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THE CONSTITUTION OF MORELLIN

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B. S. RAO[1] assigned the molecular formula $C_{30}H_{34}O_6$ to morellin, an orange-yellow pigment isolated from the seeds of Garcinia morella, and he recorded the following data. Treatment with potassium hydroxide in ether gave isomorellin. Morellin contained four hydroxyl groups yielding a tetra-acetate, but formed only a trimethyl ether; two carbonyl groups were indicated by an amorphous dioxime. Fusion with alkali yielded methylheptenol ($Me_2C{=}CHCH_2CH_2CHOHMe$), phloroglucinol, and acetic, isovaleric, methylsuccinic and homophthalic acids. Subsequent work by Bringi and others[2] led to a revision of the molecular formula of morellin to $C_{33}H_{36}O_7$ and the development of the partial structure I or the linear

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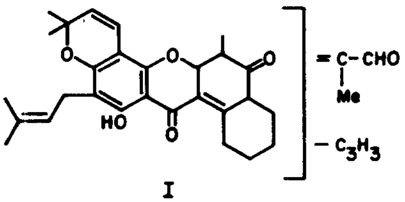
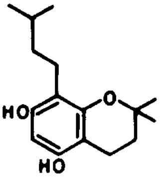
[1] B. S. Rao, J. Chem. Soc. 853 (1937).

[2] a N. V. Bringi, K. H. Shah and K. Venkataraman, J. Sci. Ind. Res. 14B, 135 (1955); b N. V. Bringi, M. R. Padhye and K. Venkataraman, Ibid. 15B, 128 (1956); c V. K. V. Raghavan, Ph.D. Thesis, University of Bombay (1960); d H. B. Bhat, Ph.D. Thesis under submission to the University of Poona.

chromene.



I



III

X-Ray crystallographic data

The complete structure of morellin has now been elucidated as II from an X-ray crystallographic study of its p-bromobenzenesulphonyl ester, which forms large needles elongated along the c axis and has an orthorhombic unit cell with $a = 15.56$ Å, $b = 20.55$ Å, $c = 11.33$ Å, with the space group $P2_12_12_1$. Three dimensional intensity data were obtained on the GE XRD5 diffractometer using Cu $K\alpha$ radiation. Out of about 4500 possible reflections, about 3600 had observable intensities. The positions of the bromine atoms were obtained from a sharpened Patterson diagram. A Fourier synthesis using the phases obtained from the positions of the bromine atoms alone revealed the sulphur atoms. An SF calculation (F_c) was made with Br + S, and this was used for performing a β-synthesis,[3] in which the moduli of the Fourier coefficients used were $(|F_o|^2-|F_c|^2)/|F_c|$ and the phases were the same as F_c. Terms with $|F_o|/|F_c| > 2.5$ were omitted from the calculations. This revealed a number of light atoms (some of which turned out to be spurious) and the other atoms were obtained from successive cycles of Fourier syntheses. No

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[3] G. N. Ramachandran and S. Raman, Acta Cryst. 12, 957 (1959).

distinction was made between carbons and oxygens at this stage, until 48 light atoms indicated by the molecular formula $C_{39}H_nO_9SBr$ were obtained.

Eight atoms with the higher electron densities were then identified as oxygen atoms(shown by O1 to O8 in Fig. 1). Taking the remaining light atoms to be carbons, a series of cycles of least squares refinements were made, which led to the structure in Fig. 1. The reliability factor for 3556 reflections with $F_{obs}>4.5$ was 12.9% (maximum F was 287).

A difference-Fourier synthesis showed that no atoms had been assigned wrong positions, and that all the atoms had been accounted for. The bond lengths were therefore calculated and they indicated the double bonds between carbons, as well as the C=O groups as shown in Fig. 1. All the atoms agreed with the bond length data, except atom marked O9 in Fig. 1, which was originally assumed to be a carbon atom. The distance from atom C30 to atom O9 was 1.25 Å, which agreed with a C=O bond. This, along with the fact that the molecular formula required 9 oxygens, led to the assignment of this atom as an oxygen, although its peak electron density was lower than that for the other oxygens. NMR evidence (see below) also indicated the existence of an aldehyde group. This atom was therefore changed from carbon to oxygen. Two more cycles of refinement brought the R-value down to less than 12.4%. The difference-Fourier was now very clean, and it contained no peaks larger than one-tenth of a carbon peak, except in the vicinity of bromine and sulphur atoms, which had a large anisotropic vibration. The atomic co-ordinates of the sulphur atom have a standard deviation of less than 0.002 Å, and of the other atoms less than 0.015 Å (except O9 which is of the order of 0.02 Å).

