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 dihydroageratochromene 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 $=\overset{\text{Me}}{\underset{|}{C}}-CHO$ 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 phloroisovalerophenone with β-hydroxy-isovaleric 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 C-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 γγ-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 γγ-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 Mozingo 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 C-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 $-CH_2-CH=\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}-CHO$ and a CMe_2 group attached to oxygen.

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 xanthones with dimethylallyl side chains, as well as the unique character of morellin among xanthones 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 mμ 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.