Structure and Synthesis of Crombenin, a Natural Spirocoumaranone

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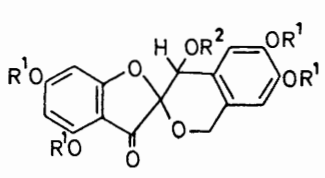
Summary Crombenin, 4,4′,6,6′,7′-pentahydroxyisochroman-3′-spiro-2-coumaran-3-one, represents a new type of flavonoid compound related to the concomitant crombeone (5-hydroxypeltogynone) in *Acacia crombei*.

CONTINUED investigations of a number of metabolites related to peltogynol in the heartwood of *Acacia crombei* C. T. White[1] have revealed the presence of a novel type of flavonoid at exceptionally low concentrations. The compound is named crombenin, and assigned a 4′-hydroxyisochroman-3′-spiro-2-coumaran-3-one structure (I) on the basis of n.m.r. and mass spectrometry of its two derivatives (II, III), and their synthesis as a diastereoisomeric mixture from crombeone[1] tetramethyl ether (IX).

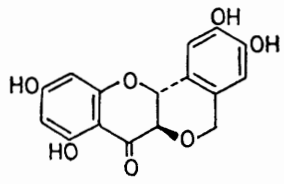
Methylation with diazomethane of an enriched fraction of high mobility obtained from preparative paper chromatography of the extract, gave an amorphous tetramethyl ether (II), $[\alpha]_D^{25} - 4{\cdot}8°$ in pyridine, M^+ 388, following separation by t.l.c. on kieselgel. The methyl ether readily affords an amorphous monoacetate (III), $[\alpha]_D^{25} - 2{\cdot}4°$, M^+ 430.

The acetate (III) in $CDCl_3$ shows a *meta*-coupled AB quartet (J_{AB} 1·6 Hz, τ 3·82, 3·95) in an upfield area of the benzenoid region, typical of phloroglucinol A-ring flavonoids, together with a pair of *para*-coupled singlets ($J_{AB} < 1$ Hz, τ 3·33, 3·40) at lower field. These closely resemble the spectrum of the trimethyl ether of crombeone[1] (IV). The benzenoid region also exhibits a lone singlet (τ 3·60) broadened by pronounced secondary coupling ($J \leqslant 1$ Hz). Comparison in deuteriated pyridine solution of the methyl ether and its acetate revealed that this signal alone undergoes a pronounced downfield shift ($\Delta\tau$ − 1·22) on acetylation, consistent with its position geminal to the hydroxy-function in the former. The persistence of a degree of line-broadening after acetylation suggests that the methine proton (and therefore the associated hydroxy-group) is benzylic.

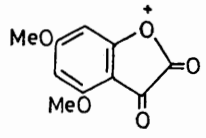
The spectrum of the acetate in $CDCl_3$ also has a broadened AB quartet (J_{AB} 14·4 Hz, τ 4·80, 5·10) analogous to the methylene D-ring systems of mopanols,[2] mopanone,[2] and crombeone.[1] Integral curves indicate the presence of four methoxy-groups [τ 6·07(3H), 6·13(3H), and 6·17(6H)] and one acetyl grouping (τ 7·98).



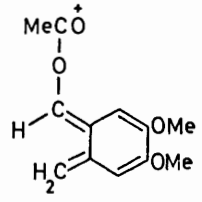
(I) $R^1=R^2=H$
(II) $R^1=Me, R^2=H$
(III) $R^1=Me, R^2=Ac$



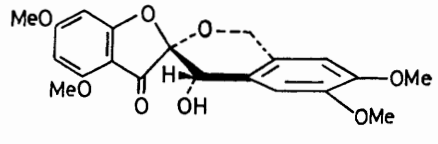
(IV)



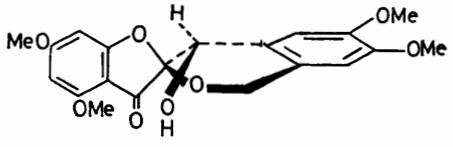
(V)



(VI)



(VII)



(VIII)

Structure (I), 4,4′,6,6′,7′-pentahydroxyisochroman-3′-spiro-2-coumaran-3-one, is alone consistent with the above from among many alternatives, and permits rationalization of the mass spectral fragmentation of both derivatives. For