The bond distances of the final structure agree closely with those in Fig. 1 and they lead to the structural formula II for morellin ($C_{33}H_{36}O_7$). The absolute configuration has not yet been determined. The details of the structure analysis will be published elsewhere.

Chemical, UV and IR data

Morellin contains only one OH group, the 5-hydroxyl of a 5-hydroxychromone or chromanone; but it formed a diacetate. The behaviour towards carbonyl reagents indicated the presence and different reactivity of three CO groups. Catalytic hydrogenation showed the presence of four ethylenic bonds, three of which are conjugated to a benzene ring or carbonyl group. Morellin formed a red copper complex ($C_{33}H_{35}O_7Cu/_2$), crystallizable from chloroform. Morellin methyl ether, tetrahydromorellin and octahydromorellin did not form copper complexes. The formation of the copper complex and its colour (cf. rottlerin) apparently involves a phenolic OH chelated with a CO group and a readily reducible ethylenic bond in conjugation with the CO group. Data on the UV and IR spectra of morellin and its reduction products have been discussed earlier.[2b] In the double bond region of the IR morellin has four absorption bands: 1730, 1668, 1628 and 1580 cm^{-1}, provisionally assigned to an unconjugated CO, an $\alpha\beta$-$\alpha'\beta'$-unsaturated CO, a chelated CO as in a 5-hydroxychromanone and aromatic absorption, and an ethylenic bond capable of very rapid reduction. In the UV, the long wavelength absorption band of morellin (λ_{max} 360 $m\mu$; ϵ_{max} 15130) is similar to that of rottlerin which has been attributed to a cinnamoyl group conjugated with a chromene nucleus.[4]

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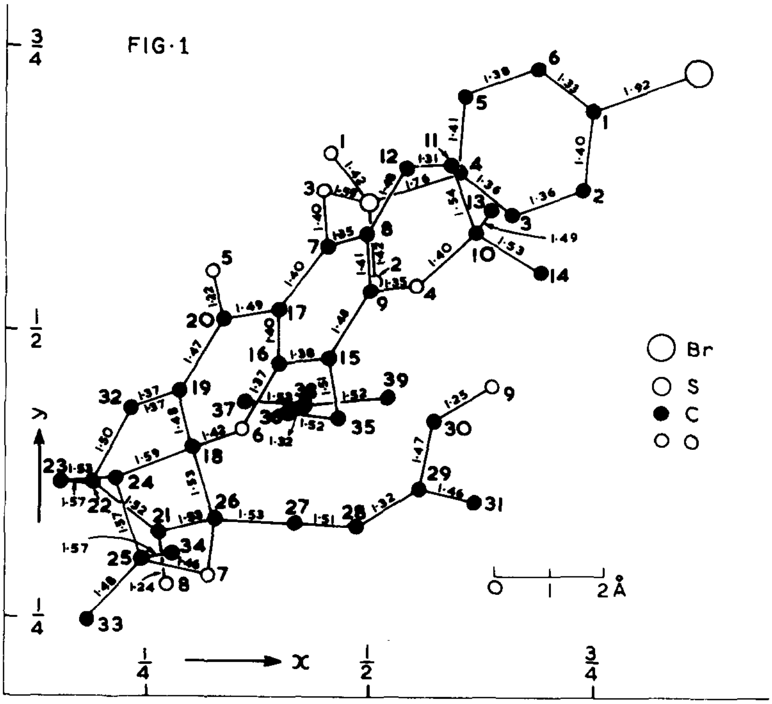
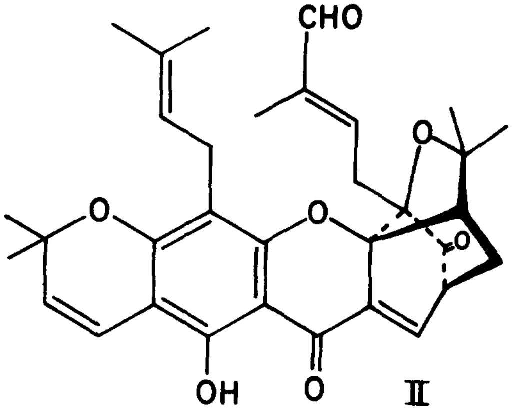
[4] R. A. Morton and Z. Sawires, J. Chem. Soc. 1052 (1940).

