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ON THE STRUCTURES OF GB1, GB1A and GB2, AND ON THE BIOSYNTHESIS OF ISOFLAVONES.

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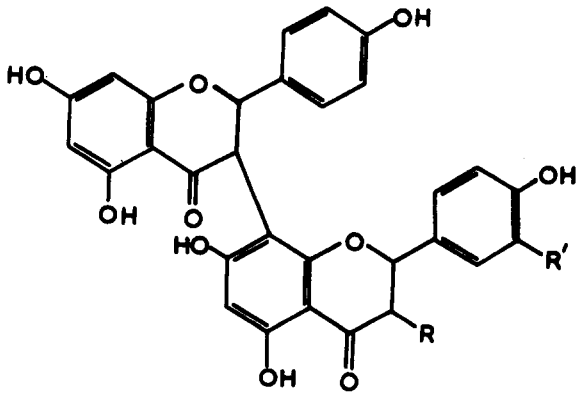
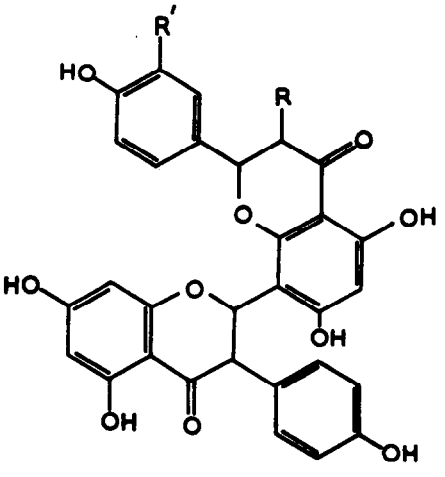
Further to a previous paper[1] commenting on the structures of GB1, GB1A and GB2, extractives from Garcinia buchananii[2], two publications have appeared[3,4] and amplification of earlier remarks is in order.

The paper[3] by Jackson et al shows that the breakdown of GB1, GB1A and GB2 to yield phloroglucinol is probably a thermal reaction, not due to electron-bombardment as previously reported[2]. This is probably true also for the production of phloroglucinol dimethyl ether from GB1 heptamethyl ether. Why this mode of degradation is so pronounced with these bisflavonoids is not clear, and further work on the thermal degradation of flavonoids may be expected to yield interesting and important results. These do not bear however on whether GB1, GB1A and GB2 are represented by formulae of type (I) or the rearranged type (II).

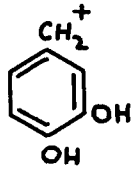


(I) (a) R = OH, R' = H
(b) R = H, R' = H
(c) R = OH, R' = OH

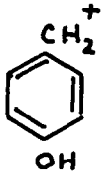


(II)

Taking up a previous suggestion[1] that if the benzylic ion at m/e 121 is assumed to arise from C(2) of a flavanone, then its presence or absence in GB2 heptamethyl ether (i.e. GB2 in which all the phenolic hydroxyl groups have been methylated, leaving the alcoholic group intact) might be indicative of structure, Jackson et al examined the mass spectrum of GB2 itself. The benzylic ions (III) and (IV) were found, and it was suggested that this favours structures (I) rather than (II).

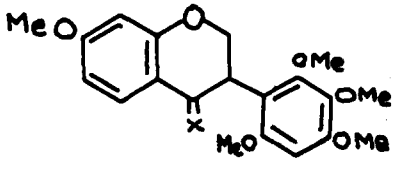


(III)



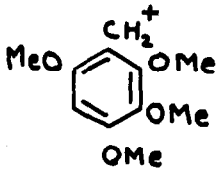
(IV)

In the original remarks it was strongly emphasised that "great caution must be exercised in the interpretation of spectra in this unexplored field" in which the compounds are both flavonoid and isoflavonoid. In particular if benzylic ions can arise from C(3) of an isoflavonoid then obviously the information is useless in structural work of this kind. In fact such ions can arise from C(3) of isoflavonoids. For example with compound (Va), the benzylic ion (VI) represents the third largest peak in the spectrum, whilst in related compounds in which ring A is not methylated the benzylic ion may be the base peak.



(V) (a) X = H_2

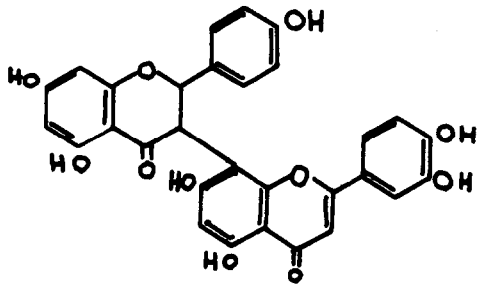
(b) X = O



(VI)

In the corresponding isoflavanone (Vb), the peak was considerably reduced, though present.

