloid, has not been included in this class of compounds, because it contains an α -pyran ring fused to a pyridone and not a benzene ring.

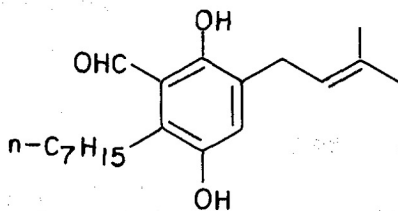


The flavone sericetin (XIII), the isoflavones munetone (XIV), mundulone (XV), toxicarol-isoflavone (XVI) and jamaicin (XVII) and the related rotenoids occur in the Leguminosae family. Osajin (XXIII) and pomiferin (XXIV), two isoflavones, occur in the osage orange (Maclura pomifera),

which belongs to the Moraceae. The xanthone derivatives, jacareubin (XVIII) and the more complex morellin (and the allied pigments of Garcinia morella), are present in the Guttiferae family. Fuscin (XIX) is the only compound of this class isolated from the culture filtrates of a mould.

Detection of the 2,2-dimethylchromene system in a molecule

The main proof for a 2,2-dimethylchromene consists in the isolation of acetone by mild alkaline hydrolysis and of α -hydroxyisobutyric acid by alkaline permanganate oxidation. However from jamaicin⁵ (XVII) acetone was not isolated, and evodione⁶ (XX) was found to be stable to alkaline hydrolysis. By the permanganate oxidation of fuscin (XIX) (a chroman derivative) and flavoglaucin^{6a} (V) α -hydroxyisobutyric acid was isolated in spite of the absence of a 2,2-dimethylchromene system. Important additional evidence for the structures of rottlerin (XXI) and toxicarol (XXII) was provided by the isolation of 5,7-dihydroxy-2,2-dimethylchroman (VI)^{7,8} from the alkaline degradation products of the hydrogenated compounds.



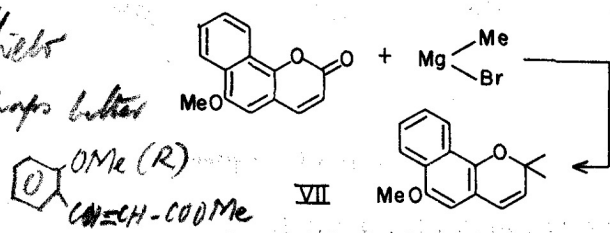
Flavoglaucin V

The NMR spectrum offers an excellent and definite method for the identification of the 2,2-dimethylchromene system in a molecule. The vinyl doublet at 3.35 and 4.43 τ with a coupling constant of 10 cps is indicative of two cis hydrogens on a double bond conjugated with an aromatic ring. OLLIS and JACKMAN⁹ have examined the NMR spectra of a series of natural products possessing the 2,2-dimethylchromene system. Isolation of acetone and α -hydroxyisobutyric acid supported by NMR evidence constitutes dependable proof for 2,2-dimethylchromenes.

General methods of synthesis of 2,2-dimethylchromenes

The three common methods of building up the 2,2-dimethylchromenes are:-

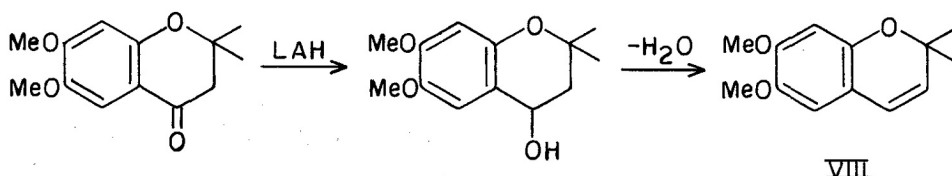
1. By the Grignard reaction on the corresponding coumarins using methyl magnesium halide. Lapachenol¹⁰ (VII) has been synthesized by this method, in which obviously protection of hydroxyl groups is necessary. The various mechanisms advanced for this reaction have been reviewed by SHRINER.^{10a}



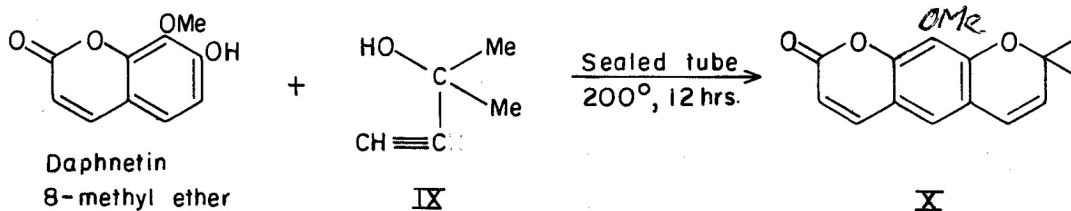
2. By the reduction of the corresponding 2,2-dimethylchromanone to the chromanol, followed by dehydration. Lapachenol¹⁰

(VII), flindersine¹ (IV) and ageratochromene¹¹ (VIII) have been synthesized by this method, which again has been

applied only to methyl ethers or to chromenes free from hydroxyl groups (cf. flindersine), so far, and not to the free phenols. For the reduction of chromanone to chromanol, a reagent such as lithium aluminium hydride,^{10,11} or hydrogenation in presence of platinum oxide¹ has been employed. Dehydration of chromanols has been effected by 1:1 sulphuric acid, phosphorus pentoxide in benzene, thionyl chloride in chloroform,¹ and by heating with alumina.¹¹



3. By the condensation of the appropriate phenol with 2-methyl-3-butyn-2-ol (dimethylethynylcarbinol; IX) in a sealed tube by heating to 200° for 12 hr, but the yields are less than 2 per cent. Luvangetin¹² (X), xanthyletin¹³ (XI) and seselin¹⁴ (XII) have been synthesized by this method.



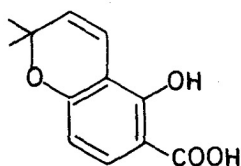
No 7-OH?

check

6 & 8-OH.

No dihydroxy-2,2-dimethylchromene appears to have been described in the literature, and synthesis of most of the

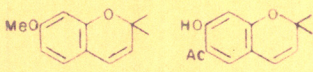
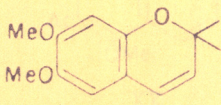
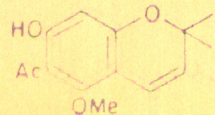
natural products which are built on a 2,2-dimethylchromene ring remains to be accomplished. β -Tubaic acid¹⁵ (XIII) has been prepared by the sodium borohydride reduction of the corresponding chromanone to the chromanol, followed by acid-catalysed dehydration. OLLIS¹⁶ also prepared the same by condensing β -resorcylic acid methyl ester with 2-methyl-3-butyn-2-ol (IX), but he did not mention the experimental details.



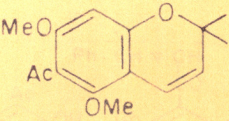
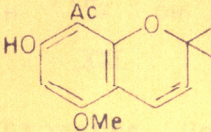
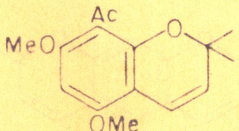
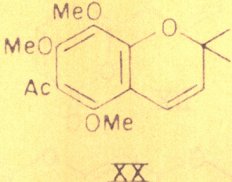
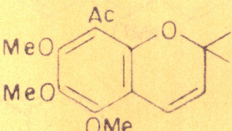
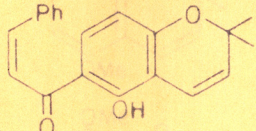
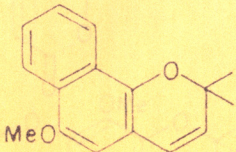
XIII

Phenol

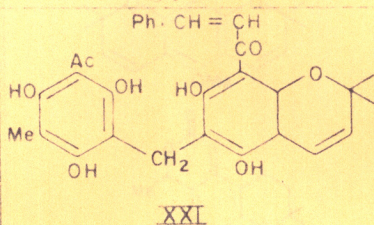
TABLE 1. NATURALLY OCCURRING 2,2-DIMETHYLCHROMENES

Karrer: No.	Name	Structure	Occurrence	References	
				Isolation, structure	Synthesis
1.	2.	3.	4.	5.	6.
		<u>Simple chromenes</u> 	Essential oil of <u>Eupatorium</u> species (Compositae)	17	
1689	Ageratochrome	 VIII	Oil of <u>Ageratum mexicanum</u> ; <u>A. conyzoides</u> (Compositae)	18	11
			Essential oil of <u>Eupatorium</u> species (Compositae); <u>Helianthella uniflora</u>	17	
1690	Evodionol		Essential oil of <u>Evodia littoralis</u> (Rutaceae)	19	

Rdx

1	2.	3.	4.	5.	6.
1691	Methyl ether of evodionol		Leaves of <u>Medicosma</u> <u>cunninghamii</u> (Rutaceae)	20	
1692	Alloevodionol		- do -	20	
1693	Methyl ether of alloevo- dionol		Leaves and bark of <u>Acra-</u> <u>denia frankli-</u> <u>nii</u> (Rutaceae)	20, 21	
1694	Evodione		Essential oil of <u>Evodia</u> <u>elleryana</u> (Rutaceae)	6	
	Alloevodione		- do -	22	
1695	Lonchocarpin		Seeds and roots of <u>Lon-</u> <u>chocarpus</u> <u>sericeus</u> (Leguminosae)	23	24, ** 24a
1701	Lapachenol		Heartwood of "Brazilian white peroba" <u>Paratecoma alba</u>	25	10, 25

1696 Rottlerin

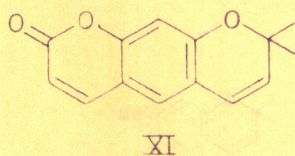


Mallotus
philippinensis
(Euphorbiaceae)

26, 26a **
8

Pyranochromenes (Benzodipyrans)

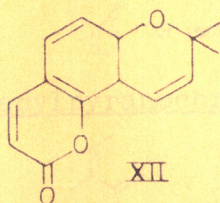
1362 Xanthyletin



Zanthoxylum
americanum
(Rutaceae)

27 13

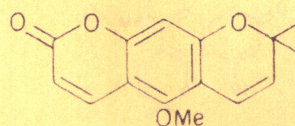
1365 Seselin



Sesela indicum
(Umbelliferae)
and Skimmia japonica
(Rutaceae)
and S. repens

28 14

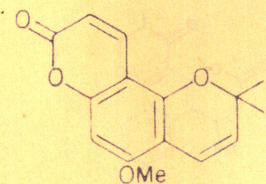
1383 Xanthoxyletin



Zanthoxylum
americanum
(Rutaceae)

29 29a * -

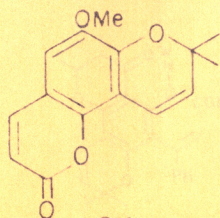
1364 Alloxanthoxyletin



- do -

30 30 *

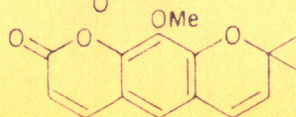
1366 Braylin



Bark of Flin-
dersia bray-
leyana
(Rutaceae)

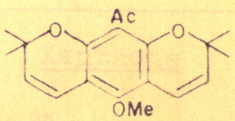
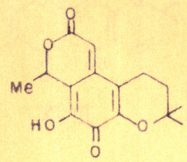
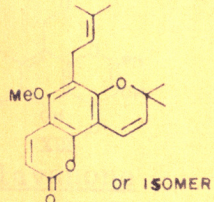
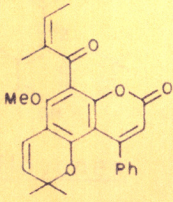
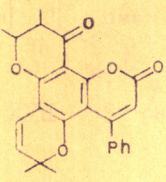
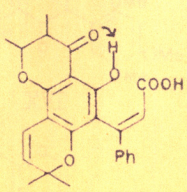
31

1363 Luvangetin

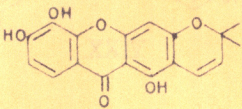
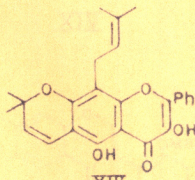
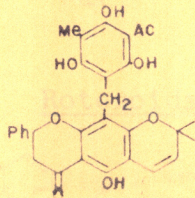
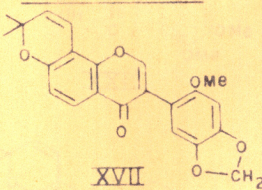
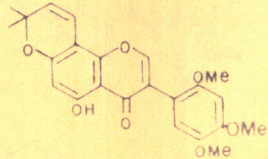
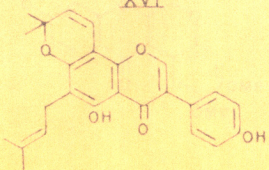


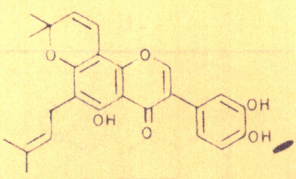
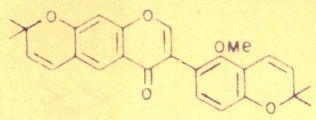
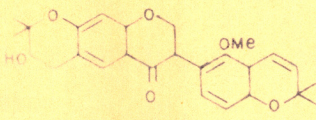
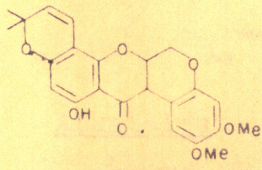
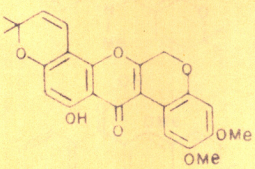
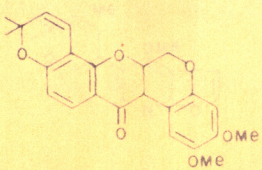
Fruits of Lu-
vunga scandens
(Rutaceae)

32 12

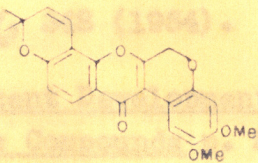
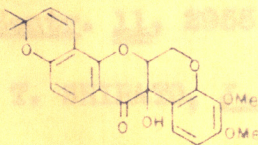
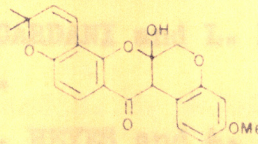
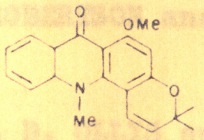
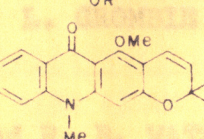
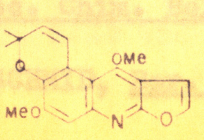
1. :	2. :	3. :	4. :	5. :	6.
	Franklinone		Leaves and bark of <u>Acradenia franklinii</u> (Rutaceae)	33	
1229	Fuscin	 XIX	<u>Oidiodendron fuscum</u>	33a	33b
	Avicenin	 OF ISOMER	Root bark of <u>Zanthoxylum avicennae</u> (Rutaceae)	34	
<u>4-Phenylpyranochromenes</u>					
	Calophyllolide		Kernels of <u>Calophyllum inophyllum</u> (Guttiferae)	35, 36, 37	
	Inophyllolide		- do -	35, 36	
	Calophylllic acid		- do -	35, 36	

1. : 2. : 3. : 4. : 5. : 6.

	Jacareubin	<u>Xanthone</u>  XVIII	Heartwood of <u>Calophyllum</u> <u>brasiliense</u> (Guttiferae)	38	
	Sericetin	<u>Flavone</u>  XIII	Root bark of <u>Mundulea seri-</u> <u>cea</u> (Legumino-	39, 40	***
		<u>Flavanone</u>			
1697	Isorottlerin (Isoallo- rottlerin)	 XIV	<u>Rottlera</u> <u>tinctoria</u> (Euphorbiaceae)	41	
		<u>Isoflavones</u>			
	Jamaicin	 XVII	<u>Piscidia</u> <u>erythrina</u> (Leguminosae)	5	
1667	Toxicarol- isoflavone	 XVI	<u>Derris</u> <u>malaccensis</u> (Leguminosae)	42	
1668	Osajin	 XXIII	Fruits of <u>Ma-</u> <u>clura pomifera</u> (Moraceae)	43, 44	44 *** 44

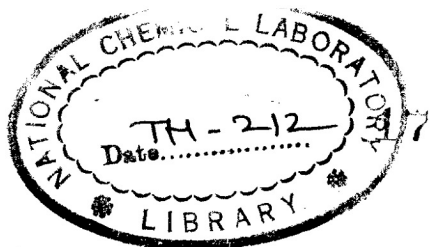
1. :	2. :	3. :	4. :	5. :	6. :
1669	Pomiferin	 XXIV	Fruits of <u>Maclura pomi- fera</u> (Moraceae)	43, 44	44 *** 44a
	Munetone	 XIV	Root bark of <u>Mundulea suberosa</u> (Leguminosae)	45, 46	
	Mundulone	 XV	Root bark of <u>Mundulea sericea</u> and <u>M. suberosa</u> (Leguminosae)	47, 48	
		<u>Rotenoids</u>			
1431	Toxicarol	 XXII	Roots of <u>Cracca (=Teph- rosia) toxica- ria</u> (Leguminosae)	49	
1432	Dehydrotoxi- carol		<u>Derris</u> wood (Leguminosae)	50	
1429	Deguelin		<u>Derris</u> wood (<u>Tephrosia</u>), <u>Lonchocarpus nicou</u> (Leguminosae)	51	

REFERENCES

1.	2.	3.	4.	5.	6.
1430	Dehydrodeguelin		<u>Tephrosia vogelii</u> (Leguminosae)	52	
1433	Tephrosin		<u>Tephrosia vogelii</u> , <u>Lonchocarpus nicou</u> , <u>Cracca virginiana</u> (=Tephrosia) (Leguminosae)	53	
1434	Isotephrosin		<u>Lonchocarpus nicou</u> (Leguminosae)	54	
		<u>Alkaloids</u>			
	Acronycin		Bark of <u>Acronychia bauri</u> (Rutaceae)	55	
	Medicosmine		Bark of <u>Medicosa cunninghamii</u> (Rutaceae)	57	
	Acronidine		Leaves of <u>Acronychia bauri</u> and bark of <u>Melicope fareana</u> (Rutaceae)	56	

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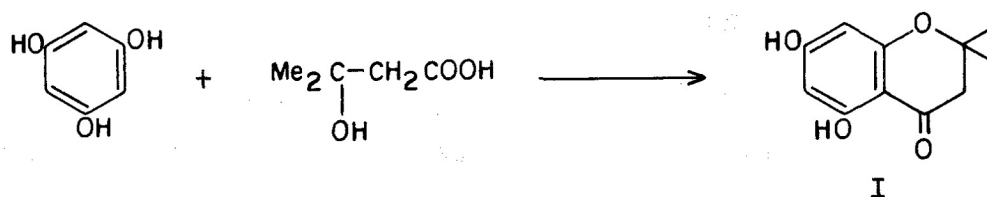
PART II

SYNTHESIS OF DIHYDROJACAREUBIN AND A NEW GENERAL METHOD
FOR THE SYNTHESIS OF 2,2-DIMETHYLCHROMANONES

chr In connection with our work on the constitution of morellin and the synthesis of certain products obtained by the alkali fusion of octahydromorellin, it became necessary to synthesize several 2,2-dimethylchromanone derivatives. 2,2-Dimethylchromanones are also of interest as intermediates for the synthesis of 2,2-dimethylchromenes, of which there are many representatives among plant products.

The first synthesis of 5,7-dihydroxy-2,2-dimethylchromanone (I) was carried out by ROBERTSON et al.¹ by the Friedel-Crafts reaction between phloroglucinol and $\beta\beta$ -dimethylacrylyl chloride; the yield of the crude product was 54 per cent. A similar yield was obtained by ROBERTSON² in a subsequent synthesis, in which $\beta\beta$ -dimethylacrylyl chloride was replaced by β -bromoisovaleryl chloride and phloroglucinol by resorcinol. More recently MIYANO and MATSUI³ reviewed the available methods and found that the most convenient procedure is to condense phloroglucinol with $\beta\beta$ -dimethylacrylic acid in presence of antimony trichloride at 140-145°; the yield was 30 per cent. Similar results were obtained by replacing antimony trichloride with zinc chloride.

A new general method for the synthesis of 2,2-dimethyl-chromanones is now described in which phenols are condensed with β -hydroxyisovaleric acid.

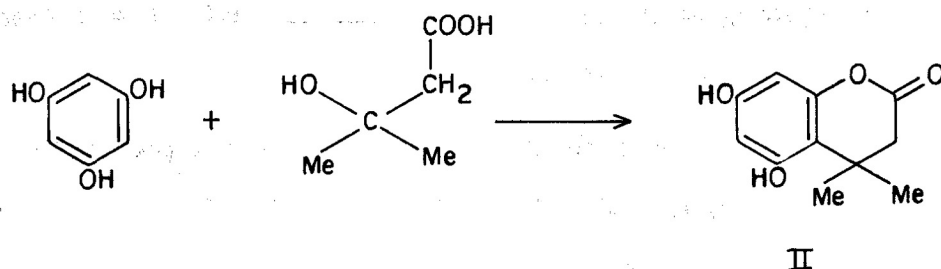


$\beta\beta$ -Dimethylacrylic acid is prepared by the sodium hypochlorite oxidation of mesityl oxide,⁴ or by the elimination of hydrogen halide from α -haloisovaleric acid, or by the dehydration of β -hydroxyisovaleric acid or various other methods. In the present method the use of β -hydroxyisovaleric acid offers the advantage that it is directly obtained by the hypochlorite oxidation of diacetone alcohol,⁵ a commercial solvent from which mesityl oxide, the starting material for $\beta\beta$ -dimethylacrylic acid, is prepared.

Condensation of phloroglucinol with β -hydroxyisovaleric acid in presence of phosphorus oxychloride and fused zinc chloride at 70° for 2 hours, a procedure developed by SHAH and co-workers⁶ in this Laboratory for hydroxyxanthenes, gave the chromanone (I) in an overall yield of 25-30 per cent; the product was accompanied by a dark-red polymer and vacuum sublimation was necessary for purification.

Similar results were obtained when polyphosphoric acid at 140° was used.⁷ The yields were improved to 65 per cent by using boron fluoride etherate as condensing agent. Phloroglucinol and β -hydroxyisovaleric acid in molar proportions were heated on a steam-bath for 2 min with boron fluoride etherate complex. After a few hours the dark-red homogeneous solution was diluted with water and boiled for 10 min, when a deep yellow crystalline complex separated. The yellow precipitate was filtered and dissolved in cold 5 per cent aqueous sodium hydroxide. Acidification of the deep red solution gave the chromanone (I), which could be readily crystallized from dilute alcohol. The IR spectrum (KBr disc) of I showed prominent bands at 3115 (OH), 1637 (chelated carbonyl), 1595 and 1575 (benzenoid in conjugation with C=O group), 1376 and 1364 (gem-dimethyl), 1295 and 1083 cm^{-1} (ether). The product recovered from the mother liquor after the isolation of the pure chromanone (I) exhibited a similar IR spectrum, and the hydroxamic acid test for lactones was negative, indicating the complete absence of the isomeric dihydrocoumarin (II). There appears to be a steric factor which is involved in the exclusive formation of I because there was no evidence of coumarin formation when several

other phenols were condensed with β -hydroxyisovaleric. However CHAMBAR⁸ showed that phenyl esters of $\beta\beta$ -disubstituted acrylic acids by treatment with aluminium chloride in carbon disulphide gave 4,4-disubstituted dihydrocoumarins. The mechanisms of both the reactions are under study.



When 1,2,4-triacetoxybenzene was condensed with β -hydroxyisovaleric acid in presence of boron fluoride-etherate, the boron complex obtained by treatment with water led to 6,7-dihydroxy-2,2-dimethylchromanone (IX; R, R' = H) or the 7-monoacetyl derivative (IX; R = Ac, R' = H) depending on the conditions of alkaline hydrolysis. The presence of the Q-acetyl group in the 7-position was shown by methylation with diazomethane and hydrolysis, which gave 7-hydroxy-6-methoxy-2,2-dimethylchromanone (IX; R = H, R' = Me), soluble in aqueous sodium carbonate.

The applicability of the new reaction as a general method of preparation of 2,2-dimethylchromanones was

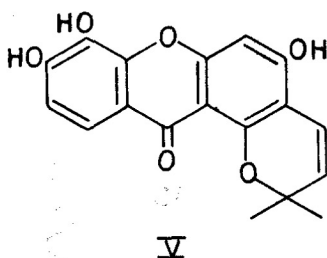
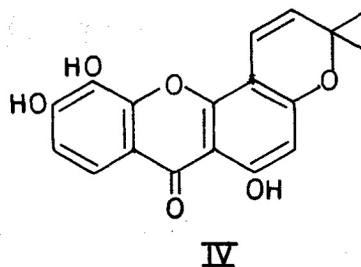
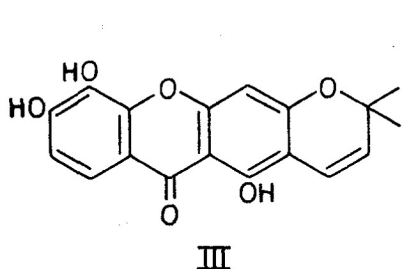
studied by condensing different phenols with β -hydroxy-
 isovaleric acid in presence of boron fluoride etherate.
 Resorcinol gave 7-hydroxy-2,2-dimethylchromanone in
 45 per cent yields. Orcinol formed 7-hydroxy-4-methyl-
 2,2-dimethylchromanone which was free from ferric colour.
 C-Methylphloroglucinol gave 5,7-dihydroxy-2,2,8-trimethyl-
 chromanone in 15 per cent yield, which was characterized
 by the negative Gibbs reaction followed spectroscopically,
 using dimethyl formamide as solvent instead of pyridine.¹⁰
 Iretol gave 5,7-dihydroxy-6-methoxy-2,2-dimethylchromanone
 characterized by the positive Gibbs test. 2-Acetyl
 resorcinol formed 8-acetyl-7-hydroxy-2,2-dimethylchromanone
 in 35 per cent yields. The optimum conditions for the
 various phenols are under study. 8-Acetyl-7-hydroxy-2,2-
 dimethylchromanone on refluxing with benzoyl chloride and
 potassium carbonate in acetone underwent Baker-Venkataraman
 transformation and gave the corresponding diketone which
 was readily cyclized with conc sulphuric acid into the
 flavone which was prepared from the point of IR
 study.

The chromanone (I), m.p. 198° , gave a deep purple
 ferric colour and readily formed a 2,4-dinitrophenylhydrazone.
 It also gave a deep orange colour with magnesium and hydro-
 chloric acid, a property not recorded by earlier workers.

It could be readily coupled with diazotized aniline to give the disazo derivative. It formed a crystalline tetrabromo derivative. The ditosyl derivative of I was prepared to study the stability of the tosyl group to Clemmensen reduction in connection with morellin work. At the end of the reduction partial ditosylation appeared to take place as shown by the -OH peak in the IR spectrum. The product on mild alkaline hydrolysis gave 5,7-dihydroxy-2,2-dimethylchroman, and on further tosylation it gave the ditosyl derivative of the chroman. ROBERTSON reduced 5,7-dihydroxy-2,2-dimethylchromanone to the chroman by the Clemmensen method in 63.27 per cent yield. In the present work the chroman has been prepared from I in 65 per cent yields by reduction with diborane.

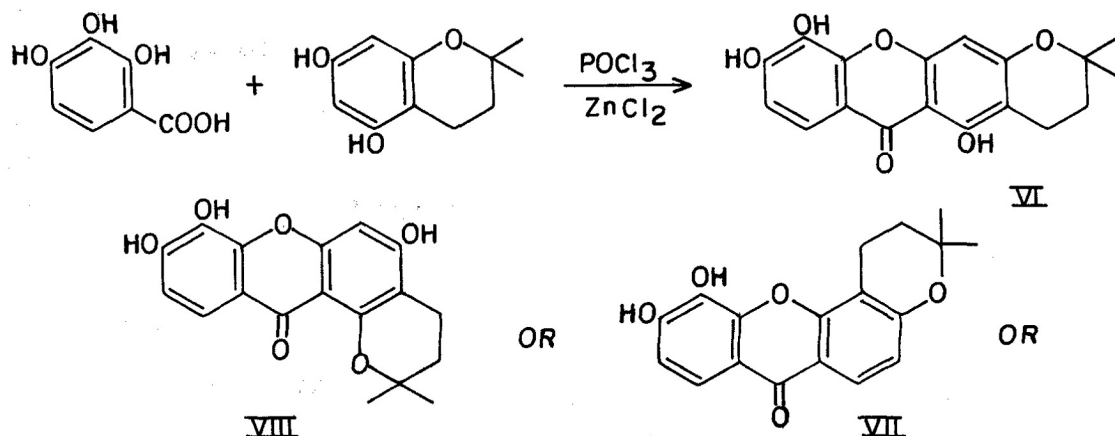
From the heartwood of the tropical American tree, Calophyllum brasiliense (Guttiferae), KING et al.⁹ isolated a deep yellow crystalline pigment to which the structure III was assigned. It formed a triacetate and a trimethyl ether and a dihydro derivative. It yielded acetone on alkaline hydrolysis with 33 per cent aqueous potassium hydroxide on a steam-bath for 8 hours. The trimethyl ether of jacareubin on oxidation with potassium permanganate in boiling acetone yielded trimethyl jacareubic acid,

which on hydrolysis gave 1,3,5,6-tetrahydroxyxanthone and α -hydroxyisobutyric acid. Thus with the isolation of acetone by alkaline hydrolysis and α -hydroxyisobutyric acid by permanganate oxidation followed by hydrolysis, the presence of 2,2-dimethylchromene was definitely indicated. The degradative experiments did not distinguish between III and the isomeric structures IV and V, but the chelate character of the hydroxyl group in jacareubin dimethyl ether excluded V. In a subsequent paper by the spectroscopic study of indophenol colour developed by dimethyl ether of jacareubin with 2,6-dichloroquinone-4-chloroimide (Gibbs reagent) and comparing it with a series of model compounds, KING¹⁰ suggested that in the dimethyl ether of jacareubin there is a free position para to a hydroxyl group which confirmed the linear structure III. But this had, however, not been confirmed by the synthesis of jacareubin or any of its derivative.