FIG·1





II

Treatment of morellin with ten times its weight of Raney nickel in boiling ethanol, cyclohexanol or cyclohexanone gave three crystalline products, A, B and C. A was convertible to B by heating with Pd-C in p-cymene; C was also obtainable by heating octahydromorellin with Pd-C and p-cymene. Alkali fusion of B at 290° gave steam-volatile fatty acids, a phenol, $C_{16}H_{24}O_4$, and a dicarboxylic acid, $C_{12}H_{12}O_4$. The acid yielded naphthalene by treatment with copper bronze in boiling quinoline, decarboxylation being accompanied by dehydrogenation; nitric acid at 230° led to mellophanic acid. Spectral evidence and synthesis ultimately showed that the acid is tetrahydronaphthaleno-5,7-dicarboxylic acid. In conjunction with B. S. Rao's observation, confirmed by us, that homophthalic acid is one of the products of alkali fusion of morellin, the assumption was made that morellin contains a partially hydrogenated naphthalene ring.

The condensation of 5,7-dihydroxy-2,2-dimethylchromanone with isovaleric acid in presence of boron fluoride or phloroisovalerophenone with β-hydroxyisovaleric acid in presence of boron fluoride etherate[5] gave a mixture of 5,7-dihydroxy-6- and 8-isovaleroyl-2,2-dimethylchromanone, which were separated by chromatography. Clemmensen reduction of the 8-isomer, carried out first with the object of preparing the corresponding isoamylchromane (III), unexpectedly yielded a compound identical with the C_{16}-phenol. Some of the properties agreed with the corresponding chromanol structure, but this was incompatible with the UV, IR and NMR data. By mild alkaline hydrolysis octahydromorellin lost six carbon atoms, one accounted for as formic acid. The major product, $C_{27}H_{40}O_6$,

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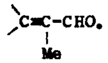
[5] H. B. Bhat and K. Venkataraman, <u>Tetrahedron</u> (1962), under publication.

had the properties of III with a $COCH_2R$ group in the 6-position; R contained a $-CMe_2OH$ group, and a peak at 1710 cm^{-1} in the IR spectrum could be explained by a cyclohexanone ring, unconfirmed by chemical tests. Drastic alkali fusion of the C_{27} compound or octahydromorellin led to the chromane (III) and the C_{16}-phenol.

The dimethylallyl group in I was confirmed by ozonization which gave acetone; more prolonged ozonization gave pyruvic aldehyde, probably resulting from the group



$>C{=}\underset{Me}{C}{-}CHO$.

NMR data

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), 8.5 and 8.67 and are attached to tert. C atoms; chemical shifts are cited on the τ scale. The remaining three give peaks at 8.2, 8.25 and 8.3 and are evidently on C=C bonds. There is no CH_3-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.[6,7] The vinyl triplet at 4.75 and the Me signals at 8.2

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[6] B. F. Burrows, W. D. Ollis and L. M. Jackman, Proc. Chem. Soc. 177 (1960).

[7] L. Crombie and J. W. Lown, J. Chem. Soc. 775 (1962).