As no further chemical evidence was presented by Jackson et al it is clear that, at the moment, no decision can be taken between structures (Ia), (Ib) and (Ic) and (IIa), (IIb) and (IIc) for GB1, GB1A and GB2 respectively. However, since the previous paper[1], a note by Venkataraman et al[5] has appeared which assigns structure (VII) to morelloflavone. on sound chemical evidence. As morelloflavone was isolated from Garcinia morella,

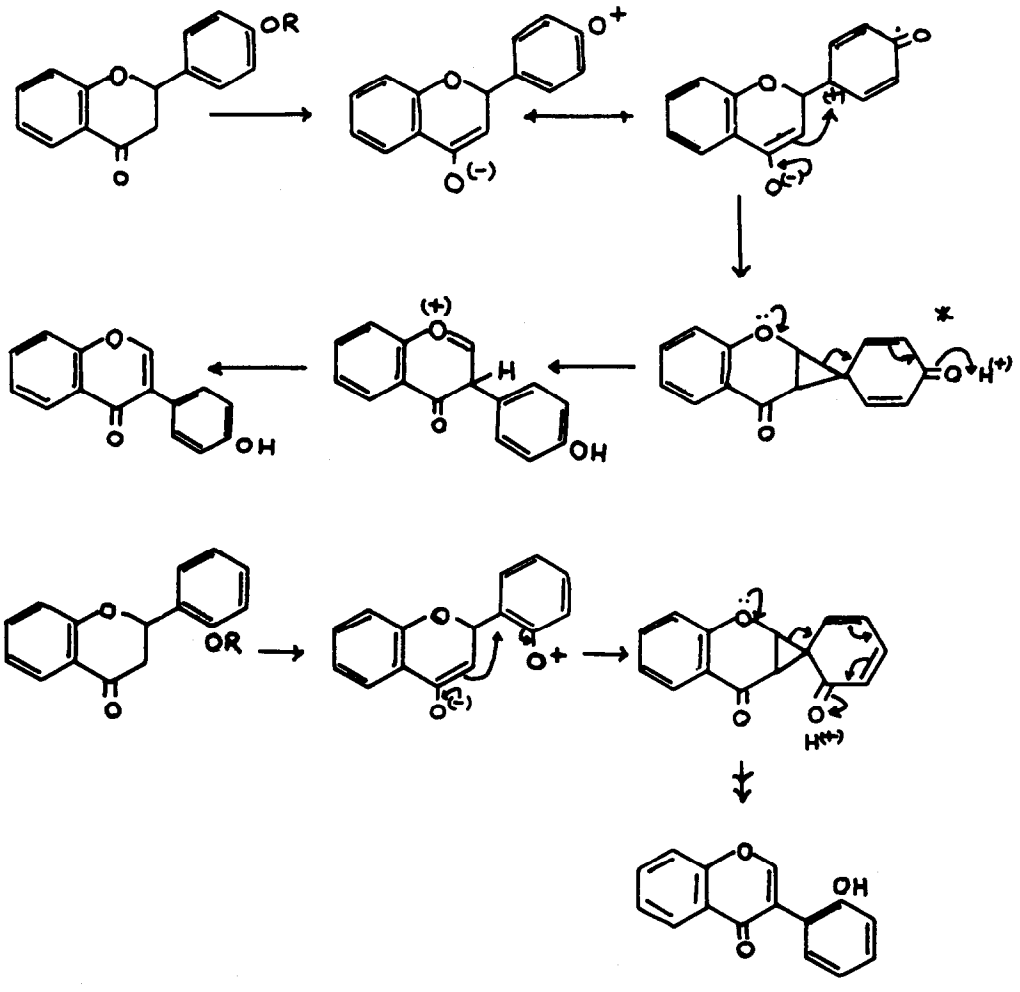


(VII)

closely related to Garcinia buchananii, this would by inference make the original formulae (Ia - c) the more plausible.

Grisebach has remonstrated[3] that in giving examples of 1,2 shifts in the flavonoid series, his work[6,7] on flavanone incorporation into isoflavones was ignored. In fact the examples given were not meant to be exhaustive, and in addition it is not absolutely certain that rearrangement occurs at the flavanone stage. Whilst incorporation of a flavanone, as a unit, into an isoflavone was demonstrated, flavanonols were excluded on the basis of negative evidence (non-incorporation) using the whole organism. Such evidence is notoriously fallible in itself, whilst the species that rearranges need not be a flavanonol but a derivate (phosphate ?). The prime example of such a differentiation is the non-incorporation of β-hydroxy-β-methyl glutarate into terpenoids, compared with the incorporation of the mono-CoA-ester. Until such time as enzyme work is available, it is not possible to exclude flavanonol derivatives as being implicated in isoflavone synthesis.