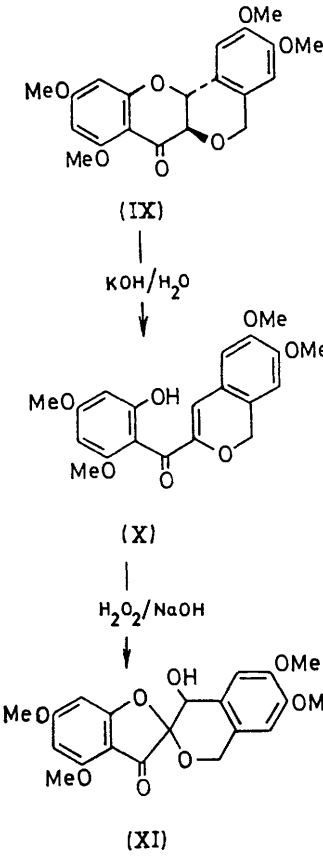
example, the tetramethyl ether acetate (III) significantly loses an acetoxy-radical in the sequence M^+ 430(0·7) $\xrightarrow{-OAc}$ *m/e* 371(5·4) $\xrightarrow{-H^{\bullet},m^*}$ *m/e* 370(5·1), and also undergoes retro Diels–Alder fragmentation to give the ions *m/e* 208(10·7) and 222(12·7), (V) and (VI), respectively. The former fragmentation confirms the benzylic position of the acetoxy-group, and the latter, taken in conjunction with n.m.r. evidence, provides corroborative proof of structure. The above ion, *m/e* 370, gives an accurate mass value of 370·1050, compared with 370·1052 calculated for $C_{20}H_{18}O_7$.

The i.r. spectrum of the methyl ether (II) exhibits a hydrogen-bonded hydroxy-group (ν_{max} 3450 cm^{-1}) as well as carbonyl function (1695 cm^{-1}), the latter shifting to a higher frequency (1725 cm^{-1}) on acetylation. This establishes the relative configuration as either 2(3′)*R*:4′*S* (VII) or 2(3′)*S*:4′*R* (VIII).

Synthesis of the derivatives of crombenin (II, III) was accomplished by conversion from crombeone tetramethyl ether (IX). However, due to its limited availability the suggested sequence was first attempted by an analogous series of conversions, starting with (+)-dihydroquercetin (taxifolin). This initially involved complete methylation of the latter with Me_2SO_4–K_2CO_3 in acetone to the (+)-dihydroquercetin pentamethyl ether, m.p. 142°; ring opening with aqueous KOH to 2′-hydroxy-α,3,4,4′,6′-pentamethoxychalcone, m.p. 116°; and finally the Algar–Flynn–Oyamada (A.F.O.) reaction (oxidation of 2′-hydroxychalcones with alkaline hydrogen peroxide) of the α-methoxychalcone[3,4] to 2-(α-hydroxybenzyl)-2,3′,4,4′,6-pentamethoxycoumaran-3-one, m.p. 178°.

In the corresponding sequence crombeone (IV) was methylated to its tetramethyl ether (IX), m.p. 192°, followed by successive conversion under identical conditions into the 2′-hydroxychalcone (X), m.p. 81°, and to the non-crystalline 4′-hydroxy-4,6,6′,7′-tetramethoxyisochroman-3′-spiro-2-coumaran-3-one (XI), m.p. 213°. In both syntheses the presence of a 6′-methoxy-group in the 2′-hydroxychalcone directs the course of the final A.F.O. oxidation.[5] The synthetic compound (XI) and its 4′-acetate gave mass and n.m.r. spectra which were identical to those of related derivatives from the natural product. However, creation of two points of chirality in the final step of the synthesis (A.F.O. oxidation) should lead to four diastereoisomers, of which the natural compound represents only one, or at most a pair of enantiomers, if partly racemized.

Crombenin (I) and crombeone (IV) may be regarded as 2-(α-hydroxybenzyl)coumaranone and dihydroflavonol analogues of 5-hydroxypeltogynols and could have common biogenetic origins in the chalcone analogue.



Crombenin is unique amongst flavonoids both as regards general structure and its 4′-hydroxy-function, although indirect evidence consistent with a 2-(α-hydroxybenzyl)-coumaranone as an intermediate in aurone biosynthesis has been obtained.[6]

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