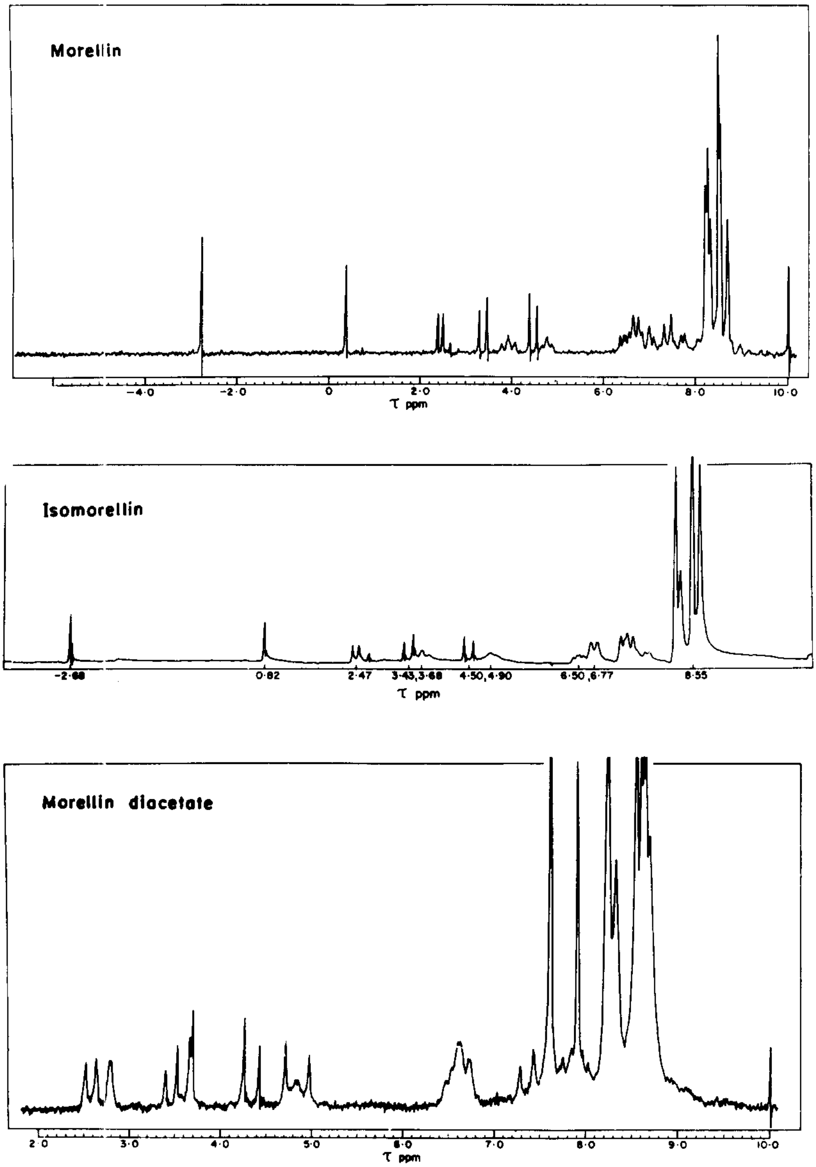

FIG. 2. NMR spectra at 60 Mc in $CDCl_3$ solution

and 8.3 may be assigned to a γγ-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,[6] 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 I or the linear isomer, 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 αβ-unsaturated ketone, which has a planar S-cis conformation[8] or is part of a cyclopentenone ring. The absorption of morellin in the near UV region (λ_{max} 360 mμ) requires that there should be a double bond in conjugation with the CO in the central ring of I, 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. Structure II confirms this assignment. In tetrahydromorellin the chromene doublets and the doublet at 2.4 disappear.

The triplet absorption at 3.9 in the morellin spectrum indicates another proton with an adjacent CH_2 and on a double bond attached to an

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[8] L. M. Jackman, Applications of NMR Spectroscopy in Organic Chemistry p. 122. Pergamon Press, London (1959).