A more basic difficulty is evident in any of the current theories that directly connect flavonoids and isoflavonoids. This concerns the gross differences in oxygenation pattern between the two groups, which have previously been pointed out[8,9]. Including the 4-hydroxy-3-phenylcoumarins, pterocarpinoids and rotenoids, ~ 60% of the isoflavonoids



SCHEME 1.

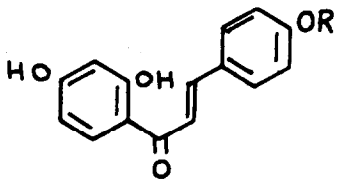
* It has been pointed out by Dr.D.J.Austen that direct alkylation could occur at this stage.

have a hydroxyl group in the 2'-position, whilst less than 10% of the flavonoids contain this group. One explanation of this which has been put forward is that the B ring of an isoflavone is derived from a coumarin, but this does not explain why such compounds furnish isoflavonoids rather than flavonoids. Another explanation could be that in the limited group of plants that produce isoflavonoids there is also, coincidentally, a predeliction for 2'-hydroxylation.

For some years[10] our group has been using the idea that isoflavonoids need not arise by a unique process, and that in some compounds hydroxylation at the 2'-position may be part of the mechanism of migration of the aryl group.

The first possibility, rendered less probable by Grisebach's work, is the migration of a derivative of a trans-flavanonol.

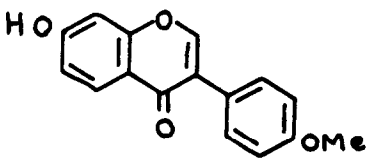
The second possibility involves oxidation of the 4'- and 2'-hydroxyl group of a flavanone (all isoflavones having one or other of these groups) either by 1 or 2 electron processes. The possibilities for a 2-electron process are shown in Scheme 1. On this basis the 2'-hydroxyl group is favourable for migration as it increases the chance of oxidation on the B ring, so that migration can occur, and the scheme would accommodate all the known isoflavones. It would imply that in the precursor flavanones a free hydroxyl group in the 4'- or 2'-positions is essential for specific incorporation of the C_{15}-unit. Most unfortunately, no data are available for any 2'-hydroxyisoflavone , but recent experiments[11] on the production of formonetin (IX) support this idea. Thus the methylated chalcone (VIIIa), suitably labelled, gave but poor incorporation into (IX) and with low specificity for ring A, as labelled biochanin A (X) is also produced, suggesting degradation processes. On the other hand (VIIIb) is converted very well into (IX) and with high ring A specificity. Whether (VIIIc) would act as an equally specific precursor remains to be seen.



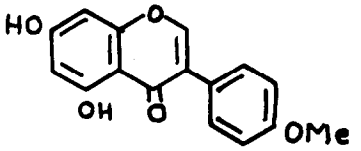
(VIII) (a) R = CH_3

(b) R = H

(c) R = Sugar

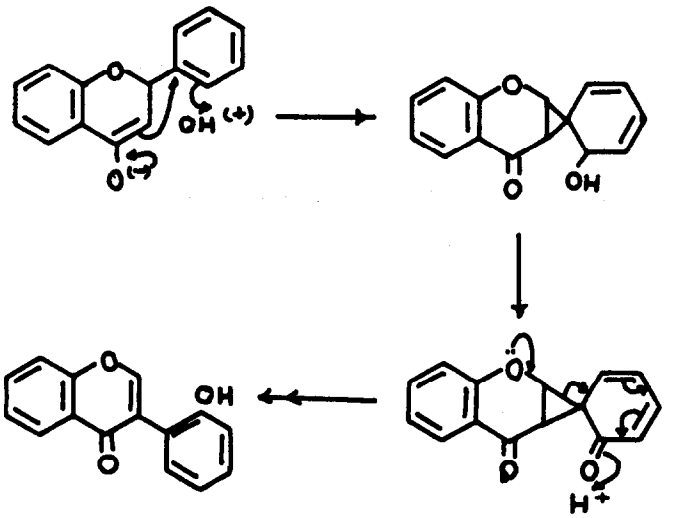


(IX)



(X)

A third possibility involves attack by the equivalent of OH^+ on the enolate of a flavanone, as in the production of a flavanonol. But instead of attack occuring at C(3), it does so at the neighbouring C(2'), and this is followed by oxidation of the allylic alcohol, and then migration as in Scheme 2.



SCHEME 2.

This differs from the other hypotheses in that incorporation of the 2'-hydroxyl group is an integral part of the migration step, and implies at least two separate mechanisms for the migration. As a rather small family of plants produce isoflavones this is, perhaps, not so probable as Scheme 1.

Experiments are in hand to attempt to provide in vitro analogies for the various processes outlined.

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