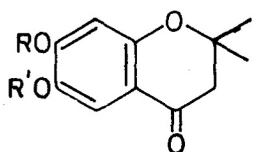


In the present work it appeared desirable to confirm the constitution of jacareubin, since both jacareubin and morellin occur in plants belonging to the Guttiferae family, and there was a possible structural relationship between the two pigments.

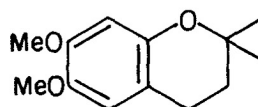
Dihydrojacareubin (VI) has now been synthesized. Pyrogallol- α -carboxylic acid was prepared by the carboxylation of pyrogallol reported by BAKER and SMITH.¹¹ By the condensation of the acid with 5,7-dihydroxy-2,2-dimethylchroman in presence of phosphorus oxychloride and fused zinc chloride at 70°, a crude product was obtained, which was purified by high-vacuum sublimation and the pale yellow crystalline sublimate on recrystallization from methanol gave dihydrojacareubin. The identity of the sample with the dihydro derivative of the natural sample supplied by Professor F. E. KING has been confirmed by m.p., mixed m.p. and superposable UV and IR spectra. Though there are three products VI, VII and VIII possible, only VI was isolated.



ALERTSEN¹² isolated 6,7-dimethoxy-2,2-dimethylchromene from the essential oil of Ageratum mexicanum; hydrogenation in presence of Raney nickel gave the chroman X which has now been synthesized by the diborane reduction (in 86 per cent yield) of 6,7-dimethoxy-2,2-dimethylchromanone (IX; R, R' = Me); Clemmensen reduction gave a 60 per cent yield. The properties (m.p. and UV spectrum) of X correspond with those of dihydroageratochromene, but direct comparison could not be made because of the nonavailability of the natural product. The IR spectrum (CCl₄) shows bands at 1616 and 1513 (benzenoid), 1377 and 1362 (gem-dimethyl), 1271, 1241 and 1125 cm⁻¹ (ether); ALERTSEN¹² has mentioned that the IR spectrum of dihydroageratochromene shows many similarities to that of 5,7-dimethoxy-2,2-dimethylchroman, but he did not record the spectra of the two compounds. Ageratochromene was synthesized earlier by HULS¹³ from 1,2,4-trimethoxybenzene and β -dimethylacrylyl chloride; the chromanone obtained by the Friedel-Crafts reaction was reduced by lithium aluminium hydride to the chromanol, which was dehydrated with alumina. HULS also reduced his synthetic ageratochromene to 6,7-dimethoxy-2,2-dimethylchroman (X).



IX



X

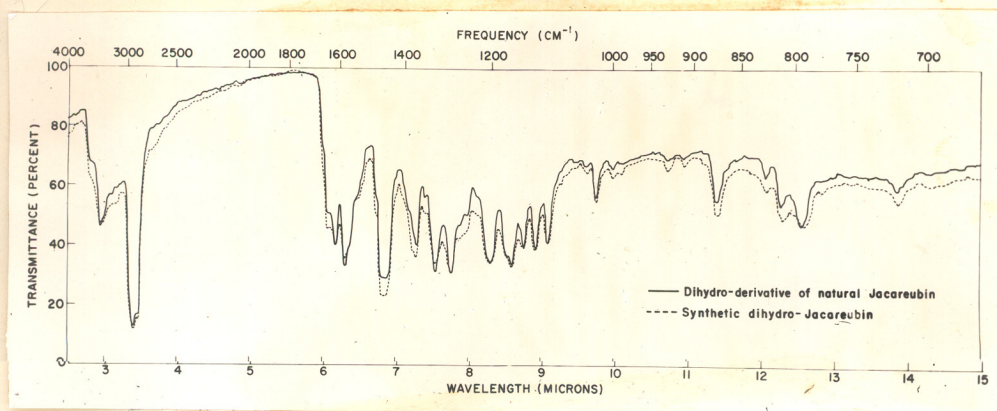
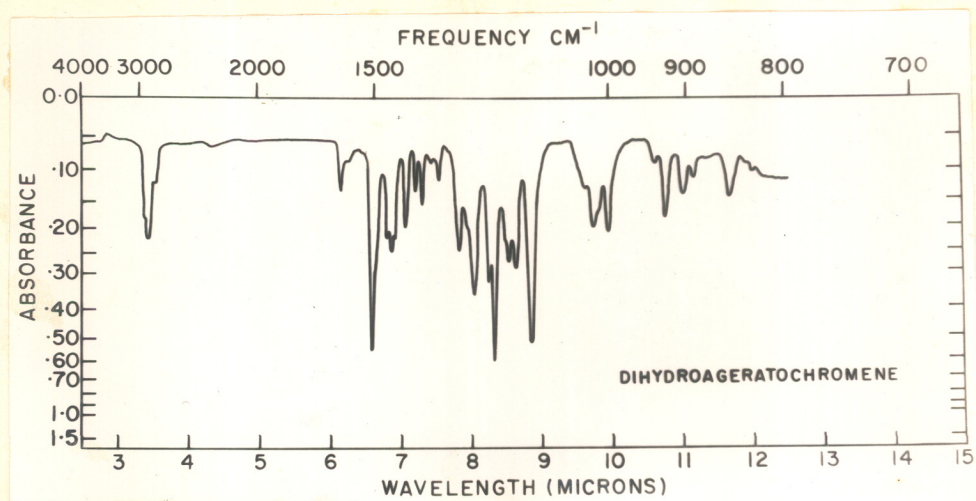


FIG. 1. Spectra in Nujol.

FIG. 2. In CCl_4 .

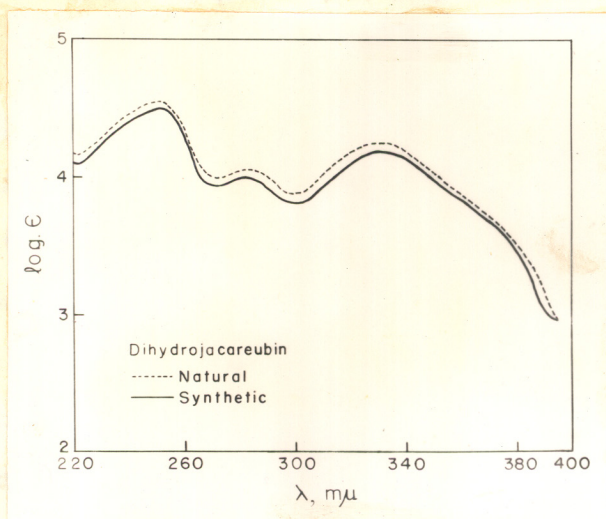


FIG. 3. In ethanol.

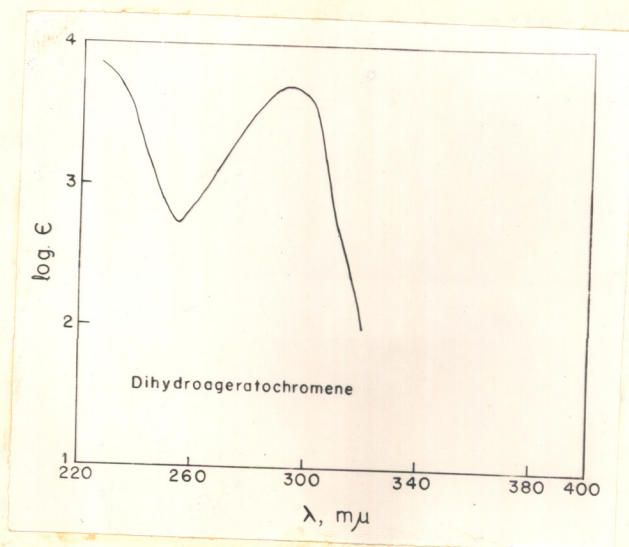


FIG. 4. In ethanol.

EXPERIMENTAL

7-Hydroxy-2,2-dimethylchromanone

A mixture of resorcinol (3.3 g), β -hydroxyisovaleric acid (3.6 g) and boron fluoride etherate (8 ml) was heated on a steam-bath for 2 min to get a deep red solution. After 24 hr at room temp the deep orange yellow crystalline complex was filtered and treated with 5% sodium hydroxide solution. It was acidified and extracted with ether and the ether extract washed with 10% sodium carbonate solution. The carbonate extract on acidification gave a colourless crystalline product, which was recrystallized from water in colourless needles (2.5 g; 47%), m.p. 172° (lit.² m.p. 172°). It did not give a ferric colour and gave a deep orange colour with magnesium and conc hydrochloric acid. The

The same compound was obtained in 25% yield when resorcinol (3.6 g), β -hydroxyisovaleric acid (3.6 g), phosphorus oxychloride (20 ml) and freshly fused zinc chloride (5.0 g) were heated to 70° under stirring for 2 hr; the dark-red mixture was poured into crushed ice and the solid purified as above.

5,7-Dihydroxy-2,2-dimethylchromanone (I)

(a) Phosphorus oxychloride-zinc chloride method. Phloroglucinol (1.3 g), β -hydroxyisovaleric acid (1.2 g), phosphorus oxychloride (10 ml) and freshly fused zinc chloride (3 g) were heated to 75° under stirring for 2 hr and poured into crushed ice. The dark-red solid was filtered and sublimed at 7.7×10^{-3} mm press at 250° , and the colourless sublimate was crystallized in colourless needles from aqueous ethanol (0.6 g; 30%), m.p. 198° (lit.¹ m.p. 198°).

(b) Boron fluoride etherate method. A mixture of phloroglucinol (2.0 g), β -hydroxyisovaleric acid (1.87 g; 1 mole) and boron fluoride etherate (10 ml) was heated on a steam-bath for 2 min and the deep wine-red solution left at room temp overnight. The reaction mixture was then poured into water and boiled for 10 min. The yellow crystalline product proved to be a boron complex, which was decomposed by dissolving it in 10% aqueous sodium hydroxide. Acidification of the red solution gave a precipitate, which was collected and warmed with aqueous sodium carbonate. The solution was filtered to remove a small amount of insoluble material and acidified. The precipitate readily crystallized from aqueous ethanol in

colourless needles (2.0 g; 65%), m.p. 198° (lit.¹ m.p. 198°). (Found: C, 63.5; H, 5.8. Calc. for $C_{11}H_{12}O_4$: C, 63.5; H, 5.6%). The substance gives a deep purple ferric colour and an orange colour with magnesium and hydrochloric acid; the latter colour reaction of chromanones does not appear to have been recorded earlier, although red to violet colourations are characteristic of flavanones. The mother liquor gave a negative hydroxamic acid test indicating the absence of a dihydrocoumarin derivative. The traces of carbon-insoluble product also gave a purple ferric colour and negative hydroxamic acid test. The chromanone I on coupling with diazotized aniline yielded 6,8-bisbenzeneazo-5,7-dihydroxy-2,2-dimethylchromanone which was crystallized from ethanol in orange-red needles, m.p. 237° . (Found: C, 66.5; H, 5.1; N, 13.9. $C_{23}H_{20}N_4O_4$ requires: C, 66.3; H, 4.8; N, 13.5%).

8-Acetyl-7-hydroxy-2,2-dimethylchromanone

2-Acetylresorcinol (1.9 g), β -hydroxyisovaleric acid (1.5 g), and boron fluoride etherate (20 ml) were heated on a steam-bath for 1 hr. The mixture was diluted with water and warmed to remove the ether. It was extracted with ether and washed with 5% sodium hydroxide solution and acidified. The product was extracted with ether, excess of ether removed and distilled at $135^{\circ}/7.7 \times 10^{-3}$ mm. The

distillate which solidified crystallized readily from methanol in colourless plates (1.0 g; 35%), m.p. 121° . (Found: C, 66.6; H, 5.9. $C_{13}H_{14}O_4$ requires: C, 66.2; H, 6.0%). The compound gave a violet ferric colour in alcoholic medium.

Baker-Venkataraman transformation. The above compound (0.3 g), anhydrous potassium carbonate (1.5 g), acetone (30 ml) and benzoyl chloride (0.22 ml; 1.2 moles) were refluxed for 15 hr. After distillation of acetone it was diluted with water, acidified, and the product extracted with ether and washed with aqueous 5% sodium bicarbonate solution. The ether was distilled and the diketone was crystallized from methanol in pale yellow needles (130 mg), m.p. 99° . (Found: C, 71.4; H, 5.7. $C_{20}H_{18}O_3$ requires: C, 71.0; H, 5.3%). It gave a deep purple ferric colour in alcohol.

Cyclization of the diketone to the flavone. The diketone (180 mg) was dissolved in conc sulphuric acid (1 ml) at room temp (30°) and after 10 min it was diluted with ice. The fluffy colourless crystalline solid was filtered, washed and crystallized from alcohol (100 mg), m.p. 207° . (Found: C, 75.2; H, 4.7. $C_{20}H_{16}O_4$ requires: C, 75.0; H, 4.9%). It gave an orange yellow

colour with magnesium and hydrochloric acid.

Disazo derivative of 5,7-dihydroxy-2,2-dimethylchromanone

The chromanone (50 mg) was dissolved in aqueous sodium hydroxide (5%; 5 ml) and the solution cooled in ice, to which diazotized aniline (4 moles) was added when an orange dye precipitated, which was filtered and washed (150 mg). It was dissolved in benzene and chromatographed through a column of alumina (15 x 1 cm). The major slow-moving red band was eluted with ethyl acetate. The dye was crystallized from alcohol in fluffy orange needles, m.p. 237° . (Found: C, 66.5; H, 5.1; N, 13.9. $C_{23}H_{20}N_4O_4$ requires: C, 66.3; H, 4.8; N, 13.5%).

Bromo derivative of 2,2-dimethyl-5,7-dihydroxychromanone

The chromanone (200 mg) was dissolved in acetic acid (5 ml) and a solution of bromine in acetic acid was added to it till excess. The mixture was diluted and neutralized with sodium bicarbonate. The solid obtained was filtered, washed and readily crystallized from benzene (120 mg; m.p. 170° dec). (Found: Br, 62.9. $C_{11}H_8Br_4O_4$ requires: Br, 61.1%).

6-Acetyl-5,7-dihydroxy-2,2-dimethylchromanone

The chromanone (I; 0.2 g) was mixed with boron trifluoride-acetic acid complex (1 ml) and heated on a

steam-bath for 1 hr. The pale yellow crystalline complex was collected and washed. It was dissolved in warm 5% sodium hydroxide and acidified. The colourless crystalline solid was readily crystallized from ethanol in needles (180 mg; m.p. 147°). (Found: C, 62.3; H, 5.8. $C_{13}H_{14}O_5$ requires: C, 62.5; H, 5.6%). It gave a deep red ferric colour and positive Gibbs test, but no colour with magnesium and conc hydrochloric acid.

Hydrolysis of 5,7-dihydroxy-2,2-dimethylchromanone (I)

The chromanone (0.5 g) was dissolved in 10% sodium hydroxide (30 ml) and heated on a steam-bath with a reflux condenser for 2 hr. The reaction mixture was cooled and carbon dioxide was passed until neutral to phenolphthaleine, when a colourless crystalline compound separated (0.45 g), m.p. 198° and mixed m.p. with the starting material was undepressed.

Alkali fusion of 5,7-dihydroxy-2,2-dimethylchromanone (I)

In a nickel crucible the chromanone (0.5 g) was intimately mixed with potassium hydroxide pellets (2.5 g) and water (4 drops), and heated gradually to 180° , when it formed a melt with frothing. After keeping for 3 min, it was cooled, diluted and acidified with 50% sulphuric acid and extracted with ether and washed successively

with sodium bicarbonate, sodium carbonate and sodium hydroxide solutions. After acidification, the bicarbonate solution was saturated with salt and extracted with ether. On distillation of ether a crystalline solid with no ferric colour was obtained, which was crystallized from ethyl acetate-hexane (125 mg), (m.p. 211° , mixed m.p. with phloroglucinol 210°). The carbonate soluble fraction also yielded 80 mg of phloroglucinol. The sodium hydroxide soluble fraction (20 mg) gave a wine-red ferric colour similar to that of the starting material.

2,2-Dimethyl-5-hydroxy-7-tosyloxychromanone

A mixture of the 5,7-dihydroxy-2,2-dimethylchromanone (I; 1.0 g), freshly ignited potassium carbonate (5 g), *p*-toluenesulphonyl chloride (1.0 g) and acetone (50 ml) was refluxed for 17 hr. Acetone was distilled and the residue was diluted with water. The grey solid was filtered and crystallized from dil alcohol (0.8 g; m.p. 97°). (Found: C, 60.0; H, 5.1. $C_{18}H_{18}O_6S$ requires: C, 59.7; H, 5.0%). It gave a deep purple colour with alcoholic ferric chloride.

Ditosylation of 5,7-dihydroxy-2,2-dimethylchromanone (I)

The chromanone (I; 1.5 g) was refluxed with *p*-toluenesulphonyl chloride (3.3 g; 2.2 moles) and potassium carbonate (10 g) in acetone (50 ml) for 3 hr. When the

ferric colour disappeared, it was filtered, and the residue was washed with acetone. The total acetone solution was distilled and the product extracted twice with hot hexane and the residue crystallized from methanol in colourless needles (2.8 g; 76%), m.p. 115°. (Found: C, 58.9; H, 4.6. $C_{25}H_{24}O_8S_2$ requires: C, 59.1; H, 4.7%).

Clemmensen reduction. A mixture of zinc amalgam (100 g), conc hydrochloric acid (55 ml), water (120 ml), the above ditosyl derivative (2.5 g) and ethanol (25 ml) was refluxed for 18 hr with the addition of 10% acid (88 ml) every 6 hr. The crude product isolated (2.0g) by extraction with ether followed by washing, showed a strong hydroxyl band and absence of a carbonyl absorption in the IR spectrum. Thin layer chromatography on silica gel-plaster of Paris showed a fast-moving spot and a slow-moving partly detosylated product. There was no spot corresponding to 5,7-dihydroxy-2,2-dimethyl-chroman.

A portion of the reduction product (1.0 g) was further tosylated by refluxing in acetone (30 ml), potassium carbonate (5 g) and p-toluenesulphonyl chloride (0.5 g) for 1 hr. The product obtained was extracted

with hot hexane and the residue crystallized from methanol (0.7 g), m.p. 90° . (Found: C, 59.7; H, 5.2. Calc. for $C_{25}H_{26}O_7S_2$: C, 59.8; H, 5.2%). Mixed m.p. with the sample prepared by the tosylation of 5,7-dihydroxy-2,2-dimethylchroman was undepressed. The other portion (1.0 g) was hydrolyzed with 5% alcoholic caustic soda by heating on a steam-bath for 1 hr. The mixture was acidified, extracted with ether and washed with aqueous sodium carbonate. Acidification followed by extraction with ether gave 5,7-dihydroxy-2,2-dimethylchroman which was crystallized from benzene (0.2 g), m.p. 162° .

5,7-Dihydroxy-2,2,8-trimethylchromanone

A mixture of well-powdered α -methylphloroglucinol (2.8 g), β -hydroxyisovaleric acid (2.4 g) and boron trifluoride etherate (10 ml) was heated on a steam-bath for 5 min to dissolve the phenol. The dark-red solution obtained was decomposed with water, extracted with ether and washed. On removal of ether, reddish yellow crystals were obtained, which were recrystallized from benzene (yield, 0.9 g; m.p. 212°). (Found: C, 64.8; H, 6.3. $C_{12}H_{14}O_4$ requires: C, 64.9; H, 6.3%). It gave a violet ferric colour and no colour with magnesium and conc hydrochloric acid. The compound gave a negative Gibbs test.¹⁰ 2,4-Dinitrophenylhydrazone was crystallized from ethanol

in deep-red needles, m.p. 282° (dec). (Found: C, 53.3; H, 3.2. $C_{18}H_{18}O_7N_4$ requires: C, 53.7; H, 3.5%).

5,7-Dihydroxy-6-methoxy-2,2-dimethylchromanone

Iretol (1.0 g), β -hydroxyisovaleric acid (0.8 g) and boron fluoride etherate (6 ml) were heated for 5 min. The dark-red solution on working up as usual gave a product which readily crystallized from methanol in pale yellow needles (0.25 g), m.p. 191° . (Found: C, 66.6; H, 5.9. $C_{12}H_{14}O_5$ requires: C, 60.5; H, 5.9%). It gave a purple ferric colour and positive Gibbs test.

6,7-Dihydroxy-2,2-dimethylchromanone (X; R, R' = H)

1,2,4-Triacetoxybenzene (10 g), β -hydroxyisovaleric acid (4.8 g) and boron fluoride etherate (20 ml) were heated on a steam-bath for 2 min. The clear orange-red solution was diluted with water after 16 hr, when a deep-yellow crystalline complex separated. Decomposition with 5% aqueous sodium hydroxide at room temp (about 30°), acidification, purification through ether, and crystallization from dil alcohol gave colourless needles (2.5 g), m.p. 208° . (Found: C, 63.8; H, 6.2. $C_{11}H_{12}O_4$ requires: C, 63.5; H, 5.8%). The 2,4-dinitrophenylhydrazone crystallized from methanol in dark-red needles, m.p. 296° (dec). (Found: C, 53.1; H, 4.2; N, 13.9. $C_{17}H_{16}O_7N$ requires: C, 52.6; H, 4.1; N, 14.4%).

If the red solution of the complex in aqueous sodium hydroxide was cooled in ice and neutralized to pH 4.5 with hydrochloric acid, a lemon-yellow precipitate separated, which readily crystallized from benzene in needles (4.0 g), m.p. 158° , and proved to be 7-acetoxy-6-hydroxy-2,2-dimethylchromanone. (Found: C, 62.5; H, 6.1. $C_{13}H_{14}O_5$ requires: C, 62.4; H, 5.6%). Hydrolysis with hot hydrochloric acid in acetic acid yielded 6,7-dihydroxy-2,2-dimethylchromanone, m.p. 208° .

7-Acetoxy-6-methoxy-2,2-dimethylchromanone (IX; R = Ac.
R' = Me)

The monoacetate (1.0 g) in ether (30 ml) and methanol (30 ml) was treated with excess diazomethane in ether at 10° for 24 hr, and then with a few drops of acetic acid. Removal of solvent gave a pale yellow crystalline residue, which crystallized from dil methanol in pale yellow needles, m.p. 134° . (Found: C, 63.2; H, 5.8. $C_{14}H_{16}O_5$ requires: C, 63.6; H, 6.1%).

7-Hydroxy-6-methoxy-2,2-dimethylchromanone (IX; R = H.
R' = Me)

The above compound (0.4 g) was warmed on a steam-bath with 5% aqueous sodium hydroxide (15 ml) and the resulting red solution was acidified with 50% sulphuric acid. The mixture was extracted with ether and washed with water.

The residue obtained after removal of the solvent was distilled at $150^{\circ}/4.33 \times 10^{-3}$ mm. The distillate crystallized from hexane in colourless needles, m.p. 81° . (Found: C, 65.0; H, 6.4; OCH_3 , 14.0. $\text{C}_{12}\text{H}_{14}\text{O}_4$ requires: C, 64.9; H, 6.7; OCH_3 , 14.0%). The compound readily dissolves in aqueous sodium carbonate indicating a free 7-hydroxyl group.

6,7-Dimethoxy-2,2-dimethylchromanone (IX; R, R' = Me)

The dihydroxychromanone (0.5 g) was refluxed with acetone (30 ml), anhydrous potassium carbonate (3.0 g) and dimethyl sulphate (3.0 g) and dimethyl sulphate (0.6 ml) for 17 hr. Crystallization from dil methanol gave colourless needles (0.35 g), m.p. 106° (lit.¹³ m.p. 106°). (Found: OCH_3 , 26.7. $\text{C}_{13}\text{H}_{16}\text{O}_4$ requires: OCH_3 , 26.3%).

Colour reactions of chromanones

Although there are well-known colour reactions for flavones,¹⁴ colour reactions with same reagents for chromanones do not appear to have been recorded and some are listed in Table 2.

TABLE 2. COLOUR REACTIONS OF 2,2-DIMETHYLCHROMANONES

Substitution	Colour reaction			
	Aqueous sodium hydroxide	Conc sulphuric acid	Magnesium hydrochloric acid	Sodium amalgam; then acid
5,7-(OH) ₂	pale yellow	deep yellow	deep orange	orange
6,7-(OH) ₂	deep yellow	deep yellow	wine red	red violet
6-OCH ₃ -7-OH	yellow	deep yellow	reddish violet	orange
6,7-(OCH ₃) ₂	yellow	deep yellow	wine red	orange

6,7-Dimethoxy-2,2-dimethylchroman (dihydroageratochromene: X)

(a) Clemmensen reduction of 6,7-dimethoxy-2,2-dimethylchromanone. Zinc amalgam (16 g) was mixed with a solution of the chromanone (0.4 g) in ethanol (4 ml) and acetic acid (2 ml). Conc hydrochloric acid (9.2 ml) and water (6.8 ml) were added and the mixture set aside for 2 days. After refluxing for 2 hr, hydrochloric acid (15%; 4 ml) was added, and heating continued for 6 hr. Ether extraction led to a gum which readily crystallized from aqueous methanol in colourless plates (0.22 g; 60%), m.p. 60°. (Found: C, 70.7; H, 8.5. Calc. for C₁₃H₁₈O₃: C, 70.3; H, 8.1%). The UV spectrum showed $\lambda_{\max}$ 293 ($\epsilon_{\max}$ 5100); the absorption max. reported by ALERTSEN is $\lambda_{\max}$ 293 m μ ($\epsilon_{\max}$ 6400) and by HULS $\lambda_{\max}$ 294 m μ ($\epsilon_{\max}$ 4900).

(b) Diborane reduction of 6,7-dimethoxy-2,2-dimethylchromanone. The chromanone (1.0 g) was dissolved in diglyme (25 ml) and through the well-cooled solution diborane gas (from 20 ml of 4% sodium borohydride in diglyme) was passed. After leaving the reaction mixture overnight at room temp, acetic acid (5 ml) was added, and the solvent distilled in vacuo. The residue on treating with ice water gave a colourless crystalline product which was recrystallized from aqueous methanol (0.81 g; 86%); the m.p. and mixed m.p. with the Clemmensen reduction product was 60°.

Diborane reduction of 5,7-dihydroxy-2,2-dimethylchromanone (I) to 5,7-dihydroxy-2,2-dimethylchroman

Tetrahydrofuran (50 ml) cooled in ice was saturated with diborane prepared by the gradual addition of a 4% sodium borohydride solution in diglyme (20 ml) to boron fluoride etherate (5 ml), and the chromanone (1.0 g) was added to the solution. The yellow colour which developed disappeared after 2 hr. After keeping the reaction mixture at room temp for 24 hr, excess diborane was decomposed by adding acetic acid (3 ml) and the solvent distilled. The residue was diluted with water (10 ml) and extracted with ether and washed with aqueous sodium bicarbonate. Removal of the ether gave a colourless crystalline mass which was recrystallized from benzene

(0.6 g; 65%), m.p. 163° (lit.¹ m.p. $162-163^{\circ}$). (Found: C, 68.0; H, 7.7. $C_{11}H_{14}O_3$ requires: C, 68.1; H, 7.6%).

Bromo derivative of 5,7-dihydroxy-2,2-dimethylchroman

The chroman (100 mg) was dissolved in acetic acid (4 ml) and diluted with water (10 ml). Bromine in acetic acid was added with stirring till excess. The excess acetic acid was neutralized with sodium bicarbonate and the pale yellow precipitate filtered and washed (150 mg). It was crystallized from benzene (m.p. $112-113^{\circ}$ dec). (Found: Br, 62.0. $C_{11}H_{10}O_3Br_4$ requires: Br, 62.7%).

p-Azobenzenesulphonyl derivative of 5,7-dihydroxy-2,2-dimethylchroman

The chroman (0.1 g) was refluxed with p-azobenzenesulphonyl chloride (0.3 g) in acetone (30 ml) in presence of potassium carbonate (3 g) for 5 hr. It was filtered and the filtrate distilled to dryness. The orange-red dye was dissolved in benzene and chromatographed through a column of alumina. The fast-moving major orange band was eluted and the eluent distilled. The orange-red compound was crystallized from ethyl acetate-methanol mixture in needles (200 mg), m.p. 129° . (Found: C, 61.9; H, 4.8; N, 7.8. $C_{35}H_{30}O_7N_4S_2$ requires: C, 61.5; H, 4.3; N, 8.2%).