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 of 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 αβ-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 2.8, 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 αβ-unsaturated and is present in a side chain, the observed changes will be consistent with the presence of a $-CH_2-CH=\underset{|}{C}-CHO$ group in morellin, converted to $-CH=CH-\underset{|}{C}=CH-OAc$ in the diacetate, the γ- and δ-protons giving rise to the doublet absorptions at 3.52 and 4.84. If the methylene group of $-CH_2-CH=\underset{|}{C}-CHO$ is cis to the substituent at the α-position in morellin, the driving force for the isomerization to isomorellin is the repulsion between these groups. In addition, a conformational preference involving rotation around the $-CH_2-CH=$ bond may also be a factor. The Me group absorbing at 8.25 may be conveniently assigned as the α-substituent. 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. These considerations show the presence in morellin of the group $-CH_2-CH{=}\underset{|}{C}-CHO$, and that morellin and isomorellin are *cis*-*trans* isomers.

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 γγ-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;[9] the proton at the bridge-head α to the keto group of the bicyclo-octenone part in II has the latter type of environment. 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. These are readily identified in structure II as they are the only ones of their types left unassigned.

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. Although

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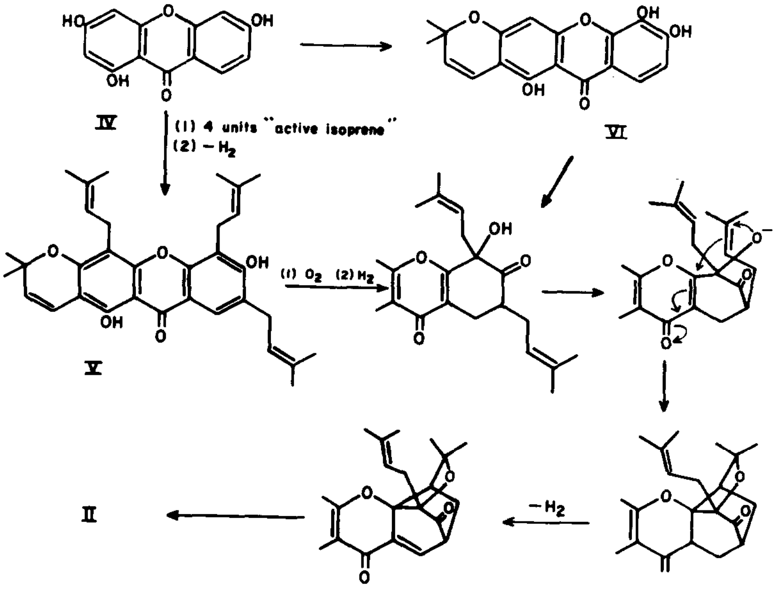
[9] L. Crombie and J. W. Lown, *J. Chem. Soc.* 108 (1962).

they may form a gem-dimethyl system, their environments are appreciably different. In isomorellin these Me groups are in similar environments and lead to a single sharp resonance at 8.67.

Biogenesis

Morellin can be derived biogenetically from 1,3,7-trihydroxyxanthone (IV) and four units of "active isoprene" by the scheme outlined in Chart I. 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 is remarkable. 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 V.

CHART 1



Jacareubin (VI),[10] mangostin,[11] and celebixanthone[12] are other xanthones 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 xanthones 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 type[13] and the bisditerpene, maytenone.[14]

We are indebted to Dr. W. D. Ollis and Dr. R. I. Reed for the mass spectrum of morellin, Dr. M. Caserio, Dr. A. Melera and Dr. C. S. Barnes for the NMR spectra, and Dr. W. D. Ollis and Dr. Sukh Dev for stimulating discussions.

Note: Structure II represents isomorellin, and morellin has the structure in which the aldehyde and methylene groups are in the *cis*-configuration. The chemical shifts of the groups concerned in the NMR spectra of morellin and isomorellin are more consistent with the modified structures. The facile isomerization of morellin to isomorellin is under investigation in relation to the proposed structures.

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[10] F. E. King, T. J. King and L. C. Manning, *J. Chem. Soc.* 563 (1957).

[11] P. Yates and G. H. Stout, *J. Amer. Chem. Soc.* **80**, 1691 (1958).

[12] G. H. Stout, V. F. Stout and M. J. Welsh, *Tetrahedron Letters* No.13, 541 (1962).

[13] K. Wiesner and Z. Valenta in *Fortschr. Chem. Org. Naturstoffe* **16**, 44 (1958)

[14] A.W. Johnson, T.J. King and R.J. Martin. *J. Chem. Soc.* 4420 (1961).