Dihydrojacareubin (VI)

5,7-Dihydroxy-2,2-dimethylchroman (1.0 g) and

pyrogallol- α -carboxylic acid (1.4 g) were mixed with phosphorus oxychloride (20 ml) and freshly fused zinc chloride (5 g) in a current of carbon dioxide and stirred for 1 hr at room temp and at 75° for $2\frac{1}{2}$ hr. The deep red mixture was poured into ice, and the precipitate collected, washed with aqueous sodium bicarbonate, and extracted with ethyl acetate. Removal of the solvent gave a pale yellow solid (0.5 g) which was sublimed initially at 170° at 7.7×10^{-3} mm. The colourless sublimate (50 mg) containing pyrogallol and unreacted chroman was discarded. Subsequent sublimation at 300° and 7.7×10^{-3} mm press, followed by crystallization of the sublimate from methanol, gave pale yellow needles (0.34 g), m.p. 245° (dec). The compound was dried at 170° for 24 hr at 0.05 mm and analysed. (Found: C, 65.7; H, 5.4. $C_{18}H_{16}O_6$ requires: C, 65.9; H, 4.9%). The mixed m.p. with dihydrojacareubin was undepressed. The substance gives a green ferric colour and an orange-red colour with magnesium and hydrochloric acid. The UV of both natural and synthetic dihydrojacareubin showed maxima at 251, 284, 330 m μ ($\epsilon_{\max}$ log 4.55, 4.05, 4.24). The IR spectra of the natural and synthetic samples were superposable. The UV spectra were determined in ethanol

using Beckman DK-2 recording spectrophotometer, and the IR spectra in paraffin mull on a Perkin-Elmer 221 with NaCl optics.

Dihydrojacareubin dimethyl ether

Synthetic dihydrojacareubin (73.2 mg) in methanol (3 ml) was treated with excess of diazomethane in ether, and after 24 hr the mixture was decomposed with a few drops of acetic acid. Removal of the solvent gave a pale yellow residue, which crystallized from methanol in pale yellow needles (55 mg), m.p. 139° , which is the m.p. of the dimethyl ether of the natural product recorded by KING.⁹ The compound gives a deep green ferric colour.

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PART III

CONSTITUTION OF MORELLIN

M. G. RAO¹ first noticed in the seeds of Garcinia morella an orange colouring matter, which was isolated in crystalline form by extraction alcohol. He named it as morellin. The constitution of morellin has been of considerable interest since then, and special reference may be made to the work of B. S. RAO² and P. L. N. RAO.³

B. S. RAO's Work

B. S. RAO assigned the molecular formula $C_{30}H_{34}O_6$ and observed that "morellin yields a tetraacetate, m.p. 178° . Two of the hydroxy groups are readily methylated by methyl iodide in acetone solution in the presence of potassium carbonate. The dimethyl ether has m.p. 156° , and a trimethyl ether, m.p. 172° , can be prepared from its sodio-derivative. Two ethylenic linkages are also present, since morellin yields a dihydrochloride and a tetrabromide." He further observed "On treatment with hydroxylamine, an amorphous dioxime is obtained, which suggests two carbonyl groups, the presence of one of them being confirmed by the preparation of a crystalline mononitroguanylhyazone." Morellin, m.p. 154° , could be isomerized to isomorellin, m.p. 116° , by treating an ethereal solution of morellin with aqueous sodium hydroxide

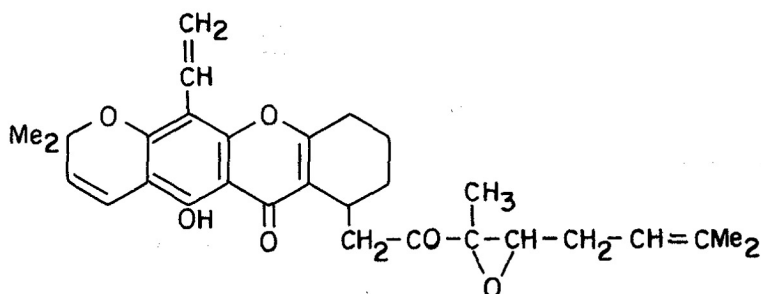
or by digesting morellin with potassium carbonate and acetyl chloride in benzene. "On fusion with alkali morellin gives a variety of products, of which the following have been identified: dl-methylheptenol (2-methylhepten-2-ol-6), phloroglucinol, acetic, isovaleric, methylsuccinic and homophthalic acids."

P. L. N. RAO's Work

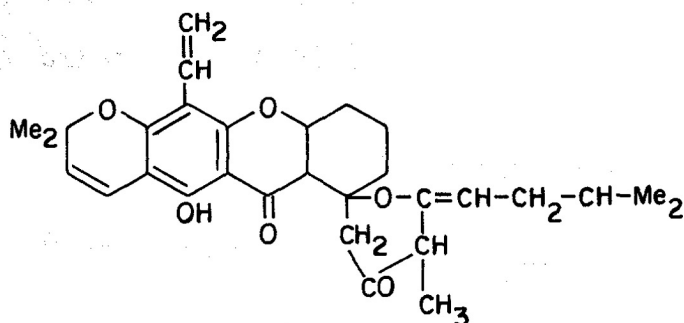
P. L. N. RAO and co-workers³ have published a series of notes without describing their experimental work. They observed that B. S. RAO's morellin was not homogeneous, since it could "be separated into three distinct pigments by chromatographic procedure, using silica gel as adsorbent." The pigments were designated as "morellin T (m.p. 80°), M (m.p. 156°) and L (m.p. 60°)." Later they reported that since "the properties of morellin and morellin M are similar, the analytical figures for the latter indicate the possible hydration of morellin during chromatographic separation." Isomorellin, m.p. 120-121°, was obtained by treating morellin with boiling pyridine for 6 hr, and they attributed the isomerization to the epimerization of groups round an asymmetric centre or to the rearrangements of double bonds. Morellin and its derivatives readily absorbed four moles of hydrogen in presence of Adams

platinum oxide catalyst. The octahydro derivatives of morellin and isomorellin were identical. Octahydro-Q-dimethylmorellin on treatment with cold alcoholic potassium hydroxide gave a phenol containing no carboxyl group, and they therefore excluded a lactone structure. P. L. N. RAO et al. obtained the "known dimethyl ether" by further methylation of monomethyl morellin, m.p. 156° . By the action of boiling aqueous sodium hydroxide, they obtained acetaldehyde and acetone. By oxidation with 2 per cent aqueous potassium permanganate they obtained oxalic acid (5 moles) and α -hydroxyisobutyric acid (0.6 moles estimated as zinc salt) besides acetic, benzoic and other acids. On the basis of the isolation of acetone and α -hydroxyisobutyric acid they postulated a chromene ring system and suggested the structures I and II based on $C_{30}H_{34}O_6$, which were modifications of a structure proposed earlier.⁴ Though they found a higher molecular weight for morellin by the X-ray method, they "reserve an explanation for this discrepancy." While the proposed structures indicated only one phenolic group, P. L. N. RAO obtained the "known dimethyl ether"; several other features of I and II, such as the vinyl and epoxide groups, have no experimental support. More recently MURTHY and RAO⁵ suggested a further

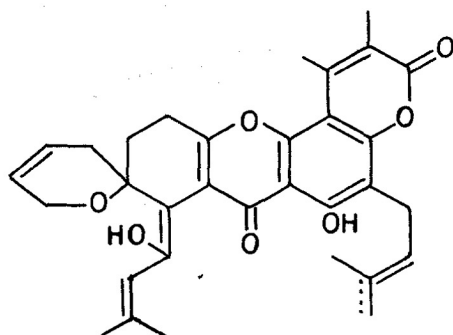
modification (III) of structures I and II. Structure III is even more at variance with the experimental data recorded by BRINGI⁷ and does not merit a serious discussion.



I



II



III

Antibacterial Properties of Morellin

R. R. RAO and NATARAJAN⁶ reported morellin to be "highly antibacterial," but also "highly toxic and therefore not likely to assume any importance in chemotherapy." But P. L. N. RAO and VERMA³ found that a 2-4 per cent solution of morellin in olive oil could be "administered subcutaneously to mice in doses up to 450 mg per kg body

weight without causing any mortality or necrosis."

Mr. C. E. COULTHARD of the Boots Pure Drug Co., Nottingham,⁷ found that morellin, isomorellin and desoxymorellin showed no activity against any of eleven organisms, including Streptococcus haemolyticus and Staphylococcus aureus using the ditch plate technique and blood agar.

BRINGI's Work

In this laboratory BRINGI^{7,8} re-investigated the chemistry of morellin. He studied the chromatographic behaviour of B. S. RAO's morellin, revised the molecular formula, prepared a series of crystalline derivatives, carried out degradative experiments, and suggested a tentative structure.

When B. S. RAO's morellin was chromatographed in hexane or benzene on Florex XXX (an extruded Fuller's earth) or magnesium carbonate, four orange zones were formed. The colourless percolate gave a fat, and the bottom zone gave a new pigment (m.p. 126°) named as desoxymorellin. The next band gave isomorellin in 85 per cent yield, owing to the isomerization of morellin by the adsorbent. Hence only crystallization methods were preferable for the purification of morellin. BRINGI extracted crude morellin in a Soxhlet with hexane to

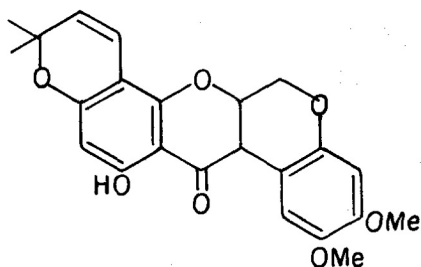
remove wax and desoxymorellin; two crystallizations from ethanol and methanol then gave glistening prismatic needles of morellin, m.p. 158-159°. BRINGI observed that morellin could be isomerized by adding aqueous sodium hydroxide to an acetone solution of morellin, followed by immediate acidification of the red solution.

On the basis of repeated elementary analysis (C, H and O) and molecular weight determination by the X-ray method of morellin and isomorellin monomethyl ether, the molecular formula was revised to $C_{33}H_{36}O_7$ or $C_{33}H_{38}O_7$.

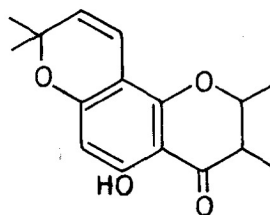
Morellin gave a brownish-green ferric colour, indicating the presence of a chelated hydroxyl. It formed only a monomethyl ether, but a crystalline diacetate which was explained by one phenolic and one enolic hydroxyl group. Morellin absorbed four moles of hydrogen in presence of Raney nickel or palladium-charcoal to give an amorphous octahydromorellin. Selective hydrogenations, using palladium on calcium carbonate or the LINDLAR catalyst, gave crystalline dihydro and tetrahydro derivatives. Both morellin and isomorellin gave the same crystalline reduction product, m.p. 110-111°, on treatment with ten times the weight of Raney nickel in boiling ethanol; elementary analysis of the product (called MRP-I, because

the reduction conditions were similar to those used by MOZINGO)⁹ indicated the addition of 10 or 12 hydrogen atoms. Tetrahydromorellin gave a crystalline monomethyl ether, m.p. 174°, identical with the monomethyl ether of tetrahydroisomorellin; but morellin monomethyl ether gave a different tetrahydroderivative, m.p. 137-138°. Unlike morellin, all the hydrogenated morellins exhibited a wine-red colour, characteristic of γ -pyranones and γ -pyrones other than flavonols, on treatment with sodium amalgam and then with acid.

Fusion of morellin with five times its weight of potassium hydroxide at 220° led to acetic, isovaleric, methylsuccinic and homophthalic acids, confirming B. S. RAO's results. Hydrolysis of morellin with 7.5 per cent ethanolic sodium hydroxide gave acetone, propionaldehyde and traces of acetaldehyde. On the other hand tetrahydromorellin did not yield acetone on hydrolysis. On oxidation with alkaline permanganate, morellin gave acetone and α -hydroxyisobutyric acid. The formation of acetone by hydrolysis and α -hydroxyisobutyric acid by oxidation suggested the presence of a 2,2-dimethylchromene system as in toxicareol (IV).¹⁰



IV



V

This analogy with toxicarol was further strengthened by the fact that morellin, like toxicarol, gave a monomethyl ether but a diacetate. In toxicarol the formation of diacetate was explained by the enolization of the chromanone carbonyl group.

Morellin showed no free hydroxyl band in the infrared, while the tetrahydro and octahydro derivatives showed weak bands at 3280 and 3550 cm^{-1} . Hexahydromorellin and MRP-I showed prominent bands at 3690 and 3550 cm^{-1} . In the double bond region morellin had four bands at 1730, 1668, 1628 and 1585 cm^{-1} . In dihydromorellin the 1628 cm^{-1} band had broadened with maxima at 1625 and 1645 cm^{-1} ; the 1585 cm^{-1} had almost disappeared and this was attributed to an ethylenic bond capable of rapid reduction, being conjugated with a benzene ring or included in a ring system as in an $\alpha\beta$ -unsaturated steroidal ketone. There was no further change in the double bond region in tetrahydromorellin. The 1668 cm^{-1} band in morellin was assigned to $\alpha\beta$ - $\alpha'\beta'$ -unsaturated carbonyl, in which one alkene bond was part of

a cyclohexene ring. MRP-I showed only one bond in the double bond region at 1642 cm^{-1} which was assigned to a chelated carbonyl in a 5-hydroxychromanone. The characteristic bands at 875 and $1030-1124\text{ cm}^{-1}$ regions in morellin probably were due to a tetrahydropyran ring.

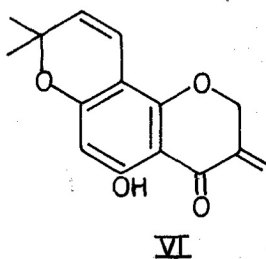
The UV spectrum of morellin had three maxima at 236 , 288.5 and $360\text{ m}\mu$. Dihydroporellin exhibited a more complex spectrum with additional maxima in the $260-80\text{ m}\mu$ region. The other reduction products including MRP-I had a peak $300-30\text{ m}\mu$ region in addition to a weak band at $345\text{ m}\mu$, which is characteristic of $\underline{C}$ -methylphloracetophenone and 5,7-dihydroxychromanone. The spectra of dihydrotoxicarol and hexahydro-osajin, when compared with those of the reduction products of morellin, showed higher intensity absorption in the $300\text{ m}\mu$ region, which was suggested as being due to the substituted phenyl ring in the 3-position of the chromanone nucleus in the former compounds.

RAGHAVAN's Work

RAGHAVAN¹¹ continued the investigation in this laboratory. He assumed the molecular formula $\text{C}_{33}\text{H}_{38}\text{O}_7$ for morellin, although the molecular weight (X-ray method)

of the methyl ether, benzenesulphonate and p-bromobenzene-sulphonate of morellin did not rule out $C_{33}H_{36}O_7$. He also confirmed the presence of four double bonds in morellin. By controlled ozonolysis of morellin and tetrahydromorellin one mole of acetone was isolated, showing the presence of a $Me_2C=$ group. Drastic ozonolysis of morellin gave in addition to acetone, formaldehyde, acetaldehyde and pyruvic aldehyde. Formaldehyde was apparently not formed from a vinyl group, since morellin on periodate-permanganate oxidation¹² gave no formaldehyde.

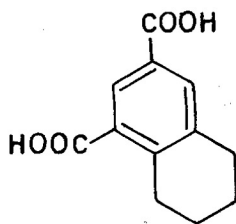
Morellin and isomorellin gave crystalline copper complexes, while the methyl ethers and hydrogenated derivatives did not; in the light of BRINGI's evidence for a chromene ring the partial structure (VI) was therefore postulated.



By the treatment of morellin with massive amounts of Raney nickel in boiling cyclohexanol or cyclohexanone *two* stable crystalline derivatives (MRP-II and MRP-III) were prepared. MRP-I could be converted to MRP-II by the action

of palladium-charcoal in boiling p-cymene, and MRP-III was obtained by similar action on octahydromorellin.

MRP-II was stable to 30 per cent refluxing ethanolic potassium hydroxide, but on fusion with potassium hydroxide at 290° gave a crystalline dicarboxylic acid, $C_{12}H_{12}O_4$, a crystalline phenol, $C_{16}H_{24}O_4$, and n-valeric acid. These three components accounted for 33 carbon atoms of morellin. The $C_{12}H_{12}O_4$ acid was proved to be 5,6,7,8-tetrahydronaphthalene-1,3-dicarboxylic acid (VII), and a partially hydrogenated naphthalene ring system in morellin was therefore postulated.

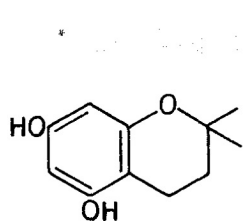


VII

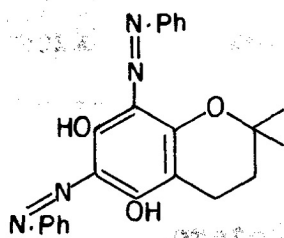
Although considerable evidence was already available for the presence of a 2,2-dimethylchromene system in morellin, it was necessary to isolate 5,7-

dihydroxy-2,2-dimethylchroman (VIII) from the alkali fusion products of hydrogenated morellin (cf. Part I). The phenol (VIII) was readily isolable, even in high dilution in aqueous solution, by coupling with excess of diazotized aniline, when the bisazo derivative (IX), m.p. 258° (dec.), separated. However, the alkali fusion products of octahydromorellin and MRP-II gave no reaction with diazotized aniline. Alkali fusion of octahydromorellin also

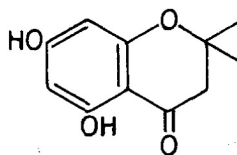
gave the $C_{16}H_{24}O_4$ phenol, which obviously arose from the phloroglucinol part of morellin. It was soluble in aqueous sodium carbonate and was not a carboxylic acid. Active hydrogen analysis gave a figure of 2.8. The C_{16} -phenol gave no ferric colour, but on oxidation with manganese dioxide or with aluminium isopropoxide it gave an amorphous product with a purple ferric colour, somewhat similar to the ferric colour of 5,7-dihydroxy-2,2-dimethylchromanone (X); a benzylic or secondary alcohol group appeared to be oxidized to a ketone. Oxidation with permanganate in acetone yielded acetic and isovaleric acids and a nonvolatile residue, which gave a purple ferric colour and a wine-red colour with magnesium and hydrochloric acid, indicating that a γ -pyrone ring was left intact. Thus the C_{16} -phenol had the properties of a chromanol.



VIII



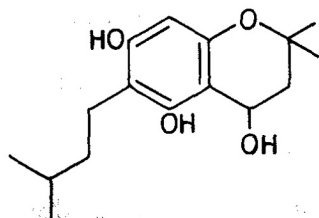
IX



X

There was already evidence for the presence of an isoamylene group in morellin, as shown by the isolation of isovaleric acid in the alkali fusion of morellin, acetone by ozonolysis, and cyclization of morellin to a compound

devoid of ferric colour. All these were the properties of osajin and pomiferin, which are the derivatives of C-isoamylenephloroglucinol. Structure (XI) was therefore considered for the C₁₆-phenol.



XI

Hydrolysis of octahydro-morellin with 5 per cent and 15 per cent ethanolic potassium hydroxide gave a crystalline phenol, C₂₆H₃₆O₆, in addition to formic acid. The action of acetic anhydride and

sodium acetate or ethyl orthoformate, pyridine and piperidine appeared to indicate the presence of a phenol nucleus with a -CO-CH₂-R substituent in the *o*-position.

Present work

The present work was commenced in 1959 simultaneously with the concluding part of RAGHAVAN's investigation, because it was clear from RAGHAVAN's extensive experimental work, subsequently incorporated by him in his Ph.D. thesis,¹¹ that no structure for morellin completely in agreement with the available experimental evidence could be formulated. All the physical and chemical data obtained by BRINGI and RAGHAVAN were therefore re-examined to isolate the incontrovertible facts, reconcile conflicting experimental results,

and collect new evidence including NMR spectra, on the basis of which a rational structure for morellin can be suggested.

Molecular formula

A [BRINGI was unable to decide between the molecular formulae $C_{33}H_{36}O_7$ and $C_{33}H_{38}O_7$ for morellin. The mass spectrum of morellin kindly determined by Dr. W. D. OLLIS and Dr. R. I. REED confirmed the molecular weight as 544 in agreement with the molecular formula $C_{33}H_{36}O_7$.]

Phenolic hydroxyl group

The existence of a single hydroxyl group, phenolic in character, and its chelation with a carbonyl group as in a 5-hydroxychromanone were confirmed by active hydrogen estimation, methoxyl estimation, and ferric colour. BRINGI prepared crystalline monobenzenesulphonyl and mono-p-toluenesulphonyl derivatives of morellin; both in RAGHAVAN's work and the present work crystalline mono-p-bromobenzenesulphonyl derivatives of morellin and isomorellin have been prepared for an X-ray crystallographic study.

Ethylenic bonds

The presence of four ethylenic bonds, three of which are conjugated to a benzene ring or a carbonyl group, was confirmed by catalytic hydrogenation experiments.

Aldehyde group

BRINGI⁸ observed a weak band at about $2700-2750\text{ cm}^{-1}$ in the IR spectra of morellin and all the hydrogenation products, except the Mozingo reduction product (MRP-I). He also noted that the band at 1730 cm^{-1} in morellin, which persists till the octahydro stage, but disappears in the Mozingo reduction product (MRP-I), may arise from an aliphatic aldehyde, unconjugated ketone, ester carbonyl or lactone, and he finally concluded that it was to be ascribed to an unconjugated carbonyl group which undergoes Raney nickel reduction. He rejected an aldehyde group because chemical evidence was lacking; morellin and octahydro-morellin did not form a dimesone derivative. The failure to form a dimesone derivative has also been confirmed in the present work, and further, as observed by BRINGI, isomorellin forms a crystalline mono-2,4-dinitrophenyl-hydrazone. No conclusion can be drawn from the reaction with hydroxylamine because the products are amorphous.

The formation of a diacetate, although morellin contains one hydroxyl group, suggested the possibility of the existence of a hindered aldehyde group capable of enolization to yield a monoacetate. The IR spectra of morellin, tetrahydromorellin and octahydromorellin were therefore re-investigated, especially in the near-IR region for the presence of overtone or combination bands in the light of the recent work of KING and VIG¹³. As stated by KING and VIG, few applications of near-IR spectra for structural elucidation have been made, although their use was suggested in the review papers of KAYE¹⁴ and WHEELER.¹⁵ [KING and VIG measured the near-IR spectra of more than 30 aldehydes and found that all of them showed two bands (around 4500 and 4400 cm^{-1}) expected from the combination of the C-O stretching mode (around 1700 cm^{-1}) with each of the formyl C-H bands (around 2800 and 2700 cm^{-1}).

[In their recent work on the structure of helminthosporal, the toxin from Helminthosporium sativum, DE MAYO¹⁶ found a band at 4480 cm^{-1} in the near-IR region useful for characterizing a conjugated aldehyde group.]

The IR spectra of morellin, tetrahydromorellin, octahydromorellin and the Mozingo reduction product (MRP-II) in carbon tetrachloride were determined on a Perkin Elmer Model 221 Spectrophotometer with a NaCl prism in the region

4500-650 cm^{-1} . Figs. 5, 6, 7 and 8 show 4500-4000 cm^{-1} region with five times expansion. [Using NaCl prism-grating interchange, the band at 1668 cm^{-1} earlier reported by BRINGI has now been found to be at 1680 cm^{-1} and it has disappeared in MRP-II. The band at 1680 cm^{-1} can well be assigned to an $\alpha\beta$ -unsaturated aldehyde group; however, since the C=O stretching vibration for conjugated aldehydes is in the range 1705-1680 cm^{-1} , additional evidence is necessary. The C-H bands at 2740 and 2770 cm^{-1} may arise from a formyl group and the sum of each of these with the 1680 frequency should appear respectively at 4420 and 4450 cm^{-1} . Although two distinct peaks are not noticed, the broad band at 4400-4480 cm^{-1} provides clear evidence of an aldehyde group. The observed C=O, formyl C-H and near-IR frequencies for tetrahydromorellin were as follows: 1685, 2725 and 2739 cm^{-1} and broad absorption around 4400 cm^{-1} , confirming the presence of an aldehyde group in tetrahydromorellin.] The formation of pyruvic aldehyde by the prolonged ozonization of morellin was confirmed, and the presence of the group =C-CHO was therefore postulated.

Me

5,7-Dihydroxy-2,2-dimethylchromene derivative with a dimethylallyl side-chain

BRINGI confirmed beyond all doubt the presence of the phloroglucinol nucleus in morellin by the isolation of

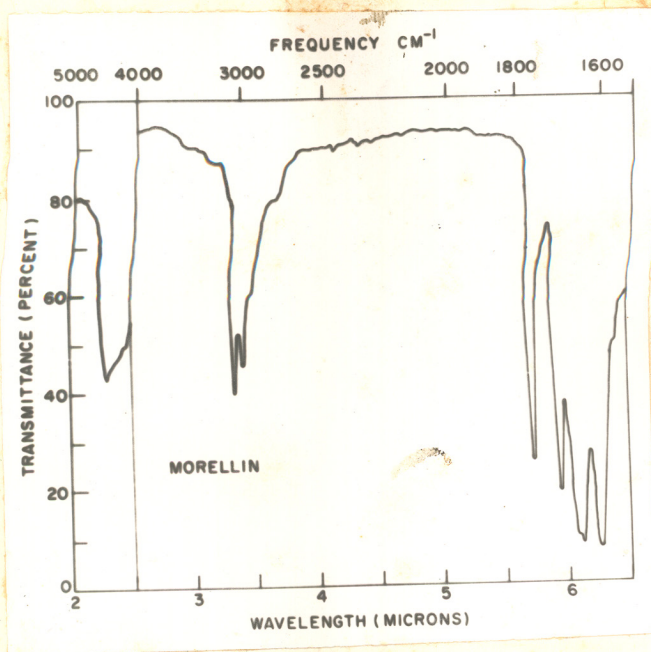


FIG. 5.

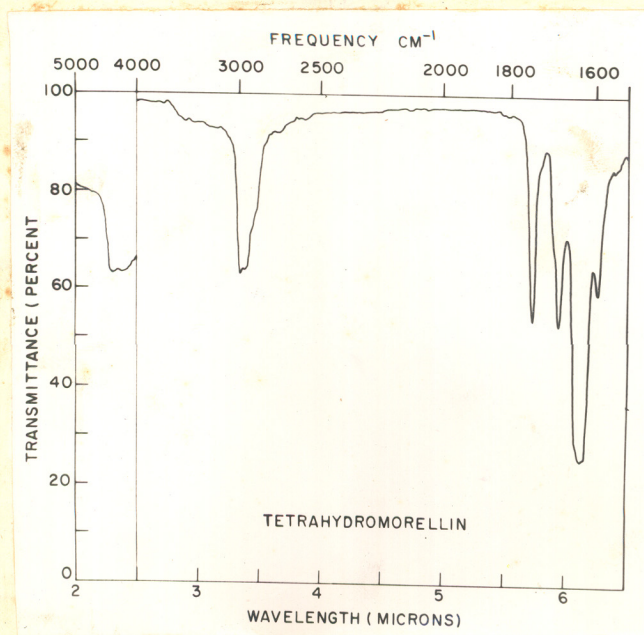


FIG. 6.

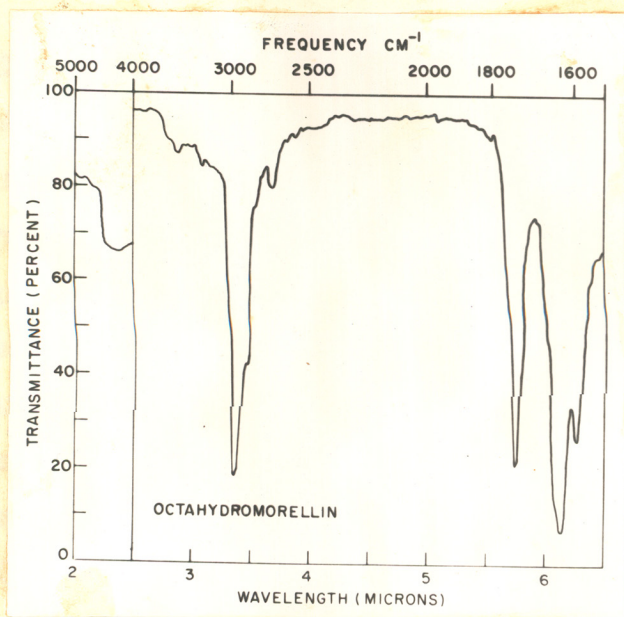


FIG. 7.

IR spectrum of octahydromorellin
-CO- region

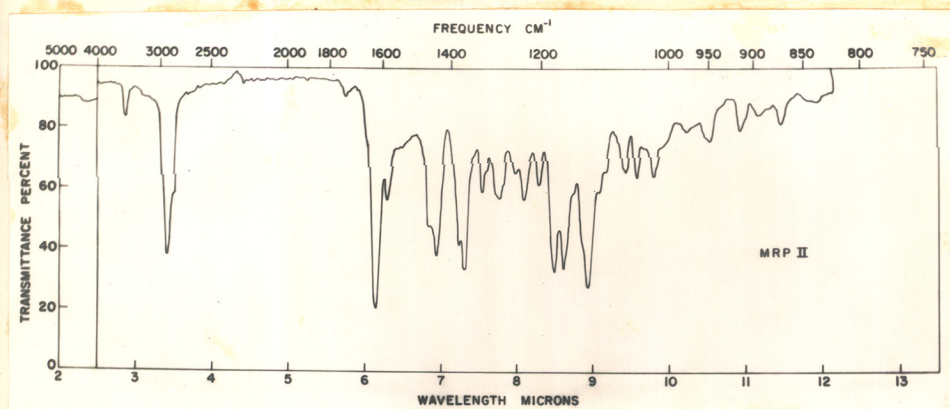
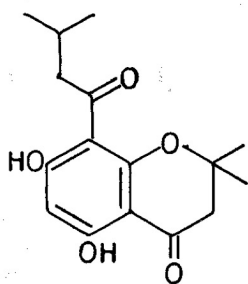
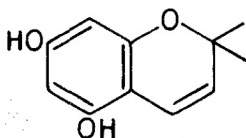


FIG. 8.

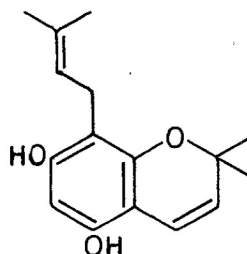
phloroglucinol, also obtained in the original work of B. S. RAO,² as one of the products of alkali fusion of morellin. The formation of acetone by mild alkaline hydrolysis of morellin and of α -hydroxyisobutyric acid by permanganate oxidation then gave reasonably definite evidence of the presence of the 5,7-dihydroxy-2,2-dimethylchromene system (XIII) (cf. Part I). Several observations subsequently led to the conclusion that the phloroglucinol nucleus is further substituted by a dimethylallyl side-chain ($\text{Me}_2\text{C}=\text{CH}-\text{CH}_2-$). Acetone was formed by the ozonolysis of both morellin and tetrahydromorellin. RAGHAVAN¹¹ isolated a C_{16} -phenol from the products of alkali fusion of octahydromorellin and MRP-II. He also obtained this phenol synthetically as the most readily crystallizable constituent of the products of Clemmensen reduction of 5,7-dihydroxy-8-isovaleroyl-2,2-dimethylchromanone (XII) prepared in the present work. These experimental results made it very probable that morellin contained a 5,7-dihydroxy-2,2-dimethylchromene nucleus with a dimethylallyl side-chain in the 8-position (XIV).



XII

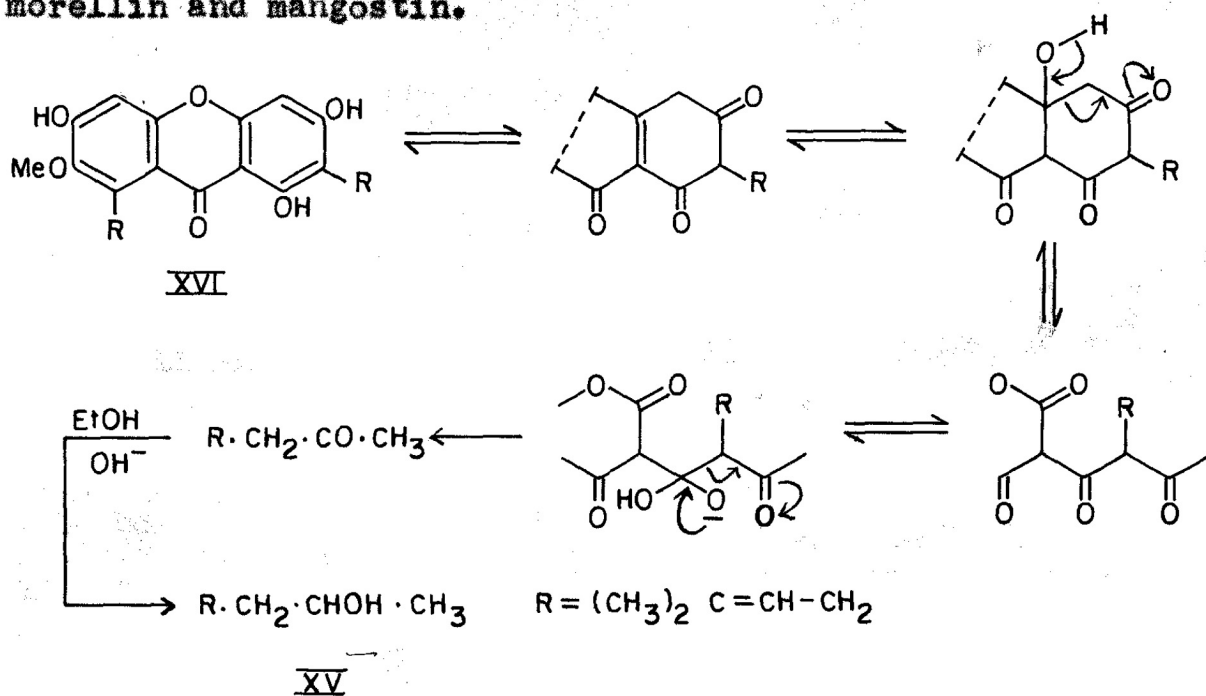


XIII

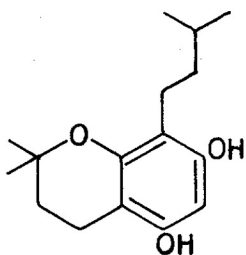


XIV

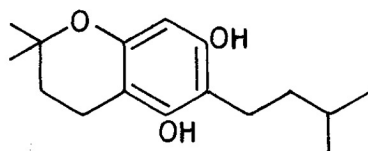
The structures of sericetin, pomiferin and osajin, mentioned in Part I, provided analogies for the occurrence of such systems (XIV) among plant pigments. Another fact to be borne in mind in this connection was the isolation of methyl heptenol ($\text{Me}_2\text{C}=\text{CHCH}_2\text{CH}_2\text{-CHOH-Me}$; XV), both by B. S. RAO² and BRINGI⁷, by the alkali fusion of morellin; YATES and STOUT¹⁷ have shown that mangostin (XVI), which has a phloroglucinol nucleus with a β -dimethylallyl substituent, yields the same methyl heptenol by alkali fusion, apparently by the following mechanism which they postulated. Isovaleric acid and isoamyl alcohol are two other products obtained by the alkali fusion of both morellin and mangostin.



In order to obtain further support for the presence of the system (XIV) in morellin an important part of the programme in the present work was to isolate 8-isoamyl-5,7-dihydroxychroman (XVII), identical with the product of this structure obtained by unambiguous synthesis. Several routes for the synthesis of (XVII) were investigated in the course of which 6-isoamyl-5,7-dihydroxy-2,2-dimethylchroman (XVIII) and a series of intermediate ketones and chromanones were prepared. These have additional interest in connection with projects in view for the synthesis of naturally occurring 2,2-dimethylchromenes such as sericetin, pomiferin and osajin.



XVII

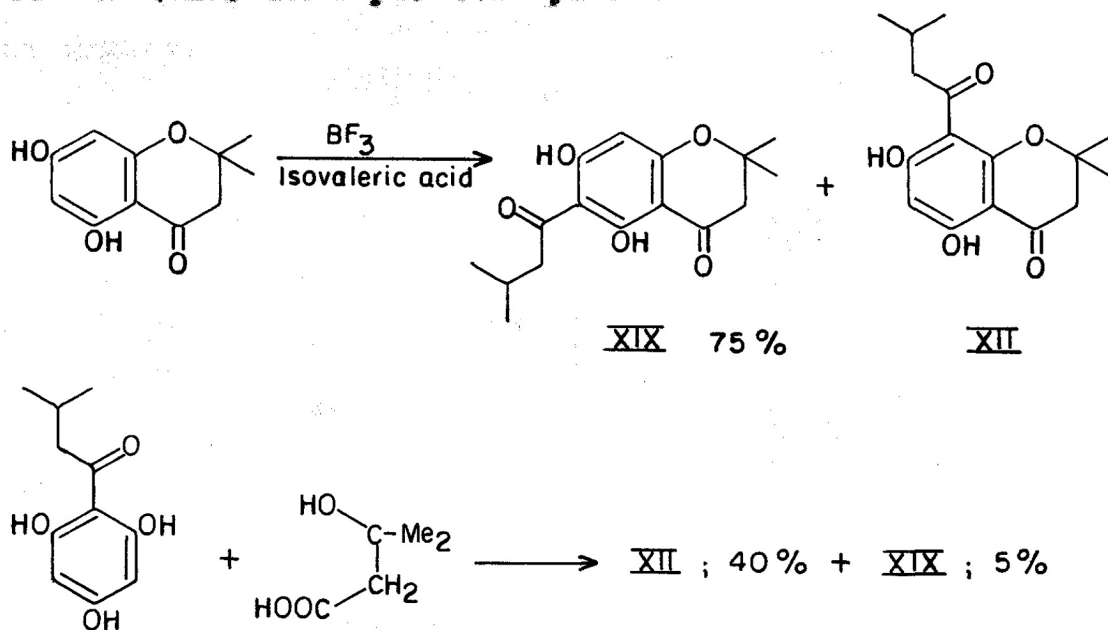


XVIII

Synthesis of 8-isoamyl-5,7-dimethoxy-2,2-dimethylchroman (XXIV)

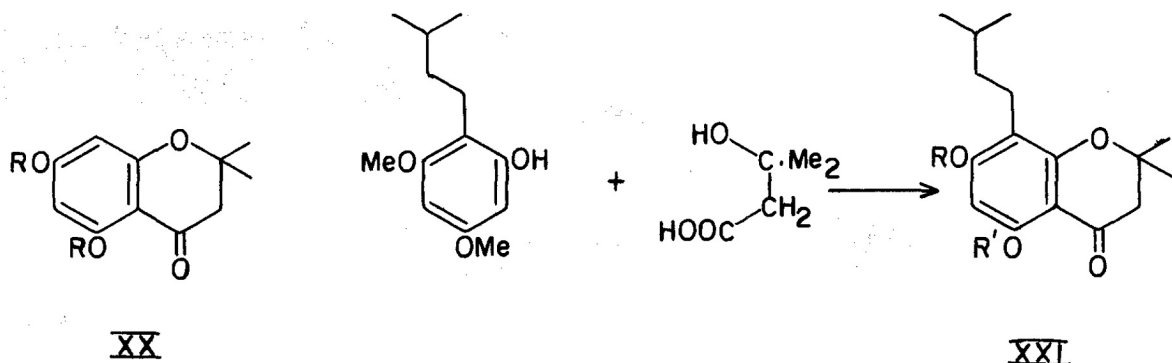
5,7-Dihydroxy-2,2-dimethylchromanone (X) on treatment with boron fluoride-isovaleric acid complex gave a mixture of 5,7-dihydroxy-6-isovaleroyl-2,2-dimethylchromanone (XIX) and the 8-isomer (XII). The former (XIX) was isolated in 75 per cent yield by crystallization. The presence of the 8-isomer (XII) was indicated by thin layer chromatography of the mother liquor on silica gel with 5 per cent ethyl acetate-

benzene as solvent. Exposure to iodine vapour was employed throughout the present work for the identification of colourless or nearly colourless spots of phenols and phenolic ethers on silica gel; the spots turned yellow immediately and deep brown after a few hours. The 8-isomer (XII) was not isolated. Condensation of phloroisovalerophenone with β -hydroxyisovaleric acid in presence of boron fluoride etherate (cf. Part II) gave the 8-isomer (XII) in 40 per cent yield, mixed with the 6-isomer (XIX) in 5 per cent yield.



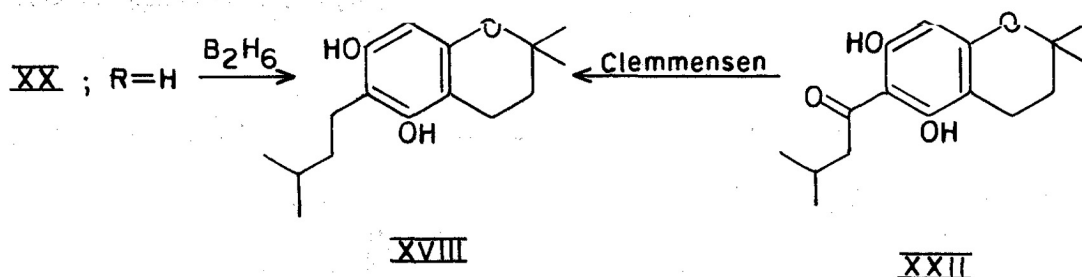
The proof for XIX being the 6-isomer was obtained by the following methods. The compound XIX on Clemmensen reduction gave 6-isoamyl-5,7-dihydroxy-2,2-dimethylchromanone (XX; R = H), which resisted total methylation even by refluxing for 100 hours with acetone,

potassium carbonate and dimethyl sulphate. The product giving faint ferric colour on chromatography on alumina gave a liquid dimethyl ether (XX; R = Me), which was different from the crystalline 8-isoamyl-5,7-dimethoxy-2,2-dimethylchromanone (XXI; R, R' = Me), which was unambiguously prepared by condensing isoamylphloroglucinol-2,4-dimethyl ether with β -hydroxyisovaleric acid. The reaction gave (XXI; R, R' = Me) in 5 per cent yield; the major product had undergone partial demethylation as shown by the ferric colour, but the Wessely-Moser rearrangement to 6-isoamyl-5-hydroxy-7-methoxy-2,2-dimethylchromanone had not taken place because the product on further methylation gave (XXI; R = R' = Me).



The compound (XX; R = H) on reduction with diborane gave 6-isoamyl-5,7-dihydroxy-2,2-dimethylchroman (XVIII), which was identical with the product obtained by Clemmensen reduction of 5,7-dihydroxy-6-isovaleroyl-

2,2-dimethylchroman (XXII), whose structure was already proved by ROBERTSON.¹⁸



RAGHAVAN¹¹ isolated the $\text{C}_{16}\text{H}_{24}\text{O}_4$ phenol as the main product of the Clemmensen reduction of a diketone which he believed to be 5,7-dihydroxy-6-isovaleroyl-2,2-dimethylchromanone (XIX); the diketone used by RAGHAVAN, prepared by the condensation of phloroisovalerophenone with β -hydroxyisovaleric acid, has now been proved to be the 8-isomer (XII). The formation of the C_{16} -phenol by the Clemmensen reduction of XII was confirmed in three experiments because of its important role in RAGHAVAN's work and the need to prove that it was derived from 5,7-dihydroxy-8-isovaleroyl-2,2-dimethylchromanone (XII) and not the 6-isomer (XIX). The difficulty in effecting a normal Clemmensen reduction of the diketone (XII) was apparently associated with the free hydroxyl groups of the phloroglucinol nucleus; ROBERTSON¹⁸ has also recorded his failure to reduce 5-hydroxy-7-methoxy-8-isovaleroyl-2,2-dimethylchroman by the Clemmensen method, although the 5-benzyl-7-methyl ether underwent reduction to the

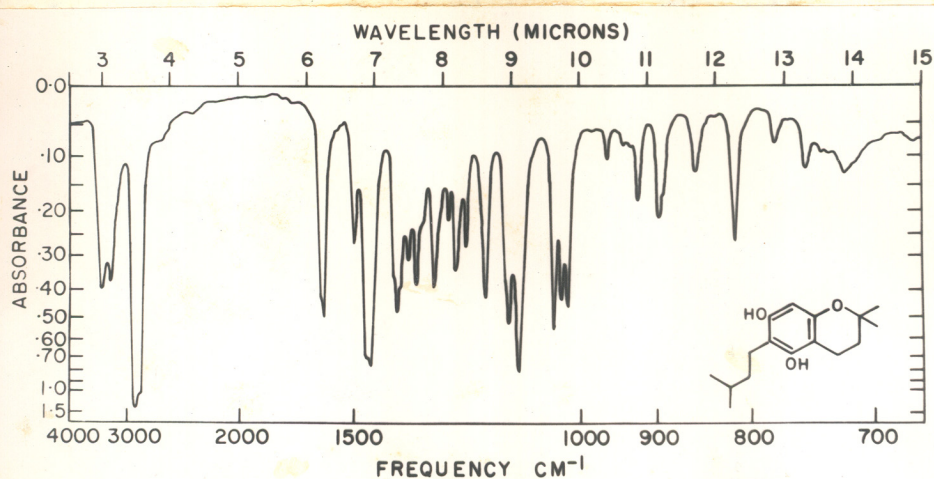


FIG. 9. Spectrum in Nujol.

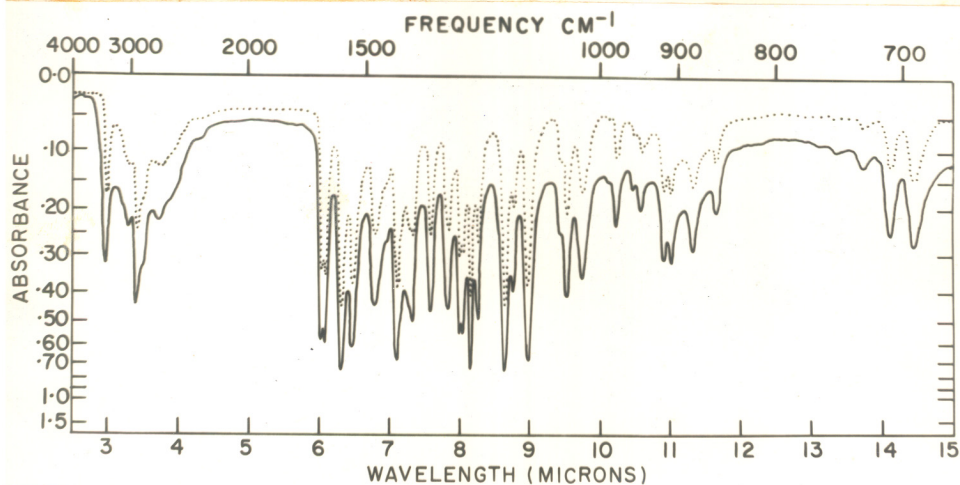
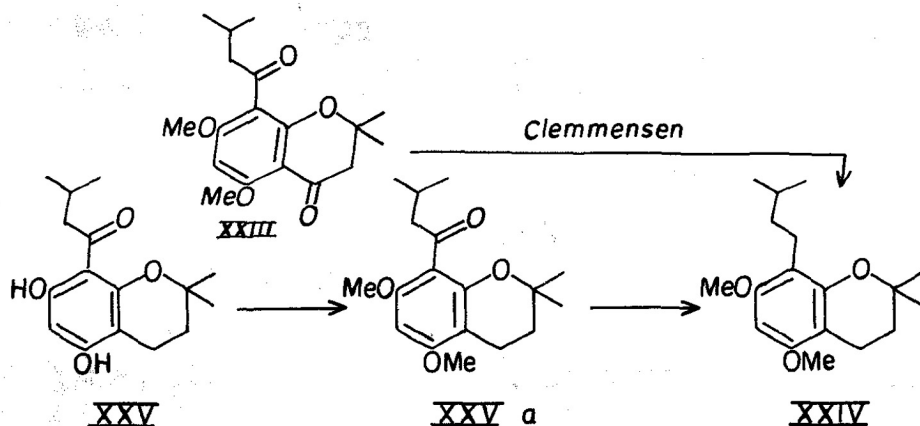


FIG. 10. Spectra in KBr of C_{16} -phenol (—) obtained from the Clemmensen reduction of XII and of the one obtained from alkali fusion of octahydromorellin (-----).

isoamyl derivative. Anticipating complexities arising from a Wessely-Moser rearrangement at the demethylation stage, the Clemmensen reduction of the ditosylate of (XII) was first studied; but the uncrystallizable product, which showed no C=O absorption in the IR, gave the C₁₆-phenol after treatment with 5 per cent ethanolic sodium hydroxide on the water-bath.

Clemmensen reduction of the dimethyl ether (XXIII) was then carried out. Chromatography of the product in hexane on alumina gave 8-isoamyl-5,7-dimethoxy-2,2-dimethylchroman (XXIV) in 55 per cent yield. The compound XXIV, m.p. 42°, showed a greenish yellow fluorescence in hexane solution in ultraviolet light and could be thus distinguished on an alumina column.



Alkali fusion of octahydromorellin and isolation of 8-isoamyl-5,7-dihydroxy-2,2-dimethylchroman (XVII)

Octahydromorellin was fused at 250° with five times the weight of potassium hydroxide and half the weight of

zinc dust and the melt was diluted with water, filtered, and the pale yellow filtrate acidified. The product was extracted with ether and washed successively with aqueous sodium bicarbonate and sodium hydroxide. Acidification of the latter extract and extraction with ether gave an orange semi-crystalline mass, which on crystallization from acetone-hexane gave the C_{16} -phenol (10 per cent). The mother liquor was evaporated, and the residue dissolved in benzene and chromatographed on silica gel (200 mesh). Elution of the first band led to a gummy product free from carbonyl absorption, and distillation at $130^{\circ}/7.7 \times 10^{-3}$ mm gave a viscous oil which analysed for 8-isoamyl-5,7-dihydroxy-2,2-dimethylchroman (XVII). Thin layer chromatography using 5 per cent ethyl acetate-benzene on silica gel showed a single spot. In its properties, including the IR spectrum, the compound was identical with a compound isolated by silica gel chromatography of the Clemmensen reduction product of 5,7-dihydroxy-8-isovaleroyl-2,2-dimethylchromanone (XII) or of XXV.

Although these observations indicated the presence of 8-isoamyl-5,7-dihydroxy-2,2-dimethylchroman (XVII) in the alkali fusion product of octahydromorellin, characterization by means of a crystalline derivative was desirable. Alkali fusion of octahydromorellin was carried out on a 15 g scale as above, and the product separated into

sodium bicarbonate soluble, sodium carbonate soluble, and sodium hydroxide soluble fractions. The bicarbonate solution was acidified, the fatty acids steam-distilled, and characterized as isobutyric, isovaleric and p-valeric acid (the last in traces) through their methyl esters by vapour-phase chromatography on a Perkin Elmer 154 at 70° using hydrogen; An ester with a higher retention time than methyl isovalerate appeared to be methyl isocaproate, but confirmation is necessary. The carbonate soluble fraction on crystallization from acetone-hexane gave the $C_{16}H_{24}O_4$ phenol (8 per cent). The mother liquor was mixed with the sodium hydroxide soluble fraction and the combined product methylated with dimethyl sulphate and potassium carbonate in acetone. Chromatography of the product in hexane on alumina gave a greenish yellow fluorescent band, which on elution, evaporation and crystallization gave a colourless fluffy crystalline compound in 35 per cent yield based on octahydromorellin. The m.p. and mixed m.p. with the synthetic sample (XXIV) were identical, and the IR spectra in liquid film were superposable (Fig. 11).

The isolation of the chroman (XXIV) provided the classical proof of the presence of the 8-dimethylallyl-5,7-dihydroxy-2,2-dimethylchromene (XIV) skeleton in morellin. However, one difference from rottlerin,

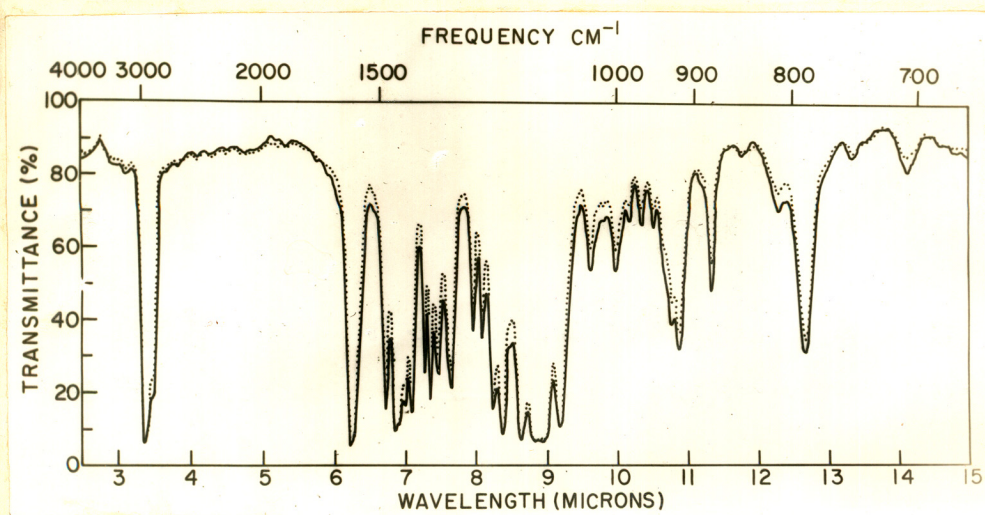


FIG. 11.

Spectrum in liquid film of synthetic 8-isoamyl-5,7-dimethoxy-2,2-dimethylchroman (——) and the one from octahydromorellin (-----).

toxicarol, osajin and pomiferin was that the chromans from the hydrogenated derivatives of these compounds were obtained by much milder alkaline hydrolysis.

Rottlerin is a chalcone; toxicarol, osajin and pomiferin are isoflavanone derivatives. The presence of a more stable ring system (such as a hydrogenated xanthone) in morellin was therefore indicated by the drastic conditions of alkali fusion required for breaking off the chroman moiety from octahydromorellin.

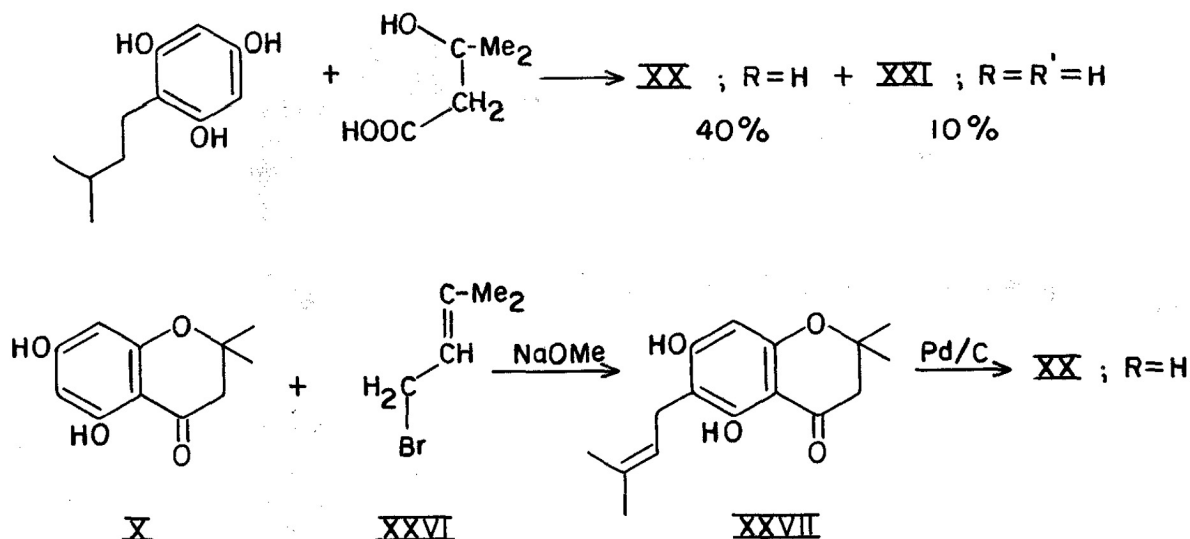
Preparation of 5,7-dihydroxy-6(and 8)-isovaleroyl-2,2-dimethylchroman

ROBERTSON prepared the two ketones by the Hoesch reaction between 5,7-dihydroxy-2,2-dimethylchroman (VIII) and isovaleronitrile. The 8-isomer (XXV) was found to be the major product. In the present work other procedures were found to be more convenient. The Friedel-Crafts reaction between 5,7-dihydroxy-2,2-dimethylchroman (VIII) and isovaleroyl chloride in ether gave a mixture of 6- and 8-acylated compounds (XXV and XXII) in addition to 10 per cent of the recovered starting material (VIII). The mixture could be conveniently separated on a silica gel column; benzene eluted only the by-products and the 6-isomer. The 6-isomer (XXII) readily crystallized in

colourless needles (yield: 5 per cent, m.p. 146° , and gave a deep purple ferric colour. Elution with 5 per cent ethyl acetate-benzene led to the 8-isomer (XXV), which readily crystallized from hexane in greenish yellow plates (yield: 30 per cent). When nitrobenzene was used as solvent in the Friedel-Crafts reaction, the 6-isomer (XXII) was obtained in larger proportion (40 per cent). The action of the isovaleric acid-boron fluoride complex on the chroman gave the acyl derivatives in 10 per cent yield, since the complex of the ketone could not be decomposed.

6-Isoamyl-5,7-dihydroxy-2,2-dimethylchromanone (XX; R = H) was obtained in 40 per cent yield by condensing isoamylphloroglucinol with β -hydroxyisovaleric acid. Crystallization of the crude product from benzene gave (XX; R = H); chromatography of the mother liquor on silica gel gave more of (XX; R = H) and the 8-isomer (XXI; R = R' = H) in 10 per cent yield. The 8-isomer (XXI; R = R' = H) was identical with the product obtained by the demethylation of 8-isoamyl-5,7-dimethoxy-2,2-dimethylchromanone (XXI; R = R' = OMe). The action of γ -dimethylallyl bromide (XXVI) on 5,7-dihydroxy-2,2-dimethylchromanone (X) in presence of sodium methoxide in ether gave 5,7-dihydroxy-6-isopentenyl-2,2-dimethylchromanone (XXVII), which on hydrogenation in presence of

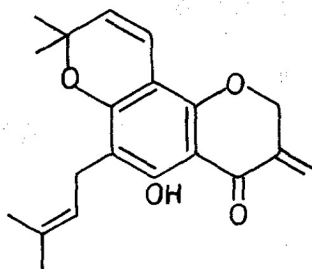
palladized carbon gave (XX; R = H).



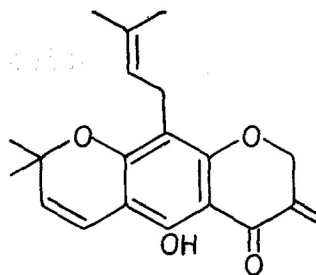
Part Structure for Morellin

The isolation of 8-isoamyl-5,7-dihydroxy-2,2-dimethylchroman (in high yield as the dimethyl ether) from the alkali fusion of octahydromorellin, the formation of acetone by the ozonolysis of both morellin and tetrahydromorellin, the distinct ferric chloride reaction of morellin, the red copper complex obtained from morellin (but not from the methyl ether or tetrahydromorellin), and the other facts to which attention has been drawn in earlier sections, led to the conclusion that morellin has the part structure (XXVIII) or (XXIX). A double bond conjugated with the carbonyl group was shown by the formation of a red copper complex and the high intensity band at about 360 mμ in the UV spectrum of morellin, reminiscent of rottlerin which has

a cinnamoyl group conjugated with a chromene nucleus. The rapidity with which two molecules of hydrogen were absorbed by catalytic hydrogenation and the consequent spectral changes gave further support. The wine-red colour in the sodium amalgam reaction given by tetrahydromorellin, but not by morellin, provided evidence of a γ -pyranone ring of the type shown in structures (XXVIII) and (XXIX).



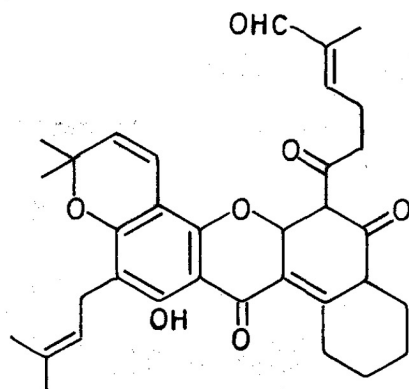
XXVIII



XXIX

Alkali fusion of octahydromorellin could have yielded 8-isoamyl-5,7-dihydroxy-2,2-dimethylchroman, whether morellin had the part structure (XXVIII) or (XXIX), in which the pyran and pyranone rings have the angular or linear arrangement respectively. Structure (XXVIII) with the angular arrangement was preferred initially on the analogy of osajin and pomiferin, the structures of which have been proved conclusively, as well as sericetin, the structure of which is very probable, but needs further experimental support. The X-ray crystallographic data discussed later have now shown the correctness of part structure (XXIX).

Part structure (XXVIII) was then elaborated to structure (XXX) for morellin on the basis of the following considerations: the isolation of 5,6,7,8-tetrahydronaphthalene-1,3-dicarboxylic acid (VII) from the alkali fusion of MRP-II, the formation of pyruvic aldehyde by the ozonolysis of morellin, and the indication of a 1,3-diketone group by some reactions. The carbonyl group in the hydrogenated naphthalene part was presumed to undergo reduction to a secondary alcohol in MRP-II, which could aromatise to give the tetralin acid (VII) during alkali fusion.



XXX

Structure XXX for morellin left several facts to be explained. The IR bands at 1626 and 1680 cm^{-1} respectively were in the expected regions for the chelated carbonyl of a 5-hydroxychromanone and for an $\alpha\beta$ -unsaturated aldehyde; but the IR band at 1730 cm^{-1} (observed at 1739 cm^{-1} in the present work) was at too high a frequency for a six-membered ring ketone and much too high for a β -diketone.

The hydrogenated naphthalene ring in XXX required more experimental support. There were other anomalies in the chemical behaviour of morellin, which will not be discussed, because NMR ruled out the tetrahydronaphthalene part of XXX.

NMR Data

The NMR spectra of morellin, isomorellin, tetrahydromorellin, octahydromorellin, and morellin diacetate are recorded in Figs. 12, 13, 14, 15 and 16. The spectra were taken in CDCl_3 solution using tetramethylsilane as internal standard at 60 Mc. I am greatly indebted to Dr. M. CASERIO of the California Institute of Technology, Dr. A. MELERA of Varian Associates, Zurich, and Dr. G. S. BARNES of CSIRO, Melbourne, for the spectra. I am grateful to Dr. P. M. NAIR for collaboration in interpreting the NMR spectra.

The NMR spectrum of morellin gives a total proton count of 36 and shows the presence of seven methyl groups. [Four of these absorb at 8.47 (2), 8.50 and 8.67 and are attached to tert. C atoms; chemical shifts are cited on the γ scale. The remaining three give peaks at 8.20, 8.25 and 8.30 and are evidently on C=C bonds.] There is no $\text{CH}_3\text{-CO-}$ group. The low field part of the spectrum shows singlet

single proton absorptions due to a strongly chelated hydroxyl at -2.77 and an aldehyde at 0.37 . The former is broadened by exchange with trifluoroacetic acid, while the latter is unaffected. In the vinyl region there are three doublets at 2.4 ($J=7$ cps), 3.35 ($J=10$ cps), 4.43 ($J=10$ cps), and two triplets at 3.9 ($J=8$ cps) and 4.75 ($J=7.5$ cps). No aromatic hydrogen is indicated.

The vinyl doublets at 3.35 and 4.43 with a coupling constant of 10 cps, in conjunction with the two Me groups at 8.47 , indicate a 2,2-dimethylchromene system.^{19,20}

The vinyl triplet at 4.75 and the Me signals at 8.2 and 8.3 may be assigned to a γ -dimethylallyl group; if this is attached to an aromatic ring, the allylic methylene will be benzylic also and one would expect it to absorb in the region 6.6 to 6.7 ,¹⁹ giving a doublet. In morellin itself the absorption in this region shows more than two protons in a multiplet structure; however, there is a strong suggestion of a 2-proton doublet. In isomorellin, which has a very similar spectrum, the position is more satisfactory, the 2-proton doublet at 6.77 being well resolved. Together with the chelated hydroxyl signal at -2.77 , the part structure XXVIII or the linear isomer (XXIX) without the hydrogenated naphthalene ring, may be formulated.

The vinyl doublet at 2.4 ($J=7$ cps) shows that the

proton is attached to a double bond linked to a strongly electron-withdrawing group. This can be the β -proton of an $\alpha\beta$ -unsaturated ketone, which has a planar S-cis conformation²¹ or is part of a cyclopentenone ring. The absorption of morellin in the near-UV region (λ_{max} 360 m μ) requires that there should be a double bond in conjugation with the CO in XXVIII or XXIX, and the proton under consideration can well be on this double bond. It is spin coupled to a lone proton on an adjacent carbon. If this carbon is part of a ring, the magnitude of the coupling constant implies that the dihedral angle between them is close to zero. In tetrahydromorellin the chromene doublets and the doublet at 2.40 disappear.

The triplet absorption at 3.9 in the morellin spectrum indicates another proton with an adjacent CH₂ and on a double bond attached to an electron-withdrawing group. This is shifted to 3.63 in tetrahydromorellin. The shift may be associated with destruction of cross-conjugation, removal of anisotropic shielding, or isomerization during hydrogenation. In this connection it is pertinent to note that for isomorellin the corresponding absorption is at 3.68. It is also suggestive that, whereas the morellin aldehyde signal is at 0.37, the corresponding signals of tetrahydromorellin and isomorellin appear at 0.68 and 0.82 respectively. It is more than likely that

isomerization has taken place during hydrogenation.]

The singlet character of the aldehyde absorption of morellin shows the absence of protons on the α -carbon atom, and the aldehyde group is therefore tertiary or $\alpha\beta$ -unsaturated with an α -substituent. In the latter case it is expected that the double bond concerned should be one of those that are readily saturated on hydrogenation; but tetrahydromorellin shows a sharp singlet aldehyde absorption. Moreover, efforts to get the usual chemical evidence for an aldehyde group were unsuccessful. These facts together suggested that the aldehyde is tertiary. If it is conjugated with a double bond that resists hydrogenation for steric reasons, the spectrum of octahydromorellin should remove the ambiguity. Unfortunately, octahydromorellin is amorphous; the spectrum gives pairs of signals that are not very sharp for the chelated hydroxyl and aldehyde functions, and the compound is evidently a mixture of isomers. The aldehyde signals obtained are definitely broadened, but it is not certain if spin coupling is involved. There is a shift at 0.45 p.p.m. in the position of the aldehyde signal in going from morellin to isomorellin. This is too large for a change from a saturated to an $\alpha\beta$ -unsaturated aldehyde. The shift is probably due to anisotropic shielding factors

affecting the aldehyde group in isomorellin, but not in morellin.

The spectrum of morellin diacetate shows some very revealing features. The vinyl triplet at 3.9 and two protons, probably belonging to a CH_2 , coming in the region of 6.2 to 7.15 in the morellin spectrum, as well as the aldehyde signal, have disappeared; and three new vinyl protons appear at 2.80, 3.52 and 4.84. The first gives a singlet absorption, and the remaining two constitute a pair of trans vinyl protons (doublets, $J=15.5$ cps). The first appears to be the α -proton of a vinyl acetate formed by acylation at the aldehydic oxygen of morellin. If morellin has an angular aldehyde group, the formation of a pair of trans vinyl hydrogens in the acetylation of morellin implies that one ring has opened up. Alternatively, if this aldehyde group is $\alpha\beta$ -unsaturated and is present in a side-chain, the observed changes will be consistent with the presence of a $-\text{CH}_2-\text{CH}=\underset{\text{f}}{\text{C}}-\text{CHO}$ group in morellin, converted to $-\text{CH}=\text{CH}-\underset{\text{f}}{\text{C}}=\text{CH}-\text{OAc}$ in the diacetate, the γ - and δ -protons giving rise to the doublet absorptions at 3.52 and 4.84. The formation of pyruvic aldehyde in the ozonolysis of morellin would tend to suggest that the α -substituent here is a methyl group. If this is correct, the methyl resonance seen at 8.25 may be conveniently assigned to it.] If the

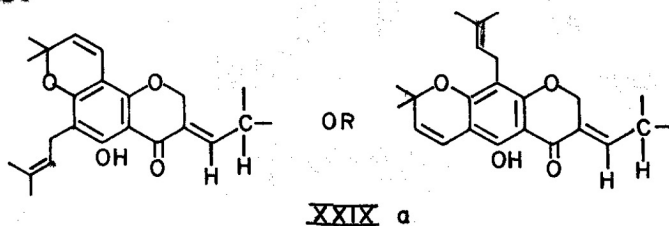
aldehyde group is attached to a double bond in a ring, it is very unlikely that acylation at the aldehydic oxygen would be accompanied by the formation of a trans-disubstituted double bond.

In the morellin diacetate spectrum there is a broad three proton multiplet signal centered at 6.6 that is well separated from others. Two of these protons have been already assigned to the γ -dimethylallyl group on the aromatic ring. The remaining proton, which shows up at 6.4 and 6.5 in morellin and isomorellin, is either on a carbon bound to oxygen or may be α to a keto group and allylic at the same time.²² The absorptions in the 7.1 to 8.1 region correspond to nine protons including those of the acetyl methyls. Thus the methylene and methine protons appearing in the range of 7.15 to 7.9 in morellin are relatively unaffected by acetylation. The methine proton of this region of the morellin spectrum appears as a well resolved doublet ($J=4.5$ cps) centered at 7.7 and therefore seems to be coupled only to one proton. The methylene group gives an unsymmetrical and distorted quartet centered at 7.35; it is apparently under the deshielding influence of one or more multiple bonds.

E [The three proton peaks at 8.5 and 8.67 in the spectrum

of morellin occur in the expected region for Me groups on C attached to O. In isomorellin these Me groups are in similar environments and lead to a single sharp resonance at 8.67, suggesting that they may form a gem-dimethyl system. In morellin itself they are probably differentiated by magnetic anisotropy of the double bonds in their neighbourhood.]

Summarizing the NMR results, it may be said that the evidence for the part structure XXVIII or XXIX is very good, and that these may be improved to XXIXa. In addition the data suggested the probable presence of a C₅ side-chain like -CH₂-CH-C-CHO and also a second gem-dimethyl system bound to oxygen. ^{CH₃} The precise relationship of the CH₂ of this C₅ side-chain to the rest of the molecule could not be obtained from the NMR data. Also the specification of the position of the remaining methylene and methine hydrogens in greater detail was not possible.



X-Ray Crystallography

Almost from the commencement of the work on morellin in this laboratory, it was realized that X-ray crystallography may prove to be the only technique by which the complete structure of morellin can be proved. [Professor J. D. BERNAL, during a visit in 1955, was attracted by the

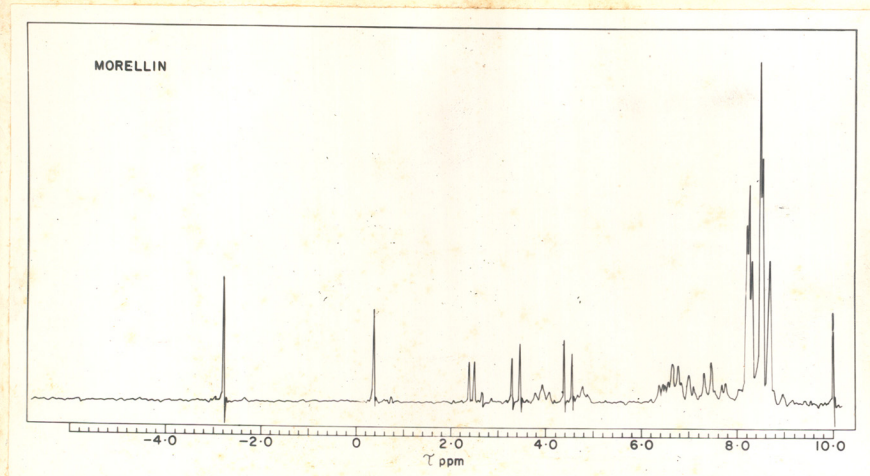


FIG. 12.

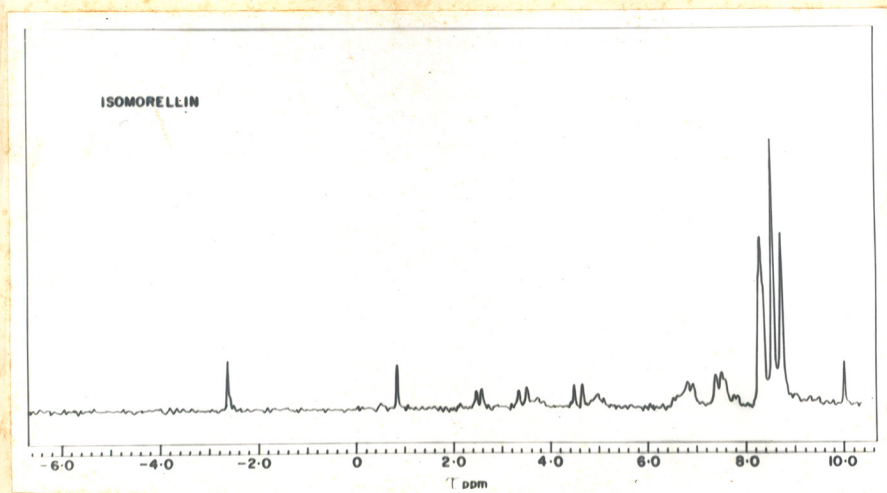


FIG. 13.

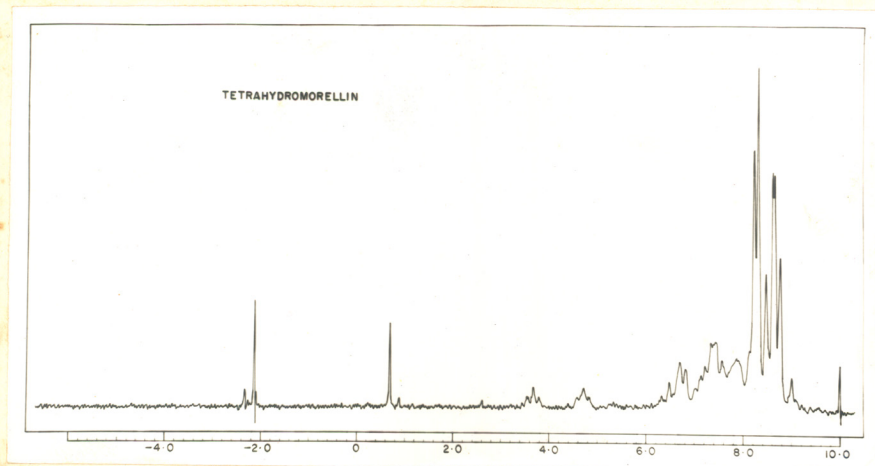


FIG. 14.

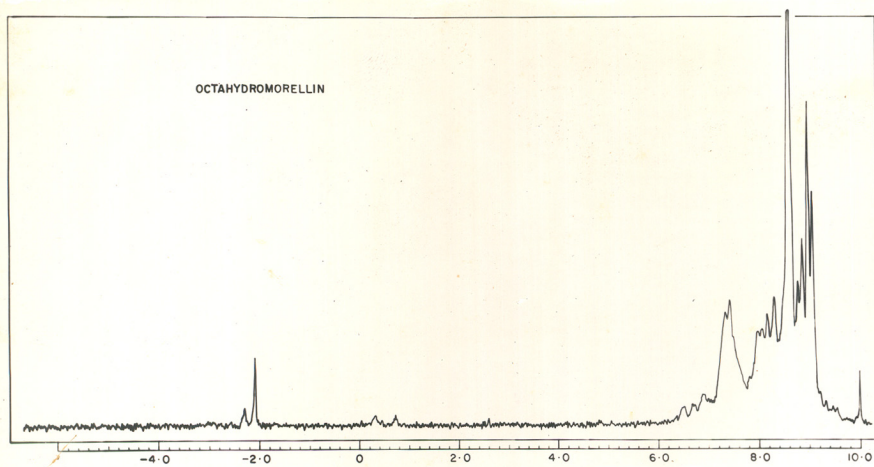


FIG. 15.

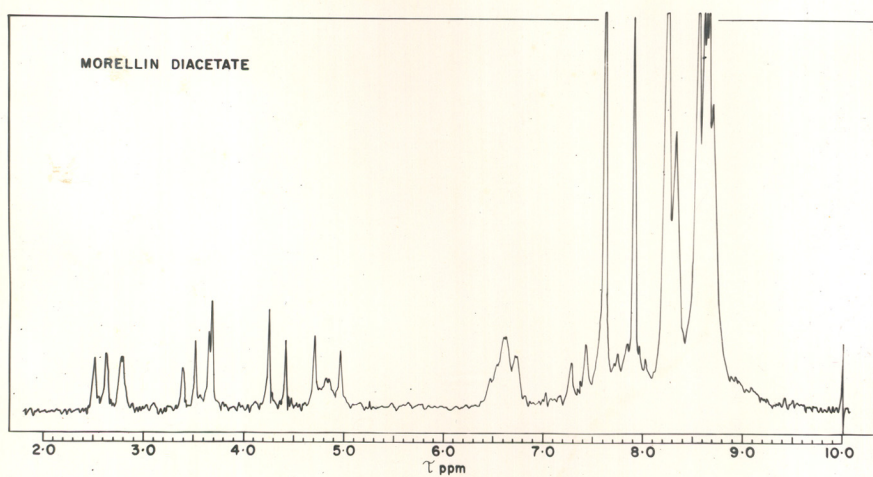


FIG. 16.

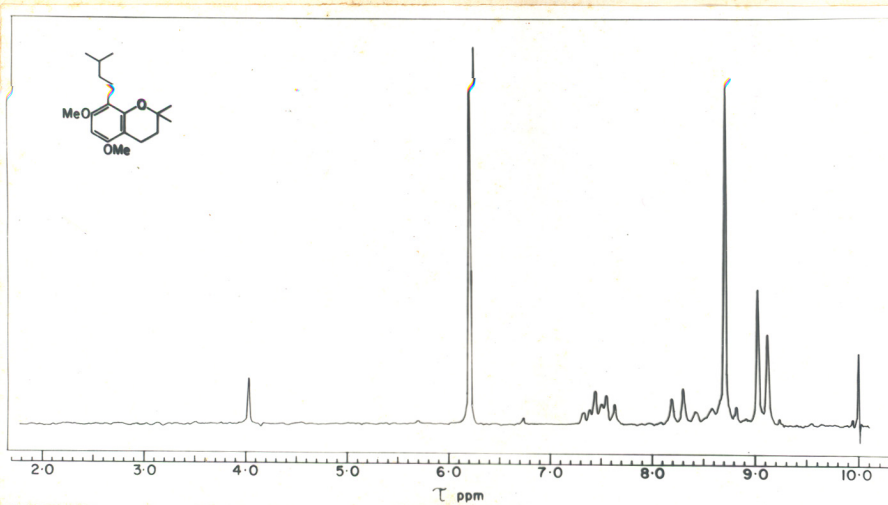
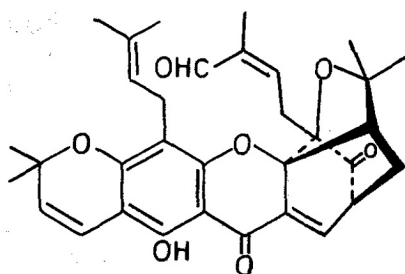


FIG. 17.

size and beauty of the crystals of morellin and he took with him a sample for X-ray study. Morellin was investigated by Dr. CARLISLE and Dr. DAYAL in Birbeck College, London, and subsequently by the latter in Banares University. Although Dr. DAYAL had no contact with the workers on morellin in this laboratory since 1955, he and S. C. MATHUR have referred in a recent note²³ to the preliminary chemical data provided to him casually. DAYAL and MATHUR have included in their note a "provisional chemical formula" in which a double bond in a benzene ring is omitted and a double bond in the hydrogenated naphthalene ring is in a wrong position. They finally state: "Trials of atomic positions based on the formula have shown reasonable agreement between calculated and observed structure factors but, owing to the complexity of the molecule and its awkward projections on (001) and (010), are not sensitive to further refinement. It is clear that the analysis needs to be carried out in three dimensions and this is now being done."

It was observed by Dr. L. M. PANT in this laboratory that the main difficulty in the X-ray crystallographic study of morellin by two dimensional methods is that there is too much overlapping of peaks in the Fourier maps and the molecule therefore cannot be identified. It was not possible to use three-dimensional methods, because the necessary computing facilities were not available.

Professor G. N. RAMACHANDRAN, who has been in touch with us continuously, and Dr. G. KARTHA have carried out an X-ray crystallographic study of the *p*-bromobenzenesulphonyl ester of morellin. The first structure suggested by them was similar to XXXI, but in place of the aldehydic oxygen there was a methylene group. This was not compatible with the presence of seven oxygen atoms in morellin, one of them as an aldehyde group as shown by NMR evidence and confirmed by the formation of pyruvic aldehyde on ozonolysis. The X-ray structure was therefore modified to (XXXI), which was then confirmed by X-ray crystallography. Full details of the X-ray will be published by KARTHA and RAMACHANDRAN.



MORELLIN

XXXI

The X-ray structure (XXXI) is in excellent agreement with the NMR data discussed earlier. The part structure (XXIX_a) arrived at from NMR and chemical data forms the left

half of the X-ray structure. As expected, there is a double bond in conjugation with the CO conjugated to aromatic ring and the proton on this double bond has been correctly placed as the one that gives rise to the absorption at 2.4 in the morellin spectrum. It was deduced with the help of the spectrum of morellin diacetate that there is one proton which is either on a carbon bound to oxygen or α to a keto group and allylic at the same time. The proton at the bicyclo-octenone bridgehead has the latter type of environment. Since the signal concerned overlaps with that of the benzylic CH_2 , the splitting is not observable. The probable presence of a C_5 side-chain like $\text{CH}(\text{CHO})-\text{C}=\text{CH}-\text{CH}_2-$ was indicated by the NMR spectrum of the diacetate and has now been firmly established. The cage system formed by the bicyclo-octenone and oxide ring of the right part of the molecule could, of course, not be inferred from the NMR or other chemical data available. However, the disposition of remaining groups with respect to each other revealed by the X-ray structure makes possible a rationalization of the more obscure features of the NMR spectra of morellin and its derivatives. The unsymmetrical quartet representing two protons in the spectrum of morellin is due to the methylene group of the bicyclic system. The proton at the bridgehead α to the

gem-dimethyl group seems to be coupled to only one of the methylene protons. It gives a doublet at 7.7 ($J=4.5$ cps) in the spectrum of morellin.

It was observed earlier in the discussion of the spectrum of morellin diacetate that there is a methylene group in morellin absorbing below 7.15, and that this may be part of a side-chain. If the methylene group is cis to the aldehyde function, only part of the observed strong paramagnetic shift of the group from its normal range can be accounted for. The X-ray structure shows that the rest of the shift is produced by the other double bonds in its vicinity.]

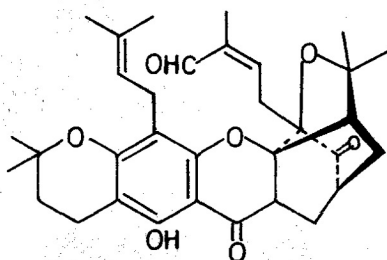
In going from morellin to isomorellin the absorption of the methylene group under discussion shifts to a higher field. The associated change of the position of vinyl triplet at 3.9 of morellin is in the opposite direction, i.e. downfield. These changes indicate that morellin and isomorellin are cis-trans isomers and that the aldehyde and vinyl hydrogen of the C_5 side-chain are cis in isomorellin. If morellin and isomorellin are cis-trans isomers, one would expect from what has been discussed earlier that they would give the same diacetate. In fact BRINGI had shown that isomorellin also gives a diacetate and that this diacetate is identical with that of morellin.

[The *p*-bromobenzenesulphonyl ester of morellin supplied to Professor RAMACHANDRAN was prepared by refluxing morellin and *p*-bromobenzenesulphonyl chloride in acetone in presence of potassium carbonate. Since isomerization to isomorellin is a possibility, the fact that the structure XXXI is that of morellin and not isomorellin was confirmed by the preparation of *p*-bromobenzenesulphonyl ester of isomorellin and comparison of the NMR spectra in the aldehyde region.]

Tetrahydromorellin

The NMR spectrum of tetrahydromorellin shows that, on absorption of 2 moles of hydrogen, three doublets in the morellin spectrum, including the two assigned to the vinyl protons of 2,2-dimethylchromene, have disappeared. Tetrahydromorellin did not form a copper complex like morellin, and the UV absorption spectrum of tetrahydromorellin was very similar to that of *o*-methylphloracetophenone or 5,7-dihydroxy-2,2-dimethylchromanone, indicating that hydrogenation of two double bonds had destroyed conjugation with the chromanone chromophore. It is clear that the two double bonds reduced are the double bond conjugated with the benzene ring in 2,2-dimethylchromene and the double bond conjugated with the chromanone carbonyl group. The remaining two double bonds were intact in tetrahydromorellin as

indicated by the formation of acetone by ozonolysis and the presence of the aldehyde signal in the NMR spectrum. Structure XXXII can therefore be assigned to tetrahydromorellin.

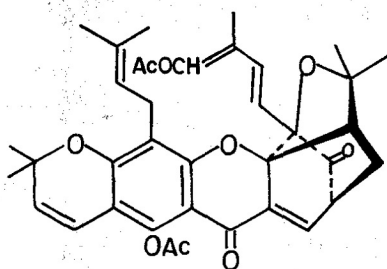


TETRAHYDROMORELLIN

XXXII

Morellin diacetate

The formation of a diacetate by morellin, although it contains only one hydroxyl group and forms a monomethyl ether, is explained by structure XXXIII and by the NMR spectrum. This was confirmed by the fact that morellin diacetate absorbed 5 moles of hydrogen in presence of palladized carbon, but the product was amorphous.



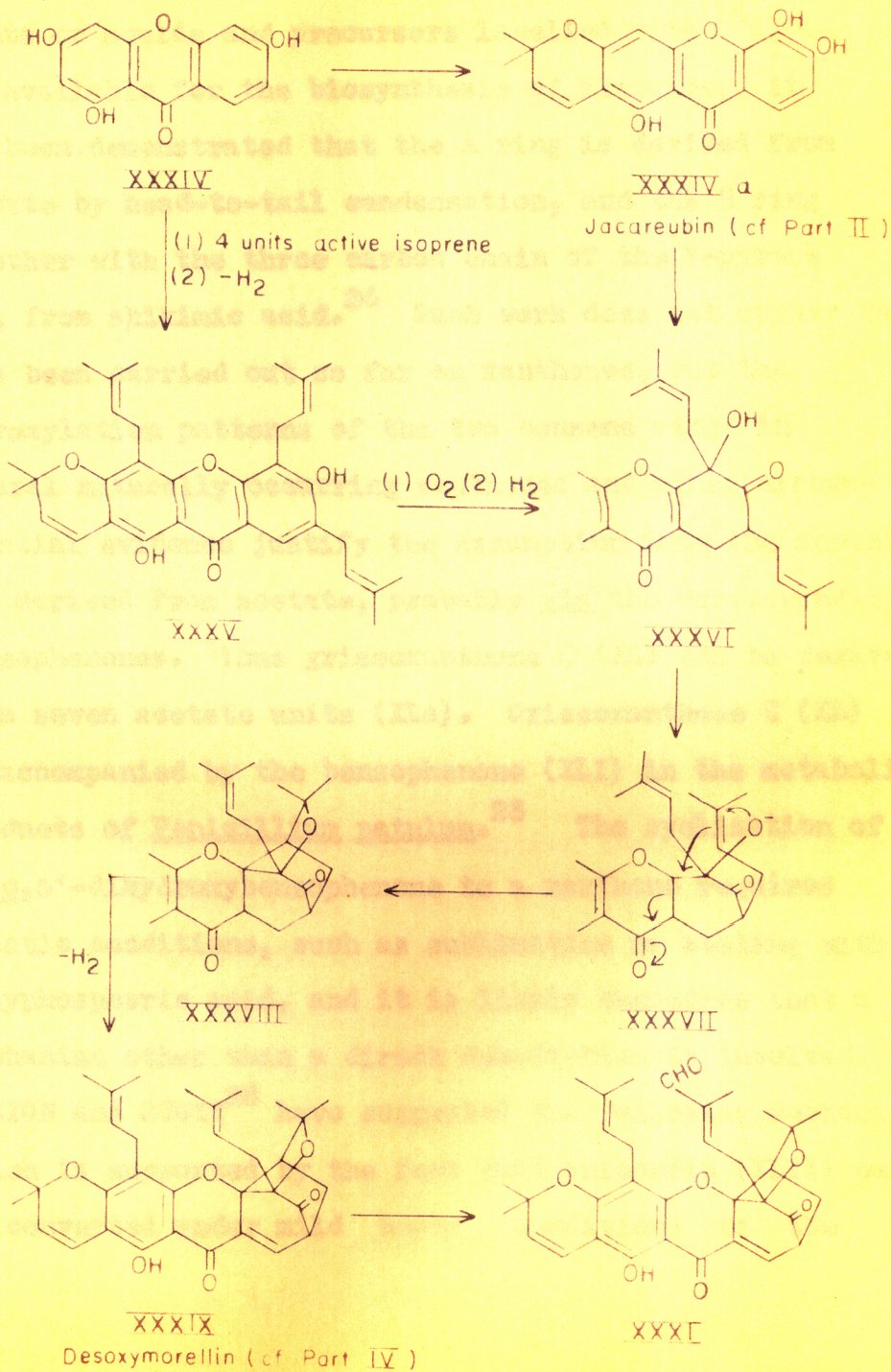
MORELLIN DIACETATE

XXXIII

Biogenesis

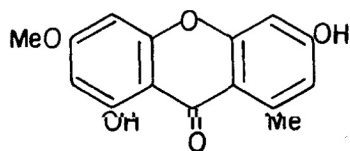
A scheme for the biosynthesis of morellin is outlined in Chart 1, from which it is clear that morellin can be derived from 1,3,7-trihydroxyxanthone (XXXIV) and four units of "active isoprene" by a simple and mechanistically acceptable series of reactions.

CHART 1

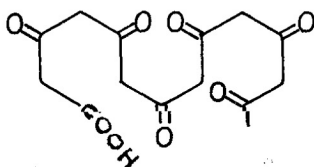


Extensive experimental evidence, using living plants or moulds and precursors labelled with ^{14}C , is now available for the biosynthesis of flavones; it has been demonstrated that the A ring is derived from acetate by head-to-tail condensation, and the B ring together with the three carbon chain of the γ -pyrone ring from shikimic acid.²⁴ Such work does not appear to have been carried out so far on xanthenes, but the hydroxylation patterns of the two benzene rings in several naturally occurring xanthenes and other circumstantial evidence justify the assumption that the xanthenes are derived from acetate, probably via the corresponding benzophenones. Thus griseoxanthone C (XL) can be derived from seven acetate units (XLa). Griseoxanthone C (XL) is accompanied by the benzophenone (XLI) in the metabolic products of Penicillium natulum.²⁵ The cyclization of an o,o' -dihydroxybenzophenone to a xanthone requires drastic conditions, such as sublimation or heating with polyphosphoric acid, and it is likely therefore that a mechanism other than a direct dehydration is involved. BARTON and SCOTT²⁶ have suggested the following mechanism, which is supported by the fact that sulochrin (XLII) can be converted under mild basic conditions to the

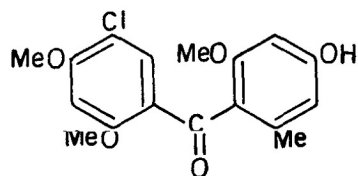
corresponding xanthone.²⁵



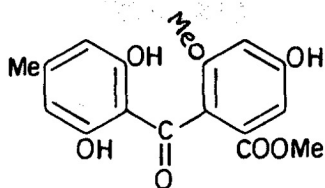
XL



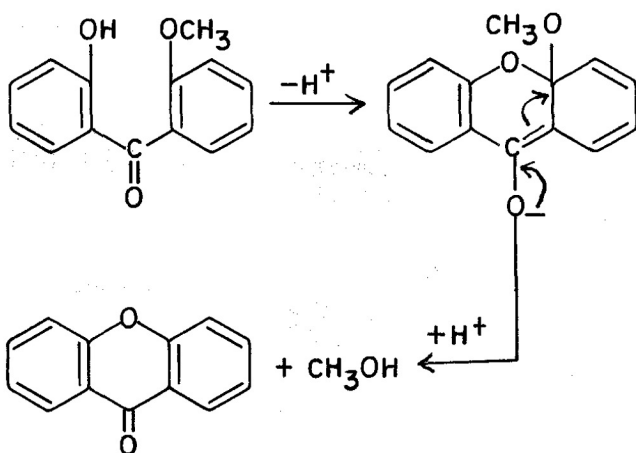
XLα



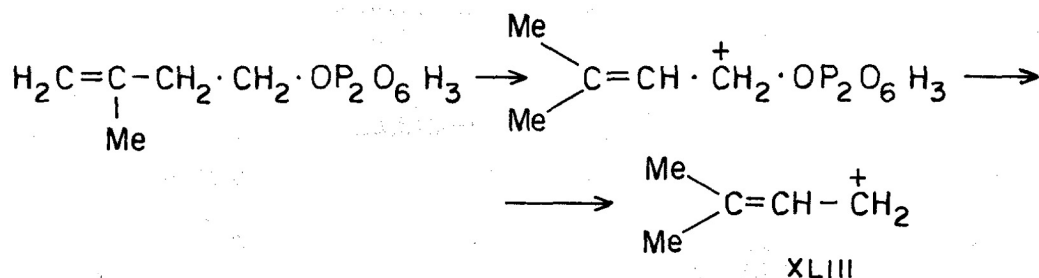
XLI



XLII



The resorcinol and phloroglucinol nuclei have strong nucleophilic reactivity, as shown for instance by the ease with which they couple with diazonium salts. The biological introduction of dimethylallyl groups²⁷ by the attack of 3,3-dimethylallyl pyrophosphate (XLIII) or the cation $\text{Me}_2\text{C}=\text{CH}-\text{C}^+\text{H}_2$ is easy to picture. If the trihydroxyxanthone (XXXIV) thus reacts with four units of "active isoprene," and one *o*-dimethylallyl group cyclizes with the phenolic hydroxyl group to 2,2-dimethylchromene, the intermediate XXXV is obtained.

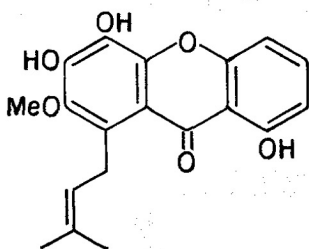


The intermediate XXXVI may be formed from XXXV by several steps of oxidation and reduction. Jacareubin (XXXIVa) (cf. Part II), which also occurs in a plant of the family Guttiferae to which Garcinia morella belongs, is a possible precursor of morellin as indicated in Chart 1. The folding of a dimethylallyl side-chain of XXXVI as shown in XXXVII, in which cyclization can then take place by the loss of a proton and the concerted mechanism indicated in the Chart has many analogies in biological systems. RUZICKA^{25a} has discussed ionic and radical mechanisms by which such coupled cyclizations take place by enzyme action. Intermediate XXXVI is thus transformed to XXXVIII, which then undergoes dehydrogenation and oxidation of a methyl to an aldehyde group to yield morellin (XXXI). It should be added, however, that this appears to be the first example of the transformation of a phenol (presumably derived from acetate or acetate-malonate units) to a bicyclo-octenone by the cyclization of an isoprenoid side-chain. There is obviously no evidence for the reaction sequence shown in Chart 1; a mechanism can also be written which does not involve hydrogenation and dehydrogenation after

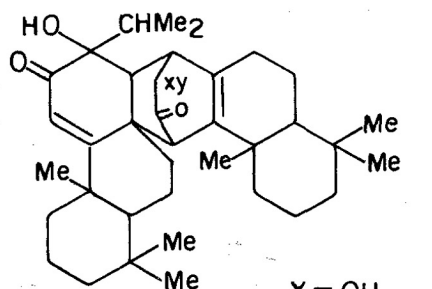
the formation of the chromene (XXXV).

Support for the suggested mechanism is found in the occurrence of desoxymorellin and dihydroisomorellin (the aldehyde corresponding to XXXVIII) in Garcinia morella as shown in Part IV.

Jacareubin (XXXIVa),²⁸ mangostin (XVI),¹⁷ and celebixanthone (XLIV)²⁹ are other xanthenes with dimethylallyl side-chains, and they all occur in plants of the family Guttiferae to which Garcinia morella belongs; in jacareubin, as in morellin, a dimethylallyl group has cyclized with an adjacent phenolic hydroxyl to form a 2,2-dimethylchromene. However, among xanthenes and flavonoids morellin is unique in possessing a carbocyclic ring derived from an isoprenoid side-chain. Morellin is also one of the few natural products containing a bicyclo[2.2.2]octane ring system; other examples are the diterpene alkaloids of the atisine type³⁰ and the bisditerpene, maytenone (XLV).³¹



XLIV



X = OH
Y = CHMe₂

XLV

EXPERIMENTAL

5,7-Dihydroxy-6-isovalerovyl-2,2-dimethylchromanone (XIX)

Isovaleric acid (5 ml) was cooled in ice, and boron trifluoride was passed until saturation. To this was added 5,7-dihydroxy-2,2-dimethylchromanone (1 g), and again the gas was passed till saturation. After leaving the mixture in an ice-bath, it was poured into ice and the excess fatty acid was neutralized with sodium bicarbonate. The solid was filtered, suspended in water (30 ml), and boiled for 5 min. After cooling, the solid was crystallized from dil alcohol (0.8 g), m.p. 83° . (Found: C, 65.6; H, 6.4. $C_{16}H_{20}O_5$ requires: C, 65.8; H, 6.9%). The mother liquor on thin layer chromatography on silica gel showed two spots corresponding to XIX and XII. It gave a red colour with alcoholic ferric chloride. It was soluble in 1% sodium hydroxide and did not couple with diazotized aniline. The IR spectrum (Nujol) showed no hydroxyl. It showed intense bands at 1630 (chelated carbonyl), 1588 (aromatic), 1325, 1258, 1220, 1198, 1163, 1117, 1096, 1075 and 1010 cm^{-1} .

The same compound was obtained when the chromanone (0.2 g) was heated on a steam-bath for an hr with boron trifluoride-isovaleric acid complex (1 ml) and diluted

and neutralized with sodium bicarbonate. The solid obtained was crystallized from dil alcohol (0.15 g), m.p. 83° .

Clemmensen reduction of 5,7-dihydroxy-6-isovaleroyl-2,2-dimethylchromanone (XIX)

A mixture of zinc amalgam (120 g), acetic acid (15 ml), water (7 ml), conc hydrochloric acid (51 ml), and a solution of the 5,7-dihydroxy-6-isovaleroyl-2,2-dimethylchromanone (XIX; 3.0 g) in alcohol (30 ml) was kept aside. After 18 hr hydrochloric acid (30 ml; 15%) was added to it and again kept aside. After 18 hr more acid (30 ml; 15%) and alcohol (15 ml) were added, and on the following day the mixture was refluxed on a steam-bath for 1 hr. More acid (30 ml) and alcohol (15 ml) were added and the refluxing was continued for 6 hr more. On cooling, the mixture was extracted with ether, washed with water, sodium bicarbonate solution followed by water. Removal of ether gave a semi-solid, which on treating with hexane ($60-80^{\circ}$) gave colourless crystalline needles, which were recrystallized from benzene (0.5 g), m.p. 174° . (Found: C, 69.0; H, 8.0. $C_{16}H_{22}O_4$ requires: C, 69.1; H, 7.9%). The IR spectrum (Nujol) showed bands at 3100 (OH), 1645 (chelated carbonyl), 1620 and 1580 (benzenoid in conjugation with carbonyl group), 1310, 1205, 1160, 1060 cm^{-1} . The compound

gave a purple violet ferric colour. The mother liquor, from which a red gum was isolated, was chromatographed through a column of Florex XXX, using benzene as solvent. The eluent on evaporation gave a semi-solid which, on crystallization from cyclohexane, gave more of the product (0.4 g), m.p. 174° .

6-Isoamyl-5,7-dihydroxy-2,2-dimethylchromanone (XX; R = H)

Isoamylphloroglucinol (2.0 g), β -hydroxyisovaleric acid (1.2 g) and boron trifluoride etherate complex (10 ml) were heated on a steam-bath for 3 hr. The product was diluted with water and warmed for 10 min. On cooling, the mixture was extracted with ether and washed. Removal of ether gave a reddish-yellow gum which readily crystallized from cyclohexane (1.0 g), m.p. 174° . The mixed m.p. with the Clemmensen reduction product of 5,7-dihydroxy-6-isovaleroyl-2,2-dimethylchromanone (XIX) was undepressed. It gave a purple violet ferric colour, but did not answer the magnesium-hydrochloric acid test, and did not couple with diazotized aniline.

2,4-Dinitrophenylhydrazone was prepared by refluxing the compound (0.1 g) in methanol (3 ml) with a solution of 2,4-dinitrophenylhydrazine (0.3 g) in methanol (8 ml) in presence of conc sulphuric acid (0.5 ml) for 1 hr. The

orange-red needles that separated were filtered and a benzene solution was chromatographed through alumina and eluted with 1:1 mixture of benzene-ethyl acetate. The product obtained after the evaporation of the eluent was crystallized from alcohol, m.p. 264° (dec). (Found: C, 57.5; H, 5.3. $C_{22}H_{26}N_4O_7$ requires: C, 57.6; H, 5.7%).

The mother liquor after the crystallization of the 6-isomer was chromatographed on a silica gel (200 mesh) column, using benzene. The eluent giving ferric colour on concentration gave more of 6-isomer (0.2 g). Next elution with 5% ethyl acetate in benzene and removal of solvent gave the crystalline 8-isomer (XXI; $R = R' = H$) (60 mg), m.p. 96° . (Found: C, 68.9; H, 7.8. $C_{16}H_{22}O_4$ requires: C, 69.1; H, 7.9%). It gave a purple ferric colour. The IR spectrum (Nujol) showed bands at 3400 (OH), 1655 (chelated carbonyl), 1610 (aromatic), 1520, 1342, 1330, 1307, 1282, 1266, 1250, 1206, 1183, 1163, 1131, 1111, 1070 cm^{-1} .

5,7-Dihydroxy-6-isopentenyl-2,2-dimethylchromanone (XXVII)

5,7-Dihydroxy-2,2-dimethylchromanone (X; 1.1 g) in dry ether (35 ml) was treated with a cold solution of sodium methoxide in methanol, prepared by dissolving

sodium (0.25 g; 1.5 moles) in methanol (15 ml). The mixture became turbid initially and turned clear later. To the cold solution freshly distilled $\gamma\gamma$ -dimethylallyl bromide (XXVI; 0.8 g) was added with shaking and the mixture set aside for 48 hr at 15°. The mixture was acidified, diluted and extracted with ether and washed with 10% sodium carbonate followed by 10% sodium hydroxide solution. The carbonate solution on acidification gave a crystalline compound (0.25 g), m.p. 188-192°; the mixed m.p. with the starting material was 197°. The sodium hydroxide solution was acidified and the semi-solid extracted with ether and washed with water. Evaporation of ether gave a crystalline solid (0.7 g). Thin layer chromatography on silica gel, using 5% ethyl acetate-benzene showed a single spot moving faster than the starting material. The compound (XXVIII; 0.65 g), m.p. 154°, was recrystallized from benzene-hexane mixture. (Found: C, 69.2; H, 7.4. $C_{16}H_{20}O_4$ requires C, 69.6; H, 7.3%).

Hydrogenation. The compound (0.6 g) in methanol (20 ml) was hydrogenated in presence of palladium on carbon (10%; 0.1 g). When the absorption stopped with 1 mole, the mixture was filtered and the solvent distilled to get a crystalline compound. Thin layer chromatography showed a single spot corresponding to 6-isoamyl-5,7-dihydroxy-2,2-dimethylchromanone (XX; R = H), the identity with which

was confirmed by the mixed m.p.

6-Isoamyl-5-hydroxy-7-methoxy-2,2-dimethylchromanone

The chromanone (XX; R = H) (0.4 g), freshly ignited potassium carbonate (3 g), acetone (30 ml) and dimethyl sulphate (10 ml; 10 moles) were refluxed for 5 hr. Acetone was distilled and diluted with water to get a sticky product. It gave a bluish-green ferric colour. It was extracted with ether, evaporated and chromatographed through a column of alumina, using 40-60° pet ether. The eluent on evaporation gave a colourless oil. It was distilled at 150° at 7.7×10^{-3} mm. The distillate was crystallized from dil methanol in colourless needles (0.25 g), m.p. 60°. (Found: C, 70.5; H, 8.0. $C_{17}H_{24}O_4$ requires: C, 69.9; H, 8.2%).

6-Isoamyl-5,7-dimethoxy-2,2-dimethylchromanone (XX; R = Me)

The chromanone (XX; R = H) (0.5 g), methyl-n-propyl ketone (35 ml), freshly ignited potassium carbonate (5 g) and dimethyl sulphate (1.2 ml; 10 moles) were refluxed gently for 16 hr. Since the compound showed colouration with ferric chloride, it was refluxed for 120 hr with more potassium carbonate (5.0 g) and dimethyl sulphate (2.0 ml). It was diluted with water and extracted with

ether. After removal of the ether, it was steam-distilled and the compound was again isolated with ether. The compound still gave a faint green ferric colour. The ether extract was washed with 0.5% sodium hydroxide and distilled. The gum obtained was chromatographed through a column of grade I alumina and the oil obtained from the hexane eluent was distilled at 120° at 4.81×10^{-4} mm. (Found: C, 70.3; H, 8.6; OMe, 19.9. $C_{18}H_{26}O_4$ requires: C, 70.6; H, 8.5; OMe, 20.3%).

8-Acetyl-6-isoamyl-5,7-dihydroxy-2,2-dimethylchromanone

A mixture of 6-isoamyl-5,7-dihydroxy-2,2-dimethylchromanone (XX; R = H) (0.2 g) and boron trifluoride-acetic acid complex (2 ml) was heated on a steam-bath for 2 hr. It was diluted with water and neutralized with solid sodium bicarbonate. The solid obtained was warmed with 10% sodium hydroxide and acidified. The semi-solid that was formed crystallized from aqueous methanol in colourless needles (150 mg), m.p. 78° . (Found: C, 67.3; H, 7.8. $C_{18}H_{24}O_5$ requires: C, 67.5; H, 7.8%). It gave a reddish purple ferric colour.

2,4-Dimethoxyphloroisovalerophenone

Phloroisovalerophenone (10.0 g) in acetone (250 ml)

was refluxed with anhydrous potassium carbonate (50 g) and dimethyl sulphate (9.7 ml; 2.1 moles) for 18 hr. Distillation of acetone to dryness and treatment of the residue with water gave an oily product which was extracted with ether, washed with water, and dried over sodium sulphate. The oily product obtained on removal of ether was distilled ($100^{\circ}/4.81 \times 10^{-4}$ mm) (10 g). (Found: C, 65.2; H, 7.9; OMe, 25.7. $C_{13}H_{18}O_4$ requires: C, 65.5; H, 7.6; OMe, 26.1%). It gave a cherry red colour with 1% alcoholic ferric chloride.

2,4-Dimethoxyisoamylphloroglucinol

A solution of 2,4-dimethoxyphloroisovalerophenone (8.0 g) in alcohol (80 ml) was added to 12% hydrochloric acid (320 ml) containing amalgamated zinc (200 g) and with the addition of more acid (20 ml) two days later, the mixture was heated on a steam-bath for 6 hr. It was cooled, extracted with ether, and washed with water, sodium bicarbonate and again water. The ether extract was dried over sodium sulphate, filtered and evaporated. The oily product was distilled at $110^{\circ}/4.8 \times 10^{-4}$ mm and then readily crystallized from hexane in colourless needles (5.0 g), m.p. 55° . (Found: C, 69.8; H, 8.8; OMe, 27.3. $C_{13}H_{20}O_3$ requires: C, 69.7; H, 8.9; OMe, 27.9%). The product was soluble in sodium hydroxide.

8-Isoamyl-5,7-dimethoxy-2,2-dimethylchromanone (XXI:
R = R' = Me)

A mixture of isoamylphloroglucinol-2,4-dimethyl ether (1.0 g), β -hydroxyisovaleric acid (0.47 g; 1 mole) and boron trifluoride etherate (5 ml) was heated in a steam-bath for 2 min, when a yellow crystalline complex separated. After it was poured into water, the complex was collected. The complex was boiled with alcohol (50 ml) for 14 hr. Alcohol was distilled and the product was in ether and washed with 5% sodium hydroxide (50 ml) followed by water. The ethereal layer was dried over sodium sulphate, filtered and distilled to dryness. The product gave a purple ferric colour. It was dissolved in hexane and chromatographed on alumina (grade I). Elution with hexane (60-80°) gave a colourless product (0.02 g), m.p. 79°. Elution with benzene and evaporation of the extract gave a pale yellow product, which was crystallized from hexane in colourless plates (0.20 g), m.p. 115°. (Found: C, 70.6; H, 8.5; OMe, 19.9. $C_{18}H_{26}O_4$ requires: C, 70.6; H, 8.5; OMe, 20.3%). The compound did not give ferric colour and gave a red colour with magnesium and hydrochloric acid. The last band was eluted with 1:1 benzene-ethyl acetate and evaporated. The product gave a purple ferric colour. It was distilled at 105°/4.8 x 10⁻⁴ mm (yield: 0.5 g).

The oil (0.2 g) was refluxed with acetone (25 ml),

potassium carbonate (3 g) and dimethyl sulphate (1.0 ml; 10 moles) for 20 hr. Acetone was distilled and the residue was diluted with water. The oily material was extracted with ether, washed with water, and dried over sodium sulphate. The oil obtained on evaporation of ether was chromatographed through a short column of alumina using hexane. The eluent on evaporation gave a product which was crystallized from hexane in colourless plates (0.25 g), m.p. 116° ; the mixed m.p. with the 8-isoamyl-5,7-dimethoxy-2,2-dimethylchromanone (XXI; $R = R' = Me$) was undepressed.

8-Isoamyl-5,7-dihydroxy-2,2-dimethylchromanone (XXI;
 $R = R' = H$)

8-Isoamyl-5,7-dimethoxy-2,2-dimethylchromanone (0.2 g) was refluxed with anhydrous aluminium bromide (1.0 g) in benzene (20 ml) for 2 hr. The mixture was poured into ice containing hydrochloric acid. It was extracted with ether, washed with water and the solvent distilled. The reddish-orange gum was crystallized from hexane in pale yellow needles (100 mg), m.p. 96° ; the mixed m.p. with the minor fraction obtained from isoamylphloroglucinol was undepressed.

6-Isoamyl-5,7-dihydroxy-2,2-dimethylchroman (XVIII)

(a) Anhydrous tetrahydrofuran (50 ml) was cooled in

ice and saturated with diborane gas, to which 6-isoamyl-5,7-dihydroxy-2,2-dimethylchromanone (XX; R = H) (1.0 g) was added. The solution turned deep yellow and then became colourless in 2 hr. After 24 hr at room temp excess diborane was destroyed by careful addition of acetic acid. The solvent was distilled, the residue diluted with water, extracted with ether, and washed repeatedly with 10% aqueous sodium hydroxide. The alkali solution acidified. The semi-solid isolated with ether was distilled at $250^{\circ}/7.7 \times 10^{-3}$ mm and crystallized from benzene-hexane in colourless needles (75 mg), m.p. 99° . It gave no ferric colour.

(b) In a 3-necked 100 ml flask equipped with condenser, guard tube, dropping funnel and mechanical stirrer, isoamylphloroglucinol (1.0 g), benzene (freshly distilled over P_2O_5) (45 ml), and freshly fused zinc chloride (3.0 g) were refluxed under stirring for 20 min. YY-Dimethylallyl bromide (XXVI) (freshly distilled; b.p. $31-33^{\circ}$ at 11-13 mm; 1.5 g) dissolved in benzene (10 ml) was added in lots in 45 min. After the addition was complete, the mixture was refluxed under stirring for 90 min, filtered and evaporated. The dark-red residue was diluted with water, isolated with ether, and mixed with the main benzene soluble fraction. After washing with water, it was

extracted with 5% aqueous sodium carbonate followed by 5% sodium hydroxide. The sodium hydroxide soluble fraction (0.2 g) was crystallized from benzene-hexane mixture in colourless needles (150 mg), m.p. 99° . (Found: C, 73.0; H, 9.2. $C_{16}H_{24}O_3$ requires: C, 72.7; H, 9.1%). The mixed m.p. with the above sample obtained by diborane reduction was undepressed. The IR spectrum (Nujol) (Fig. 9) showed bands at 3350, 3225 (OH), 1600 (aromatic), 1498, 1460, 1440, 1370 and 1360 (gem-dimethyl), 1340, 1320, 1275, 1240, 1222, 1200, 1160, 1118, 1100, 1040, 1029, 1020, 960, 920, 895, 855, 815 and 750 cm^{-1} .

(c) Clemmensen reduction of 5,7-dihydroxy-6-isovaleroyl-2,2-dimethylchroman (XXII). A mixture of zinc amalgam prepared from zinc wool (12 g), 5,7-dihydroxy-6-isovaleroyl-2,2-dimethylchroman (XXII; 0.3 g) in ethanol (4 ml), and hydrochloric acid (10%; 17.7 ml) was refluxed in a steam-bath. After 3 hr additional hydrochloric acid (10%; 17.7 ml) was added and further refluxed for 3 hr. On cooling, the mixture was isolated with ether, washed with water, sodium bicarbonate solution and again water. Removal of ether gave a crystalline solid which was recrystallized from hexane ($60-80^{\circ}$) in colourless needles (0.2 g), m.p. 99° . The mixed m.p. with the above sample

was undepressed and the IR spectrum in Nujol was superposable. The compound gave no colour with ferric chloride. It did not couple with diazotized aniline.

The UV spectrum in ethanol showed one peak at $\lambda_{\max}$ 276 m μ ($\epsilon_{\max}$ 10350).

5,7-Dihydroxy-8-isovaleroyl-2,2-dimethylchromanone (XII)

A mixture of phloroisovalerophenone (1.0 g), β -hydroxyisovaleric acid (0.6 g) and boron fluoride etherate (5 ml) was heated on a steam-bath for 30 min and the orange-red mixture diluted with water and heated on a steam-bath for 10 min. The mixture was extracted with ether and washed with water. The orange gum obtained was readily crystallized from dil methanol (norit) in colourless needles (0.7 g) (50%), m.p. 112°. (Found: C, 65.3; H, 6.7. $C_{16}H_{20}O_5$ requires: C, 65.7; H, 6.9%). The compound gave a cherry-red colour with alcoholic ferric chloride. It did not couple with diazotized aniline.

The mother liquor of the compound on thin layer chromatography on silica gel, using 5% ethyl acetate-benzene as solvent, showed a spot identical with that of the isomeric compound (XIX) obtained by the action of isovaleric acid-boron fluoride complex on 5,7-dihydroxy-

2,2-dimethylchromanone (X). The IR spectrum of the compound (CCl_4) showed no hydroxyl band. It showed intense bands at 1635 (chelated carbonyl), 1615 and 1575 (benzenoid in conjugation with carbonyl), 1430, 1418, 1380, 1355, 1335, 1255, 1205, 1180 and 1095 cm^{-1} .

Clemmensen reduction of 5,7-dihydroxy-8-isovaleroyl-2,2-dimethylchromanone (XII) and isolation of $\text{C}_{16}\text{H}_{24}\text{O}_4$ phenol

Zinc amalgam (96 g) was mixed with water (55 ml), acetic acid (18 ml) and conc hydrochloric acid (49 ml). The compound (XII; 1.1 g) in alcohol (42 ml) was added and the mixture set aside. After 12 hr, alcohol (41 ml) and conc hydrochloric acid (28 ml) were added and again set aside for 12 hr. The mixture was treated with more alcohol (41 ml) and acid (28 ml) and refluxed for 6 hr. It was extracted with ether, washed with water, aqueous sodium bicarbonate and again water. Removal of ether gave a brownish gum (1.0 g) free from ferric colour. It was crystallized from acetone-hexane mixture (60 mg), m.p. 162° . The mixed m.p. with C_{16} -phenol obtained from the alkali fusion of octahydromorellin was undepressed. The IR spectra of the two (KBr disc) were superposable (Fig. 10), and showed bands at 3340 (OH), 1661, 1640, 1585, 1548, 1455, 1404, 1372 and 1360 (gem-dimethyl), 1316, 1274, 1250, 1226, 1208, 1156, 1136, 1111, 1047, 1026, 975

945, 918, 908 and 885 cm^{-1} .

The mother liquor was chromatographed through a column of silica gel (200 mesh) in benzene. The first band was eluted and the gum (0.2 g) obtained from it was distilled at $175^{\circ}/7.7 \times 10^{-3}\text{ mm}$. The IR spectrum of the pale yellow distillate (liquid film) was free from carbonyl absorption. It gave no ferric colour.

Tosylation of 5,7-dihydroxy-8-isovaleroyl-2,2-dimethyl-chromanone (XII)

The chromanone (1.0 g) was refluxed with p-toluenesulphonyl chloride (1.7 g) in acetone (30 ml) in presence of potassium carbonate (12 g) for 4 hr. When the ferric colour disappeared, the solution was filtered and the residual potassium carbonate extracted with hot acetone and filtered. The combined filtrate was distilled and the residue was extracted thrice with hot hexane to remove the excess sulphonyl chloride. The hexane insoluble derivative was readily crystallized from methanol in colourless needles (1.5 g), m.p. 110° . (Found: C, 59.6; H, 5.5. $\text{C}_{30}\text{H}_{32}\text{O}_9\text{S}_2$ requires: C, 60.0; H, 5.3%). The compound gave no ferric colour and the IR spectrum (Nujol) showed the absence of hydroxyl and the presence of carbonyl group.

Clemmensen reduction. The above compound (1.0 g) was refluxed with ethanol (20 ml), conc hydrochloric acid (32 ml), water (60 ml) and zinc amalgam for 8 hr. At an interval of 3 hr more acid (41 ml; 10%) was added. The mixture was extracted with ether, washed with water and aqueous sodium bicarbonate, and again water. Distillation of ether extract gave a gum (0.8 g). The IR spectrum showed presence of a hydroxyl group and absence of carbonyl absorption.

Hydrolysis of the tosyl ester and isolation of $C_{16}H_{24}O_4$ phenol

The above Clemmensen reduction product (0.9 g) was refluxed with ethanol (40 ml), water (10 ml), and sodium hydroxide (2.5 g) for 30 min. It was acidified after cooling with dil sulphuric acid and extracted with ether. The caustic soda soluble fraction was isolated in the form of a reddish gum. The thin layer chromatography on silica gel with 1:1 ethyl acetate-benzene as solvent indicated the presence of C_{16} -phenol. The gum was distilled at 145° at 7.7×10^{-3} mm of vacuum. The distillate, on adding a few drops of ether, solidified into colourless crystals (30 mg), m.p. 162° ; the mixed m.p. with the C_{16} -phenol was undepressed. After the hydrolysis the caustic soda insoluble portion (0.4 g) was again hydrolyzed to get more of the C_{16} -phenol.

5,7-Dimethoxy-8-isovaleroyl-2,2-dimethylchromanone (XXIII)

5,7-Dihydroxy-8-isovaleroyl-2,2-dimethylchromanone (1.9 g), potassium carbonate (10.0 g), acetone (100 ml) and dimethyl sulphate (5 ml) were refluxed for 12 hr. On removal of the solvent, it was diluted with water, and the crystalline solid was filtered and recrystallized from dil methanol in colourless needles (1.6 g), m.p. 133°. (Found: C, 67.2; H, 7.5. $C_{18}H_{24}O_5$ requires: C, 67.2; H, 7.5%). The compound gave no colour with alcoholic ferric chloride.

8-Isoamyl-5,7-dimethoxy-2,2-dimethylchroman (XXIV)

Zinc amalgam was prepared from zinc wool (120 g), mercuric chloride (9.0 g), conc hydrochloric acid (9.0 ml), and water (75 ml). The compound (1.5 g) in ethanol (30 ml) and 10% hydrochloric acid (144 ml) were added and the mixture was heated on a steam-bath. After 2 hr 10% hydrochloric acid (77 ml) was added. Fifteen hours later further 10% hydrochloric acid (77 ml) was added, and totally refluxed for 24 hr. The cooled mixture was extracted with ether and washed with water, aqueous sodium bicarbonate, and again with water. Removal of solvent gave a colourless oil (1.4 g) with negative ferric colour. The IR spectrum in liquid film showed a faint hydroxyl

absorption and no carbonyl absorption. It was chromatographed through a column of grade I alumina, using hexane as solvent. The fast moving band with a greenish-yellow fluorescence in UV light was collected and evaporated to get an oil, which readily crystallized from methanol in colourless needles (0.7 g), m.p. 43° . (Found: C, 74.0; H, 9.6. $C_{18}H_{28}O_3$ requires: C, 74.0; H, 9.6%). (See Fig. 11 for IR spectrum).

5,7-Dihydroxy-8(and 6)-isovaleroyl-2,2-dimethylchroman (XXV and XXII)

(a) 5,7-Dihydroxy-2,2-dimethylchroman (VIII; 0.5 g) was heated with isovaleric acid-boron trifluoride complex (2 ml) for 2 hr on a steam-bath. The dark-red mixture was diluted with water and most of the free fatty acid was neutralized with sodium bicarbonate. The pale yellow semi-solid was extracted with ether, and after removal of ether it was refluxed with ethanol (30 ml) for 12 hr. Ethanol was distilled, and the residue extracted with hot hexane. The hexane-soluble fraction (0.25 g) gave a deep purple ferric colour. It was chromatographed on a silica gel column (200 mesh), using benzene initially and then followed by 5% ethyl acetate-benzene mixture. The latter eluent on evaporation gave lemon-yellow plates with a greenish tinge (90 mg), m.p. 137° (lit.¹⁸ 138°).

It gave a deep purple ferric colour, and on thin layer chromatography on silica gel with 5% ethyl acetate-benzene it showed a single spot. The complex could not be decomposed by further refluxing with ethanol.

(b) In a 150 ml 3-neck flask with a mechanical stirrer and guard tube, and a dropping funnel, 5,7-dihydroxy-2,2-dimethylchroman (VIII; 2.0 g) was dissolved in anhydrous ether (30 ml) and the mixture was cooled to 0° in ice. Anhydrous aluminium chloride (10 g) was added in small lots under stirring and each lot was followed by a lot of isovaleric acid chloride (1.6 ml) in ether (30 ml). Isovaleric acid chloride was prepared in 85-90% yields by distilling isovaleric acid with benzoyl chloride.

Two such batches were mixed and poured into crushed ice (200 g) containing hydrochloric acid (30 ml). The mixture was extracted with ether, washed with water, sodium bicarbonate solution, and again water. Finally, the extract was dried over sodium sulphate and distilled. The crude product from two batches (5.0 g) gave a deep purple ferric colour. On thin layer chromatography on silica gel with 5% ethyl acetate-benzene as solvent, four spots corresponding to the starting material (stationary spot) 5,7-dihydroxy-8-isovaleroyl-2,2-dimethylchroman (XXV), the 6-isomer and the ester were seen. The crude product was

refluxed with benzene (20 ml) and cooled. The colourless crystalline solid was filtered (1.5 g), m.p. 162° ; the mixed m.p. with the starting material was undepressed. The benzene solution was chromatographed on silica gel (100-200 mesh). After removal of the fast moving by-product, the 6-isomer was isolated from the benzene eluent. It was crystallized from hexane in colourless needles (0.3 g), m.p. 145° (lit.¹⁸ $144-145^{\circ}$). It gave a deep purple ferric colour. The IR spectrum (Nujol) showed intense bands at 3390 (OH), 1645 (chelated carbonyl), 1602 (aromatic), 1526, 1342, 1307, 1266, 1250, 1212, 1161, 1116 and 1096cm^{-1} .

The column was next eluted with 5% ethyl acetate-benzene mixture, and the eluent on evaporation gave lemon-yellow plates with a green lustre (1.7 g), m.p. 136° (lit.¹⁸ 137°). It gave a deep purple ferric colour. The IR spectrum (Nujol) showed bands at 3333 (OH), 1645 (chelated carbonyl), 1620 and 1587 (benzenoid in conjugation with carbonyl), 1471, 1379, 1299, 1274, 1221, 1163, 1129, 1096, 1042 and 1020cm^{-1} .

(c) 5,7-Dihydroxy-2,2-dimethylchroman (VIII; 2.0 g), nitrobenzene (50 ml), aluminium chloride (10.0 g) and isovaleryl chloride (1.3 ml) in nitrobenzene (10 ml) were reacted as above. The reaction mixture was poured into ice containing hydrochloric acid after 48 hr. The mixture

was extracted with ether, washed with water, sodium bicarbonate and water. After removal of ether, nitrobenzene was removed by steam distillation and the mixture again extracted with ether. Thin layer chromatography showed only 6- and 8-isomers and no by-product or the starting material. On removal of ether and chromatography of the residue in benzene on silica gel (200 mesh) the 6-isomer (0.6 g) followed by the 8-isomer (0.25 g) was obtained.

5,7-Dimethoxy-8-isovaleroyl-2,2-dimethylchroman (XXVa)

5,7-Dihydroxy-8-isovaleroyl-2,2-dimethylchroman (0.5 g), potassium carbonate (3.0 g), acetone (50 ml) and dimethyl sulphate (2 ml) were refluxed for 12 hr. After removal of acetone, dilution with water and isolation with ether, a viscous liquid was obtained, which was crystallized from dil methanol in colourless needles (0.42 g), m.p. 56° . (Found: C, 71.0; H, 8.2. $C_{18}H_{26}O_4$ requires: C, 70.5; H, 8.5%). The compound gave no ferric colour with alcoholic ferric chloride.

8-Isoamyl-5,7-dimethoxy-2,2-dimethylchroman (XXIV)

Zinc amalgam (17.2 g), hydrochloric acid (10%; 16.5 ml) and 5,7-dimethoxy-8-isovaleroyl-2,2-dimethylchroman (0.4 g) in ethanol (5 ml) were refluxed on a steam-bath for 2 hr. More acid (16.5 ml) was added and refluxing continued.

After 2 hr more acid (16.5 ml) was added and totally refluxed for 6 hr. It was cooled, extracted with ether, washed with water, sodium bicarbonate and again with water. The ether extract was dried over sodium sulphate and distilled. The colourless viscous liquid which was obtained was passed through a short alumina column, using hexane. The fast moving band showing a greenish fluorescence under UV light was collected, and the solvent distilled. The residue was readily crystallized from methanol in colourless needles (0.3 g), m.p. 43° . The mixed m.p. with the above sample was undepressed and the IR spectrum (liquid film) was superposable.

Alkali fusion of octahydromorellin

In a 250 ml 3-neck flask equipped with a nitrogen inlet and a mechanical stirrer, octahydromorellin (15.0 g), potassium hydroxide pellets (84.0 g) and zinc dust (7.5 g) were thoroughly mixed with a few drops of water. The flask was dipped into a hot metal-bath (120°) in presence of a stream of nitrogen and heated with constant stirring. It attained a pale-green colour and at 160° a rubber-like mass separated in a liquid. Faint peppermint odour was noted at 190° . At 200° a chocolate mass separated in a frothing liquid. A clean melt was formed at 255° , the

colour turning to brownish yellow, and it was maintained at that temp for 3 min. It was cooled, diluted with water (100 ml) and filtered to remove unreacted zinc. The lemon-yellow filtrate was acidified with 50% sulphuric acid, when a pale-yellow semi-solid separated with a strong odour of fatty acid. It was extracted with ether after saturation with salt, and washed with aqueous sodium bicarbonate, sodium carbonate (10%) and sodium hydroxide (10%).

Sodium bicarbonate solution. It was acidified to Congo Red with 50% sulphuric acid and the fatty acid steam-distilled. The distillate was saturated with salt and extracted with ether. The ether extract was dried over sodium sulphate and treated with an excess ethereal solution of diazomethane. The mixture was left at 15° for 24 hr. Ether was distilled at 45° and the residual mixture of methyl esters of fatty acids distilled and subjected to vapour-phase chromatography. The standard methyl esters were prepared by treating the commercial fatty acids with excess of anhydrous methanol saturated with dry hydrogen chloride. The mixture was kept for 24 hr and then poured into ice, extracted with ether, washed with water, sodium bicarbonate and again water. Methyl esters of 99% purity were obtained by fractionating the

crude product after removal of ether.

When the methyl esters were examined by gas liquid chromatography on Perkin Elmer 154 D Vapor Fractometer, using the stationary phase of succinic acid polyester of diethylene glycol, five peaks were obtained. The assignment of various peak identities was made from retention times of known compounds and comparison with those of unknown compounds. In this way an identification of methyl esters of isobutyric acid, isovaleric acid, and *n*-valeric acid was made. The last one was present in traces.

Retention times of methyl esters (temp. 75°; gas H₂; pressure 15 lb/sq.in; chart speed 15"/hr)

S. No.	Unknown	Known	
1.	48 sec.	48 sec. Methyl isobutyrate	Methyl- <i>n</i> -butyrate 78.8 sec.
2.	96 sec.	96 sec. Methyl isovalerate	Methyl- <i>n</i> -caproate 276 sec.
3.	147 sec.	147 sec. Methyl- <i>n</i> -valerate	
4.	221 sec.		
5.	384 sec.		

The aqueous extract containing the nonvolatile fraction was filtered to remove the resinous matter and extracted with ether. Removal of ether gave a semi-solid with a greenish brown ferric colour. It answered positive iodide-

inadequate test. It could not be crystallized.

Sodium carbonate solution. The carbonate solution on acidification gave a solid which was extracted with ether and washed with water. Removal of ether gave a pale-brown semi-solid (1.2 g), which readily crystallized from acetone-hexane in colourless needles (0.5 g), m.p. 162° . Mixed m.p. with the C_{16} -phenol was undepressed. The mother liquor was set aside for methylation along with the caustic soda soluble fraction.

Sodium hydroxide solution. The solution was acidified, extracted with ether, and washed with water. The ether extract was distilled when a pale-brown gum was obtained (4.7 g). The mother liquor of the carbonate solution was mixed with this gum and refluxed with dimethyl sulphate (5 ml), acetone (100 ml) and anhydrous potassium carbonate (20 g) for 8 hr. Acetone was distilled and the residue diluted with water (150 ml). A pale-yellow gum was isolated from the mixture by extraction with ether. It was dissolved in hexane and chromatographed through a short column of alumina. The fast-moving band with a bluish fluorescence in UV light was collected. Removal of hexane gave a colourless oil which readily crystallized from methanol (norit) in colourless fluffy needles (2.5 g; 35%), m.p. 42° . Mixed m.p. with the synthetic sample (XXIV) was

undepressed. The IR spectra (liquid film) of both the samples were superposable (Fig.11) and showed prominent bands at 1600 (benzenoid), 1495, 1460, 1430, 1410, 1385 and 1365 (gem-dimethyl), 1340, 1310, 1252 (OMe), 1242, 1215, 1200, 1156, 1085, 1040, 1000, 965, 918, 880 and 788 cm^{-1} .

Neutral fraction. The neutral fraction contained a lemon-yellow gum (1.5 g) with a strong peppermint odour and isocamyl alcohol. The gum gave a green ferric colour similar to octahydromorellin.

p-Bromobenzenesulphonate of isomorellin

[Isomorellin (0.5 g), p-bromobenzenesulphonyl chloride (0.3 g; 1.2 mols), anhydrous potassium carbonate (5 g), and acetone (50 ml) were refluxed on a steam-bath for 30 min. The pale-yellow solution was filtered, concentrated and poured into crushed ice. The solid was filtered and extracted with hot hexane. The residue ~~was~~ crystallized from acetone-hexane mixture in lemon-yellow needles, m.p. 159° . (Found: C, 61.6; H, 5.2. $\text{C}_{39}\text{H}_{41}\text{O}_9\text{BrS}$ requires: C, 61.3; H, 5.4%).

Tetrahydromorellin. Morellin (2.0 g) was hydrogenated in presence of methanol (25 ml) and palladium on calcium carbonate (0.4 g). When it absorbed hydrogen (180 ml; 2 moles), absorption was discontinued. The mixture was warmed and filtered, when pale-yellow prismatic needles separated (1.2 g), m.p. 169° . It gave a green ferric colour.

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PART IV

CONSTITUTION OF DESOXYMORELLIN AND TWO
NEW PIGMENTS FROM GARCINIA MORELLA

Desoxymorellin

The alcoholic mother liquor after the crystallization of morellin from the total colouring matters of the pericarp yields an orange-yellow resin on evaporation. BRINGI¹ chromatographed the hexane-soluble fraction of the resin on a column of Florex XXX (an extruded fuller's earth) and developed the column with hexane. The first deep orange band on elution and evaporation gave a crystalline pigment, provisionally named as desoxymorellin on the basis of elementary analysis and mol. weight. BRINGI also recorded the following data. Desoxymorellin, for which the formula $C_{33}H_{40}O_6$ was suggested on the assumption of $C_{33}H_{38}O_7$ for morellin, formed a monomethyl ether, a mono-*p*-toluenesulphonyl ester, and a stable monoacetate. It did not condense with *o*-phenylenediamine. Hydrogenation of desoxymorellin in the presence of palladium on calcium carbonate yielded a crystalline tetrahydro derivative. By alkali fusion of desoxymorellin phloroglucinol, isovaleric acid and homophthalic acid were isolated. BRINGI concluded that a carbonyl group in morellin was replaced by a methylene group in desoxymorellin, because the main feature of the IR spectrum of desoxymorellin was the disappearance of the band in the 1670 cm^{-1} region.

The UV spectrum of morellin showed three maxima at 236, 289 and 360 m μ ; in desoxymorellin the latter two bands were very similar in wavelength and intensity, but the short wave band was much lower in intensity.

In the present work the investigation of the structure of desoxymorellin was continued.

Ethylenic bonds. Desoxymorellin absorbed 4 moles of hydrogen in presence of palladium on charcoal (12 per cent). The first mole was absorbed in 5 min, the second in 10 min, the third in 30 min, and the last in 90 min.

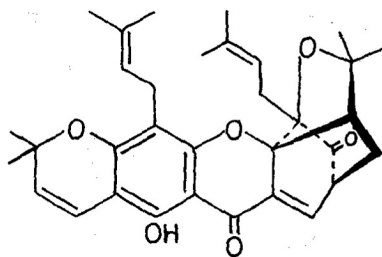
Copper complex. A dioxane solution of desoxymorellin on treatment with excess of aqueous copper acetate gave a red copper complex, which crystallized from chloroform-hexane. Tetrahydro- and octahydro-desoxymorellin, the acetate, and the methyl ether did not form the copper complex. It was therefore obvious that a phenolic hydroxyl group and a readily reducible ethylenic bond in conjugation with a carbonyl group are involved in the copper complex formation, exactly as in morellin.

Mozingo reduction. Desoxymorellin on refluxing with Raney nickel in cyclohexanol for 24 hours gave a crystalline compound, m.p. 112°, identical with the product (MRP-I) obtained by the action of Raney nickel in boiling ethanol

on morellin. The IR spectrum of a 2 per cent solution of either in CCl_4 is recorded in Fig. 19.

Alkali fusion of octahydrodesoxymorellin. Octahydrodesoxymorellin was fused with 5 times the weight of potassium hydroxide pellets and zinc dust at 280° . The phenolic fraction yielded the C_{16} -phenol and 8-isoamyl-5,7-dihydroxy-2,2-dimethylchroman characterized as its dimethyl ether (cf. XXIV - Part III).

Constitution of desoxymorellin. The isolation of 8-isoamyl-5,7-dihydroxy-2,2-dimethylchroman as a major product of alkali fusion, the formation of the copper complex, the behaviour on catalytic hydrogenation, and the UV spectrum demonstrate the identity of desoxymorellin and morellin in the chromenechromanone parts of the molecules. The only difference in fact appears to be in the replacement of the aldehyde group of morellin by a methyl group in desoxymorellin, confirmed by the identity of two Mozingo reduction products. Desoxymorellin may therefore be assigned the structure I, and it probably represents an intermediate stage in the biosynthesis of morellin discussed earlier.



DESOXYMORELLIN

Desoxymorellin - NMR Data

The NMR spectrum of desoxymorellin is given in Fig. 18. It shows that there is no aldehyde function in the molecule. In comparison with morellin, desoxymorellin has one additional $\underline{C}$ -methyl group giving a singlet absorption. However, this absorption does not occur in the region for methyl groups on double bonds. The actual positions of the methyl signals are 8.23 (1), 8.32 (2), 8.57 (2), 8.64 (1), 8.73 (1) and 8.97 (1). The vinyl triplet occurring at 3.90 and 3.68 in the spectra of morellin and isomorellin is replaced here by one at 5.7 showing that the double bond on which it is situated is no longer conjugated to a carbonyl function. The 2,2-dimethylchromene doublets appear nearly in the same place as in morellin and isomorellin. The vinyl doublet representing the proton on the double bond in the bicyclo-octenone part of the molecule shows up at 2.6. In the region from 6.3 to 8 the spectrum of desoxymorellin is similar to that of isomorellin as may be expected from the absence of the aldehyde function. The chelated hydroxyl appears at -2.84.

All the features of the spectrum, except the absorption position of the additional methyl group, are consistent with the notion that desoxymorellin and morellin differ only in that the aldehyde group of the latter is

replaced by a methyl group in the former. The signal at 8.64 is probably the one due to this additional methyl group. The abnormal position of the signal is probably due to diamagnetic shielding effects.

The change from morellin to isomorellin may involve something more than cis-trans isomerism. The methyl group affected by the isomerization does not show any accompanying large chemical shift, while the aldehyde group does. A simultaneous conformational change is also probably involved which may be responsible for the large diamagnetic shift of the aldehyde absorption as well as the abnormal position of the methyl absorption discussed above. If this turns out to be correct, desoxymorellin may more properly be called desoxyisomorellin. Further clarification of this point is required.

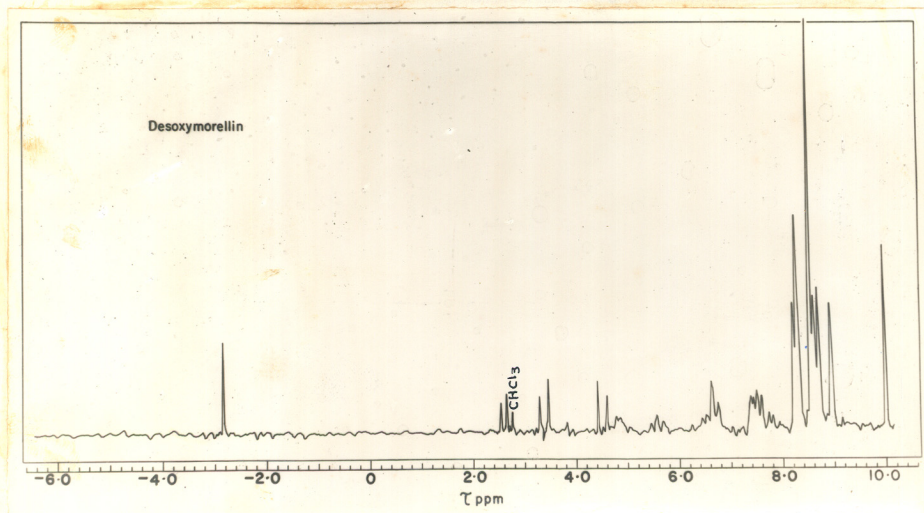
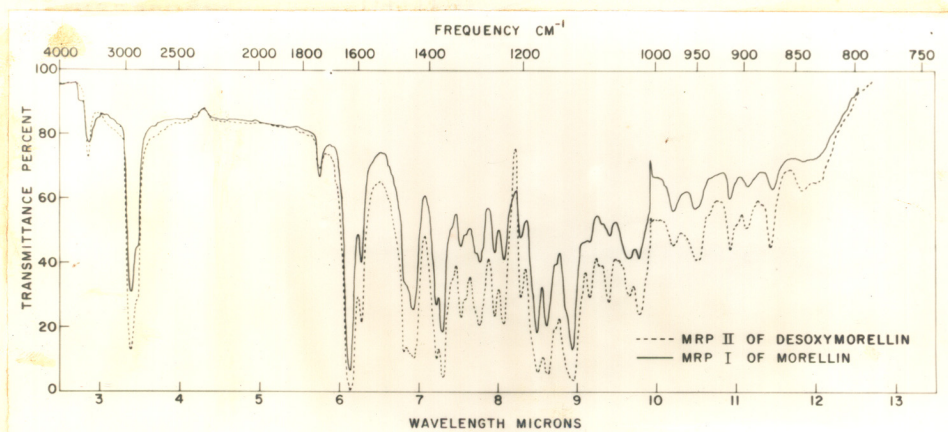


FIG. 18.

FIG. 19. Spectra in CCl_4 .

Isolation of two new pigments from *Garcinia morella*

After the isolation of desoxymorellin by the Florex chromatography of the hexane extract of the resin, the second band gave a lemon-yellow crystalline pigment, provisionally called Morellin X. The subsequent band also gave a lemon-yellow pigment provisionally designated as Morellin Y.

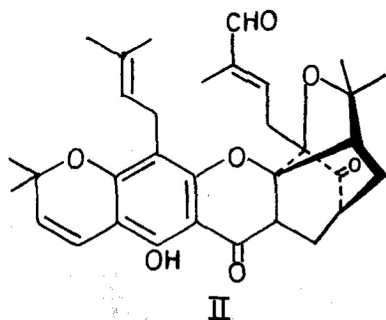
Morellin Y

Morellin Y crystallized in large lemon-yellow needles, m.p. 167° . The elementary analysis and mol. wt. (X-ray method), kindly determined by Professor G. N. Ramachandran, agreed with the molecular formula $C_{33}H_{38}O_7$. It resembled dihydro and other hydrogenated derivatives of morellin in its green ferric colour and absence of copper complex formation. It was evident that the double bond conjugated with the chromanone carbonyl was reduced. This was also confirmed by the reduction in the intensity of the band at $360\text{ m}\mu$ in the UV spectrum. The positive Tollens test and the band at 1685 cm^{-1} ($\alpha\beta$ -unsaturated aldehyde) in the IR spectrum (Fig. 23) suggested the presence of an aldehyde group as in morellin, which was also confirmed by the NMR spectrum.

The NMR spectrum of Morellin Y has many common features with those of morellin and isomorellin. The chelated hydroxyl and aldehyde groups absorb at -1.87 and 0.57. The chromene doublets appear at 3.4 and 4.5. The vinyl proton of the prenyl side-chain of the aromatic nucleus shows up at 5.0. The doublet absorption, representing the vinyl proton on the bicyclo-octenone system of morellin and isomorellin is missing in the spectrum of Morellin Y, suggesting that this double bond is saturated. The triplet absorption at 3.17 represents the vinyl proton of the C₅ side-chain containing aldehyde function. The position of this signal suggests that the side-chain of this compound is the same as in isomorellin. As in morellin and isomorellin seven methyl groups are indicated, three of which are on double bonds.

The absence of copper complex formation, similarities in ferric colour, UV and NMR data, suggested that the compound is probably a dihydro derivative of morellin or isomorellin. Dihydroisomorellin, m.p. 161°, was prepared by absorbing 1 mole of hydrogen in methanol in presence of palladized carbon, and its properties compared with Morellin Y. The mixed m.p. was undepressed. However, the NMR spectrum of the dihydro derivative of isomorellin

showed that the sample was a mixture of isomers. The chelated hydroxyl signal was split into two. Presumably isomorellin has hydrogenated from either side of the double bond conjugated with chromanone carbonyl. In the methyl region also there were small differences between the two spectra. In other respects the two spectra were identical. It is provisionally suggested that Morellin Y (II) is one of the two dihydro derivatives of isomorellin expected from catalytic hydrogenation of the double bond conjugated with the chromanone carbonyl.



MORELLIN Y

II
Morellin X

Morellin X crystallized in large lemon-yellow rods, m.p. 143° . Repeated elementary analysis and the mol. wt. (585 ± 1), kindly determined by Professor G. N. Ramachandran, corresponded to the molecular formula $C_{35}H_{40}O_8$. It resembled dihydro and other hydrogenated derivatives of morellin in its green ferric colour. In presence of palladium on charcoal it absorbed 3 moles of hydrogen, the first in 12 min, the second in 1.25 hr, and the third in about 4 hr. Alkali fusion of hexahydromorellin X yielded the C_{16} -phenol (5 per cent) and 8-isomethyl-5,7-dihydroxy-2,2-dimethylchroman (30%), the latter being isolated as the dimethyl ether. Unlike morellin and desoxymorellin

and like dihydromorellin, it did not form a copper complex, indicating the absence of the double bond in conjugation with the chromanone carbonyl which is present in morellin. This was confirmed by the marked reduction in the intensity of the band in the 360 m μ region of the UV spectrum in comparison with morellin. The positive Tollens test, formation of a diacetate, the 1690 cm⁻¹ band in the IR spectrum (Fig. 21) ($\alpha\beta$ -unsaturated aldehyde), and the signal at 0.57 in the NMR spectrum indicated the presence of an aldehyde group as in morellin. These data show that Morellin X is very similar in structure to morellin, and further work is in progress to determine the character of the C₂H₂O residue.

Morellin X - NMR data

The NMR spectrum of morellin resembles that of Morellin Y very closely. Four out of the five vinyl absorptions and seven out of the eight C-methyl absorptions are almost exactly in the same place. The chelated hydroxyl and aldehyde groups appear with very minor shifts at -1.95 and 0.57. The additional vinyl proton gives a doublet at 5.55 (J=5 cps) and the additional methyl signal is a triplet (J=6.5 cps) superposed on tertiary methyl signal at 8.86. The triplet methyl absorption shows that Morellin X has an ethyl group. In the region from 6 to 8

the spectrum is quite complex. The total proton count for this molecule has not been made very accurately. Further data have to be obtained before a structure for the compound can be suggested. However, it is clear that the left half of the structure of morellin is retained in this pigment. The C_5 side-chain containing the aldehyde group is also present in it.

In a note in 1953 MURTHY and RAO² mentioned the isolation from the seed coat of Garcinia morella of a second pigment named moreollin in lemon-yellow hexagonal prisms, m.p. 168° , which isomerized to isomoreollin, m.p. 142° , by treatment with 5 per cent alcoholic sodium hydroxide at 40° . They have also referred to another pigment, guttiferin ("a highly active antibiotic present throughout the plant"). The impossible formula $C_{24}H_{27}O_6$ (with an odd number of hydrogen atoms) was assigned to moreollin, and some colour reactions were described. No further details concerning moreollin and guttiferin appear to have been published.

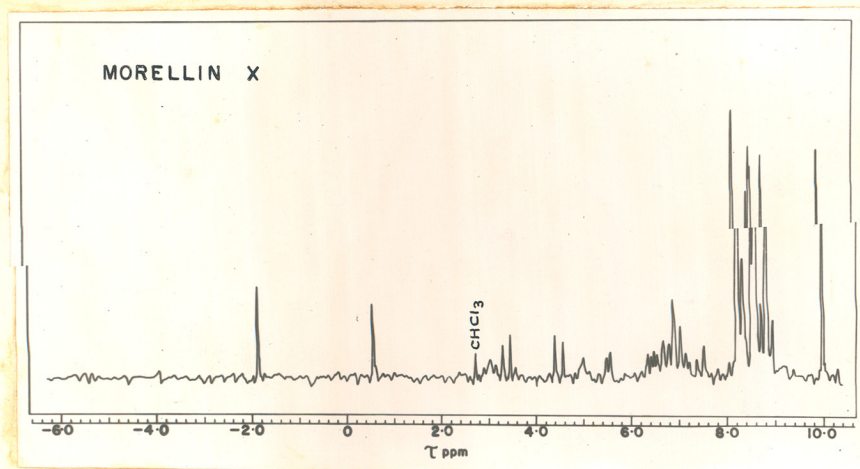
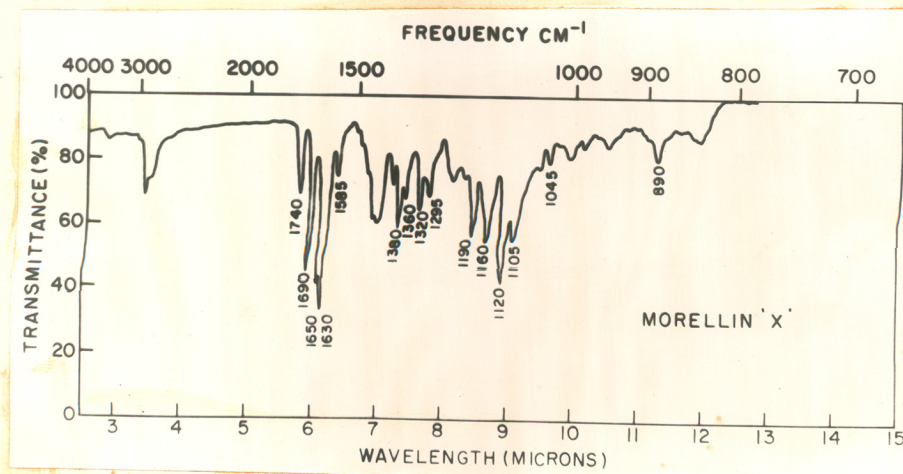


FIG. 20.



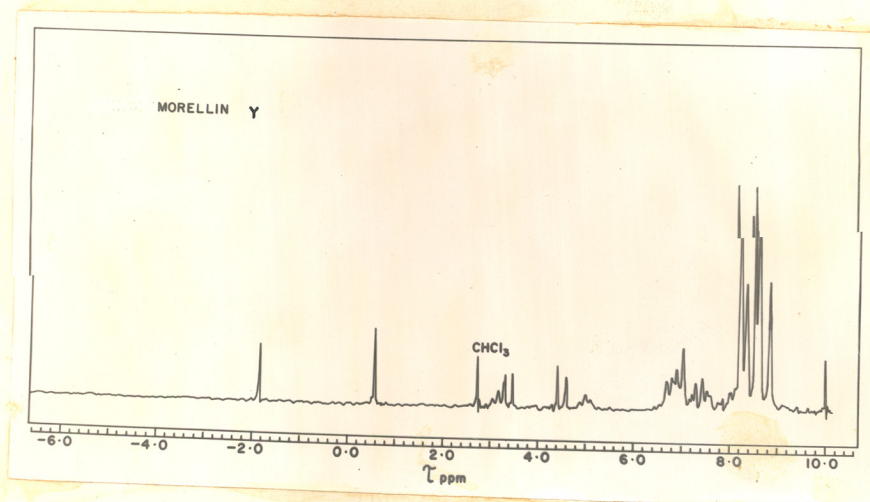
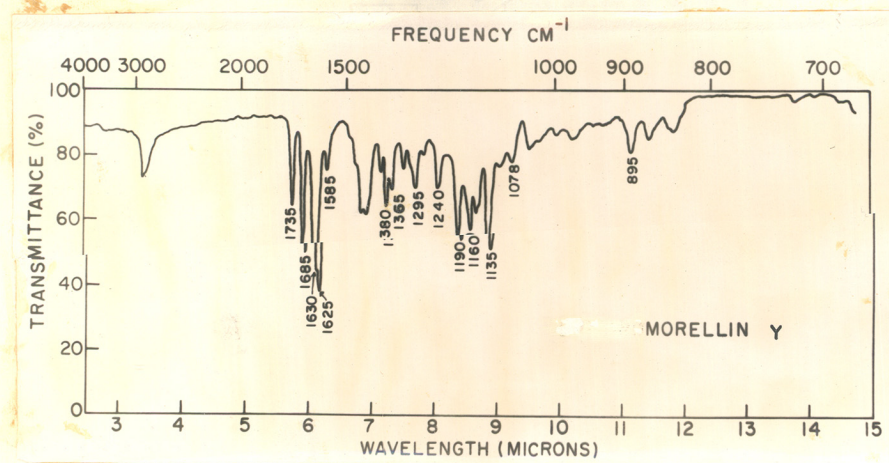


FIG. 22.

FIG. 23. Spectrum in CCl_4 .

EXPERIMENTAL

Isolation of Morellin X and Morellin Y

The orange-yellow resin isolated after the evaporation of the alcoholic mother liquor of crude morellin obtained by the extraction of the pericarp of Garcinia morella, was extracted with hot hexane (60-80°). The extract was cooled to room temp and was chromatographed through a column of Florex XXX (900 g packed in a column of 6 x 1050 cm). The first deep orange band on elution and distillation gave an orange gum which readily crystallized from methanol as orange needles, m.p. 126°, undepressed when mixed with an authentic sample of desoxymorellin (3.0 g).

The next pale-yellow band gave a lemon-yellow gum, which on crystallization from methanol yielded large rods of Morellin X, lemon yellow in colour (2.0 g), m.p. 143°. (Found: C, 71.4, 71.6; H, 7.0, 7.4. $\bar{M}$ by X-ray crystallography, 585 ± 1 . $C_{35}H_{40}O_8$ requires: C, 71.4; H, 6.8%. $\bar{M}$, 588. $C_{35}H_{38}O_8$ requires: C, 71.7; H, 6.5%. $\bar{M}$, 586). It gave a green ferric colour and did not answer Mg-HCl test. It did not form a copper complex.

The third band gave pale-yellow crystalline needles of Morellin Y, which were recrystallized from methanol in rods (0.5 g), m.p. 167°. (Found: C, 72.4, 72.5; H, 6.6, 6.6. $\bar{M}$ by X-ray crystallography method, 545 ± 1 . $C_{33}H_{38}O_7$ requires: C, 72.5; H, 7.0%. $\bar{M}$, 546). It gave a green

ferric colour and no colour with magnesium and hydrochloric acid. It also did not form a copper complex.

Copper complex of desoxymorellin

The pigment (0.2 g) in dioxane (2 ml) was treated with excess of copper acetate solution (25 ml) prepared by dissolving 5.0 g of copper acetate monohydrate and 2 g of crystalline sodium acetate in 200 ml of water. The red-brownish precipitate was collected and crystallized from chloroform-hexane mixture in blood-red needles. (Found: C, 70.2; H, 6.3. $C_{33}H_{37}O_6 \cdot Cu/2$ requires: C, 70.6; H, 6.6%).

Raney nickel-cyclohexanol reduction of desoxymorellin

In a 150 ml 3-neck flask, equipped with a mechanical stirrer and a distillation condenser, Raney nickel (12 g) over alcohol was placed and toluene (80 ml) was added and distilled with continuous stirring. When all the water and alcohol were distilled by azeotropic distillation, most of the toluene was distilled. Anhydrous cyclohexanol (30 ml) and desoxymorellin (1.0 g) were added and the mixture refluxed for 24 hr under stirring.

The mixture was filtered hot over a bed of Hyflo Super-Cel and washed with warm toluene (50 ml). The combined filtrate was steam-distilled. The colourless residue on treatment with methanol gave colourless needles (0.6 g), m.p. 110° . Mixed m.p. with MRP-I of morellin was undepressed

and the IR spectra of the two in CCl_4 were superposable (Fig. 19).

Alkali fusion of octahydrodesoxymorellin

Desoxymorellin (3.0 g) was hydrogenated in methanol (30 ml) in presence of palladium on carbon (12%; 0.8 g). When the absorption ceased, after 4 moles it was filtered into a 10 ml 3-neck flask and evaporated to dryness. Potassium hydroxide (17.0 g) and zinc dust (1.5 g) were added and the mixture slowly heated in a metal-bath under stirring with nitrogen atm. A rubber-like mass floating in milk-white fluid separated at 190° . A clear chocolate-yellow melt was obtained at 255° , when peppermint odour was noticed. After keeping it at 255° for 2 min, it was cooled and diluted with water (150 ml). It was filtered and acidified with 1:1 sulphuric acid when a pale-yellow sticky mass separated with a strong odour of fatty acids. The mixture was extracted with ether and washed with 10% aqueous sodium bicarbonate, sodium carbonate and sodium hydroxide. The bicarbonate extract was acidified and the mixture of acids kept aside.

Sodium carbonate soluble fraction

The carbonate solution was acidified and saturated with salt and extracted with ether. Distillation of the solvent gave a pale-yellow semi-crystalline mass which was

recrystallized from acetone-hexane mixture (0.1 g), m.p. 162° ; mixed m.p. with $C_{16}H_{24}O_4$ phenol was undepressed. The mother liquor was mixed with the sodium hydroxide soluble fraction.

Sodium hydroxide soluble fraction

The solution was acidified and extracted with ether. Distillation of ether extract gave a pale-yellow gum (0.6 g). Thin layer chromatography of the gum on silica gel with 5% ethyl acetate-benzene as solvent showed a small stationary spot corresponding to C_{16} -phenol and a major spot corresponding to the major spot in the similar fraction from the alkali fusion of octahydromorellin. The mother liquor of C_{16} -phenol was mixed with the gum and refluxed with acetone (50 ml), potassium carbonate (10 g) and dimethyl sulphate (3 ml) for 8 hr. After removal of acetone, the residue was diluted with water. The gum was extracted with ether and washed. The product obtained after removal of ether was chromatographed on alumina in hexane. The bluish fluorescent band was eluted and evaporated. A colourless viscous oil was obtained which crystallized from dil methanol in colourless fluffy needles (0.3 g), m.p. 43° . Mixed m.p. with the synthetic sample of 8-isoamyl-5,7-dimethoxy-2,2-dimethylchroman was undepressed and the IR spectra of the two were superposable.

Neutral fraction

Distillation of ether extract containing the neutral fraction, yielded a gum (0.2 g) with a green ferric colour. It had a strong peppermint odour.

Acetylation of Morellin X

Morellin X (0.2 g) was gently refluxed with acetic anhydride (3 ml) and pyridine (3.0 ml) for 5 hr and the pale-red solution poured into crushed ice (20 g). The pale-yellow solid that separated was readily crystallized from methanol in pale-yellow needles (0.15 g), m.p. 178° . (Found: OAc, 12.5. $C_{39}H_{44}O_{10}$ requires: OAc, 12.0%).

Alkali fusion of Hexahydromorellin X

The pigment (2.0 g) was hydrogenated in methanol (20 ml) in presence of palladized carbon (0.6 g; 10%). When the absorption stopped after 3 moles, it was filtered and evaporated. The pale-yellow product was fused with potassium hydroxide at 270° . On working up the phenolic fraction as in the case of octahydromorellin and octahydro-desoxymorellin, 8-isoamyl-5,7-dimethoxy-2,2-dimethylchroman (0.2 g) and C_{16} -phenol (50 mg) were obtained.

Dihydroisomorellin

Isomorellin (0.5 g) was hydrogenated in methanol (15 ml) in presence of palladized carbon (0.2 g; 10%). When it

absorbed (22.5 ml; 1 mole), it was filtered and concentrated, when pale-yellow needles readily separated (0.4 g), m.p. 160-161°. Mixed m.p. with Morallin Y was 166-167°.

R E F E R E N C E S

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SUMMARY OF THE PRESENT WORK

Part I. Naturally occurring 2,2-dimethylchromenes - A review

The naturally occurring 2,2-dimethylchromenes have been classified according to substitution and attached ring systems; their occurrence, structures, chemical properties, and methods of synthesis have been reviewed. Their biogenesis is discussed.

Part II. Synthesis of dihydrojacareubin and a new general method for the synthesis of 2,2-dimethylchromanones

In connection with the constitution of morellin a new general method has been developed for the synthesis of 2,2-dimethylchromanones as intermediates for 2,2-dimethylchromans and 2,2-dimethylchromenes. Earlier methods are reviewed. The new method, which offers several advantages, involves the condensation of β -hydroxyisovaleric acid with a phenol in presence of boron fluoride etherate. Phloroglucinol gave 5,7-dihydroxy-2,2-dimethylchromanone (I) in 65 per cent yield, but the yields varied from 15 to 45 per cent with various other phenols. All the phenols examined gave the corresponding 2,2-dimethylchromanones, and there was no indication of the isomeric 4,4-dimethyldihydrocoumarin (II)

being formed; the reaction appeared therefore to be directed by a steric factor.

5,7-Dihydroxy-2,2-dimethylchromanone (I) was stable to refluxing with 15 per cent aqueous sodium hydroxide, but by alkali fusion it broke down to phloroglucinol. 2,2-Dimethylchromanones with hydroxyl or methoxyl groups gave an intense orange colour with magnesium and hydrochloric acid and with sodium amalgam (followed by acidification) not recorded earlier. When methyl, acetyl, isovaleroyl or isoamyl groups were present, the Mg-HCl test was negative. Mangostin, a xanthone with isoamylene side-chains, has also been shown to give negative tests, while hydroxyxanthones normally gave red or deeper colours. The effect of substitution on the chromanone ring was also noted with respect to Clemmensen and diborane reductions.

1,2,4-Triacetoxybenzene on condensation with β -hydroxyisovaleric acid gave 6,7-dihydroxy-2,2-dimethylchromanone (IX; $R = R' = H$) or 7-acetoxy-6-hydroxy-2,2-dimethylchromanone (IX; $R = OAc$, $R' = H$) depending on the procedure for decomposing the complex. The constitution of the latter was proved by monomethylation by diazomethane, followed by mild hydrolysis, which gave 7-hydroxy-6-methoxy-2,2-dimethylchromanone (IX; $R = H$, $R' = Me$) soluble in

aqueous sodium carbonate. 6,7-Dihydroxy-2,2-dimethylchromanone (IX; $R = R' = H$) was methylated, and the product was reduced to dihydroageratechromene in 86 per cent yield by using diborane.

5,7-Dihydroxy-2,2-dimethylchromanone (I) also reduced to the corresponding chroman in 66 per cent yield, using diborane. Condensation of the chroman with pyrogallol- α -carboxylic acid in presence of phosphorus oxychloride and zinc chloride gave a xanthone identical with the dihydro derivative of natural jacareubin, kindly supplied by Professor F. E. KING. The m.p., mixed m.p., UV and IR spectra of the two samples were identical. This synthesis was undertaken to confirm the constitution of jacareubin, since morellin was considered to be biogenetically related.

Part III. Constitution of morellin

The mass spectrum of morellin showed the molecular weight to be 544, on the basis of which the molecular formula was revised to $C_{33}H_{36}O_7$. The presence of four ethylenic bonds, one phenolic hydroxyl, and other important experimental data obtained by BRINGI and RAGHAVAN were confirmed. The IR spectra of morellin, tetrahydromorellin, octahydromorellin, and the Mozingo reduction products have

been re-examined in carbon tetrachloride and discussed. A specific search in the carbonyl and overtone regions gave clear evidence of an aldehyde group, not responding to chemical tests in morellin, tetrahydromorellin and octahydromorellin, and of its disappearance on Raney nickel reduction under the Mozingo conditions. In conjunction with the formation of pyruvic aldehyde as a product of ozonization, the group $\text{=}\underset{\text{Me}}{\text{C}}\text{-CHO}$ was postulated.

On the basis of the isolation of phloroglucinol by alkali fusion, α -hydroxyisobutyric acid by alkaline permanganate oxidation and acetone by mild alkaline hydrolysis of morellin, it was assumed that morellin contained a 5,7-dihydroxy-2,2-dimethylchromene (XIII) system. Failure to isolate 5,7-dihydroxy-2,2-dimethylchroman in the alkali fusion products of octahydromorellin, the formation of acetone by ozonization of tetrahydromorellin, and the isolation by RAGHAVAN of a C_{16} -phenol (identical with a Clemmensen reduction product of 5,7-dihydroxy-6- or 8-isovaleroyl-2,2-dimethylchromanone) from the alkali fusion products of octahydromorellin, led to a search for 8-isoamyl-5,7-dihydroxy-2,2-dimethylchroman (XVII) in the alkali fusion products of octahydromorellin; the 6-isomer (XVIII) was not anticipated since morellin gave a ferric colour and a copper complex. In the course of the

synthesis of the unknown 8-isoamyl-5,7-dihydroxy-2,2-dimethylchroman (XVII) of authentic structure, several chromanones and chromans of interest in connection with naturally occurring chromenes were prepared.

5,7-Dihydroxy-2,2-dimethylchromanone (X) on reacting with isovaleric acid in presence of boron fluoride, gave 5,7-dihydroxy-6-isovaleroyl-2,2-dimethylchromanone (XIX) in 75 per cent yield, mixed with the 8-isomer (XII). Condensation of phlorisovalerophenone with β -hydroxyisovaleric acid in presence of boron fluoride etherate gave predominantly the 8-isomer (XII). Clemmensen reduction of XIX gave 6-isoamyl-5,7-dihydroxy-2,2-dimethylchromanone (XX; R = H). Prolonged methylation of (XX; R = H) gave a liquid dimethyl ether, different from 8-isoamyl-5,7-dimethoxy-2,2-dimethylchromanone (XXI; R = R' = Me) which was unambiguously prepared by condensing isoamylphloroglucinol-2,4-dimethyl ether with β -hydroxyisovaleric acid; 6-isoamyl-5,7-dihydroxy-2,2-dimethylchromanone (XX; R = H) was further confirmed to be the 6-isomer since on diborane reduction it gave 6-isoamyl-5,7-dihydroxy-2,2-dimethylchroman (XVIII) identical with the product of the Clemmensen reduction, 5,7-dihydroxy-6-isovaleroyl-2,2-dimethylchroman (XXII).

Having proved the identity of XII as the required 8-isomer, Clemmensen reduction was carried out, but only the C_{16} -phenol was isolated in crystalline form, which confirmed RAGHAVAN's earlier observations. From the mother liquor by silica gel chromatography an amorphous product was obtained, which analysed for 8-isoamyl-5,7-dihydroxy-2,2-dimethylchroman (XVII). The IR spectrum was free from carbonyl absorption. The C_{16} -phenol was also obtained when the ditosylate of XII was reduced by the Clemmensen method and hydrolysed with alkali under mild conditions. Finally, XII was methylated and reduced by the Clemmensen method when the dimethyl ether (XXIV) of 8-isoamyl-5,7-dihydroxy-2,2-dimethylchroman (XVII) was obtained in 55 per cent yield as a colourless crystalline compound. This dimethyl ether (XXIV) was obtained in 35 per cent yield when octahydromorellin was fused with potassium hydroxide in presence of zinc, and the phenolic fraction after the removal of the C_{16} -phenol was methylated.

5,7-Dihydroxy-6 (and 8)-isovaleroyl-2,2-dimethylchroman (XXII and XXV) were obtained by the Friedel-Crafts reaction of 5,7-dihydroxy-2,2-dimethylchroman (XIII) and isovaleryl chloride. The Clemmensen reduction of the 8-isomer led to an amorphous product.

Condensation of α -isoamylphloroglucinol with β -hydroxyisovaleric acid gave 6-isoamyl-5,7-dihydroxy-2,2-dimethylchromanone (XX; R = H) in 40 per cent yield, accompanied by 10 per cent of the 8-isomer (XXI; R = R' = H). The former was also obtained by the reaction between 5,7-dihydroxy-2,2-dimethylchromanone (X) and $\gamma\gamma$ -dimethylallyl bromide (XXVI) in presence of sodium methoxide, followed by hydrogenation of the product.

With the classical proof now available for the presence of the $\gamma\gamma$ -dimethylallyl-5,7-dihydroxy-2,2-dimethylchromene (XIV) skeleton in morellin, the part structure XXVIII or XXIX was formulated, which explained the ferric colour, copper complex formation, and the UV absorption spectrum. The former (XXVIII) was preferred by analogy with osajin, pomiferin and toxicarol. To explain the formation of 1,2,3,4-tetrahydronaphthalene-5,7-dicarboxylic acid by the alkali fusion of Mazingo reduction product II (MRP-II), the colour reaction of morellin with o -phenylenediamine, the formation of pyruvic aldehyde by ozonization of morellin, and several other experimental data, the part structure XXVIII was elaborated to XXX.

It was realized however that, while the part structure XXVIII was on firm ground, the hydrogenated naphthalene

moiety in the complete structure XXX required the isolation of a hydrogenated naphthalene derivative from the degradation products of octahydromorellin. Meanwhile, NMR spectra of morellin and some of its derivatives became available and they rendered several features of the hydrogenated naphthalene part of structure XXX untenable.

The NMR spectra of morellin, isomorellin, tetrahydromorellin, octahydromorellin and morellin diacetate were obtained in deuterochloroform at 60 Mc. The NMR spectrum of morellin indicated the presence of 36 protons, of which 5 vinyl hydrogens, one aldehyde group, one chelated hydroxyl, and 7 α -methyl groups could be assigned. Three of the methyl groups were attached to double bonds and the others to tertiary carbon atoms. No aromatic proton was indicated, showing that the phloroglucinol ring was completely substituted. From the detailed consideration of these groups part structure XXVIII was confirmed and expanded to XXIXa. In addition to the part structure XXIXa there was evidence for the presence of a C_5 side-chain of the type $-CH_2-CH=C-CHO$ and a CMe_2 group attached to oxygen.

$$\begin{array}{c} CH_3 \\ | \\ -CH_2-CH=C-CHO \end{array}$$

X-Ray crystallographic studies conducted concurrently with the chemical degradations revealed the structure XXXI. Initially the X-ray structure showed a methylene in the

place of aldehydic oxygen in the side-chain. But this could not explain 7 oxygen atoms in morellin and the presence of an aldehyde group. An aldehyde group was therefore placed in the side-chain as in XXXI, which was later confirmed by X-ray crystallography. Structure XXXI explains all the features of the NMR spectrum of morellin. Tetrahydromorellin is assigned the structure XXXII, which explains the failure to form a copper complex and other experimental facts.

Morellin diacetate is assigned the structure XXXIII, which was confirmed by the absorption of 5 moles of hydrogen in presence of palladized carbon.

The biogenesis of morellin from 1,3,7-trihydroxy-xanthone by the attack of four "active isoprene" units is suggested. Jacareubin (XXXIVa) is a possible precursor; and two pigments (dihydroisomorellin and desoxymorellin) accompanying morellin in Garcinia morella are undoubtedly involved in the biogenetic scheme. Attention is drawn to other naturally occurring xanthenes with dimethylallyl side chains, as well as the unique character of morellin among xanthenes and flavonoids in its possessing a carbocyclic ring derived from an isoprenoid side-chain.

Part IV. Constitution of desoxymorellin and two new pigments from Garcinia morella

In addition to desoxymorellin, isolated earlier by

BRINGI, two new pigments called Morellin X and Morellin Y have been isolated. Desoxymorellin, $C_{33}H_{38}O_6$, formed a red copper complex, and absorbed four moles of hydrogen by catalytic hydrogenation. The 1680 cm^{-1} peak, assigned to an $\alpha\beta$ -unsaturated aldehyde group in morellin, was absent in the IR spectrum of desoxymorellin. 8-Isoamyl-5,7-dihydroxy-2,2-dimethylchroman (cf. XVII in Part III), as the dimethyl ether (XXIV in Part III), was isolated by the alkali fusion of octahydrodesoxymorellin. The NMR spectrum confirmed the absence of an aldehyde group, and indicated that the difference from morellin was merely the replacement of the aldehyde by a methyl group. The crystalline product obtained by treatment of desoxymorellin in boiling cyclohexanol with Raney nickel was found to be identical with a Mozingo reduction product of morellin. Desoxymorellin is therefore assigned the structure I.

Morellin Y, $C_{33}H_{38}O_7$, unlike morellin and desoxymorellin, did not form a copper complex, and the UV spectrum was similar to that of dihydromorellin, the long wavelength absorption at about $360\text{ m}\mu$ being absent. The NMR spectrum revealed the presence of all the features of isomorellin, except the double bond conjugated to the chromanone carbonyl. The mixed m.p. of the pigment with the dihydro derivative of isomorellin (prepared by the catalytic hydrogenation of

isomorellin) was undepressed, although the NMR spectrum of the latter showed that it was a mixture of two possible stereoisomers. So Morellin Y is one of the two dihydro derivatives possible from isomorellin by the catalytic hydrogenation at the double bond conjugated to the chromanone carbonyl.

Morellin X, $C_{35}H_{40}O_8$, had an UV spectrum similar to that of Morellin Y, and gave no copper complex. Chemical proof was obtained for the part structure XIV as in morellin. An aldehyde group was indicated in the IR and NMR spectra. Morellin X is a derivative of dihydroisomorellin containing an additional C_2H_2O residue.

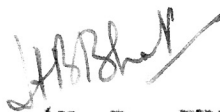
A C K N O W L E D G M E N T

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(H. B. BHAT)
CANDIDATE